National Institute for Health and Clinical Excellence

Neutropenic Sepsis
Guideline Consultation Comments Table
16.02.12 – 28.03.12

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Airedale NHS Foundation Trust	41.01	Full	General		It is important that the interaction between this clinical entity and associated services is recognised. National guidance on the recognition and treatment of sepsis in general should take into account the need to identify patients investigated for sepsis who have received chemotherapy (and cytotoxic chemotherapy is not the only cause of neutropenia, consider carbimazole reactions for example). The role of the acute oncology service should be emphasised; it is through this entity that the guidelines can most effectively be implemented and their publication should serve as a stimulus for Trusts to develop acute oncology in all relevant hospitals. Notwithstanding this, it is not in patients' interest for haematology or oncology to be over-possessive of these patients. Sepsis occurring in the presence of neutropenia should be managed as potentially severe sepsis and any acute medical team or emergency department has to be competent to do so; this should not be compromised by any concern that the patient is in the 'wrong hospital'.	Thank you for your comment. However the scope of the guideline only covers the prevention and management of neutropenic sepsis in cancer patients. Implementation of the recommendations in this guideline will be a matter for local determination
Airedale NHS Foundation Trust	41.02	Full	37	3	The need to report neutropenic septic deaths to the Coroner is also relevant here; it provides a disincentive to record causes of death	This text is from the needs assessment which describes current practice in the UK. It does not examine the evidence nor does it make

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					accurately.	recommendations for future practice.
Airedale NHS Foundation Trust	41.03	Full	41	12	A practical issue in the definition of 'fever' is the importance of the patient's own out-of-hospital measurement. A temp >38C at home may have settled after a nice cool road journey but it should still be regarded as a valid observation.	We agree. We do not think that the wording of the current recommendation would prevent this from happening.
Airedale NHS Foundation Trust	41.04	Full	43	1	Clinicians treating cancer tend to have a 'fail-safe' philosophy in managing neutropenic sepsis (NS) and so will require a strong evidence base for a definition of over-treatment.	The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of $\leq$0.5. The evidence also showed that increased temperature was associated with an increase in infection. The lowest value for fever studied in the evidence was 38^{o}C and the GDG decided to adopt this value in their definition for neutropenic sepsis.
Airedale NHS Foundation Trust	41.05	Full	44	33	Whilst wholeheartedly agreeing with this recommendation, services should not be organised on the assumption that patients will comply with instructions; satisfactory treatment	The clinical effectiveness data appraised was taken from pragmatic randomised controlled trials where such issues are incorporated into the study design. We are therefore satisfied

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					should not be contingent on their doing so.	that these issues have been taken into account and that a patient is able to make an informed decision regarding their care and choice in treatment.
Airedale NHS Foundation Trust	41.06	Full	52	14	The organisation to which patients should be directed is one providing an acute oncology service. Patients reluctant to travel to a tertiary service should not be disadvantaged.	We do not believe that the wording of the current recommendation would preclude patients being referred to an acute oncology service in secondary care. Therefore we have not made this amendment to the recommendation.
Airedale NHS Foundation Trust	41.07	Full	54	21	Non-neutrophil cell type counts are provided automatically by most labs. Their value in assessment seems not to be discussed further in this Guidance.	This text is from the background which describes why this topic needed to be investigated. It does not examine the evidence nor does it make recommendations for future practice. The indices you refer to are noted in Table 4.2.
Airedale NHS Foundation Trust	41.08	Full	59	17	A recommendation on how to use lactate in identifying patients for critical care would be valuable in this Guidance document.	We do not feel this is necessary because it would be part of standard clinical practice.
Airedale NHS Foundation Trust	41.09	Full	60	49	Comment on blood cultures in general; is anything to be said about taking blood when there is a high likelihood of bacteraemia, i.e. during a rigor, in increasing the rate of microbiological diagnosis?	Taking blood when there is a high likelihood of bacteraemia was not identified as a priority for investigation in the guideline because blood cultures should be performed in accordance with national standard operating procedures. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it.
Airedale NHS Foundation Trust	41.10	Full	65	1	It is the role of the acute oncology team to provide this assessment if the patient is not on a haematology/oncology ward. A 48hrs limit is very difficult to attain and should not be necessary if the patient is being managed by a medical team that can deal with sepsis NOS. However discussion with the on-call consultant within this time scale is a sensible	For clarity, the GDG have amended the recommendation to "a healthcare professional with competence in managing complications of anti-cancer treatment". The GDG have reviewed this recommendation, and felt that to improve the patient experience and clinical management a patients risk of septic complications should be assessed within a

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					recommendation.	maximum of 24 hours of presentation.
Airedale NHS Foundation Trust	41.11	Full	112	44	In this solid tumour service practice is to use quinolone prophylaxis in small cell lung cancer only. To widen the indication would increase the number of patients receiving these drugs and therefore potentially increase quinolone resistance in the community. This is exacerbated by the expected increase in the number of patients receiving chemotherapy. Resistance must be monitored carefully.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand

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						hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Airedale NHS Foundation Trust	41.12	Full	133	1	It is a major omission in this Guidance that no recommendation is made for patient s who are allergic to penicillin/cephalosporins .	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.
Airedale NHS	41.13	Full	154	1	Again, clinical review is the work of the Acute	We agree but setting this up will be a matter

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Foundation Trust					Oncology Service	for local implementation
Airedale NHS Foundation Trust	41.00	Full	236	8	Please note the correct name of this organisation	Thank you for your comment. We have changed Airedale NHS Trust to Airedale NHS Foundation Trust.
Amgen UK	26.00	Full	General		Summary of comments regarding the recommendation on preventing the septic complications of anti-cancer therapy The approach taken in the worthwhile attempt to evaluate the effectiveness of neutropenic sepsis prophylaxis strategies falls short of the intended goal in several important aspects. Firstly, the arbitrary restrictions imposed by the guideline scope mean that important cancer patient populations are necessarily excluded from the draft recommendations. Secondly, the draft guideline failed to adhere to appropriate scientific methodology for evidence selection, weighting and synthesis. Thirdly, the draft guideline fails to adequately address the risks associated with widespread prophylactic antibiotic use including bacterial resistance, an important public health issue. Finally the draft recommendation on prevention is based on a cost-utility analysis that does not adhere to the NICE reference case. The draft guideline assumes that febrile neutropenia (FN) and neutropenic sepsis (NS) are interchangeable definitions, with chemotherapy induced neutropenia (CIN) as a necessary preceding condition causing NS	Thank you for raising these issues. We have included our responses alongside your detailed expansion of these points below. The remit from the Department of Health was to develop a guideline on the prevention and management of neutropenic sepsis in cancer patients. As such we are required to use this term. However we agree there can be

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					almost completely ignored. This has effectively moved the focus of the guideline to preventing/managing sepsis (infection) rather than preventing/managing the neutropenia that leads to NS. This is of critical importance because only G-CSF prophylaxis significantly decreases the incidence, severity and duration of CIN, which not only decreases the risk of FN but also reduces the incidence of resulting NS, as well as CIN-related dose delays and dose reductions. This in turn facilitates achievement of optimal relative dose intensity (RDI), yielding expected patient outcomes as observed in clinical trials. Antibiotics do not alter the incidence, severity or duration of CIN nor the impact on subsequent chemotherapy RDI. Instead, prophylactic antibiotics may actually increase the severity of NS through elicitation of resistant pathogen selection that may emerge as a result of treatment. We consider it inappropriate to use the terms FN and NS interchangeably and would recommend that wording in the guideline be modified to more accurately reflect medical terminology used. However, for clarity in communication, we use the NS terminology in our comments on the draft guideline. 1. <u>Exclusion of populations benefiting from optimal chemotherapy RDI</u> RDI is the ratio of standard chemotherapy	confusion in terminology and so have clarified the terminology used by this guideline in section 1.1, first paragraph. The remit from the Department of Health was "to produce a clinical guideline on the

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					regimen dose to the actual delivered dose over a specific time period. RDI is commonly calculated over all chemotherapy cycles delivered during a course of chemotherapy as a percentage (e.g. RDI of 85% would indicate that a patient received 85% of a standard chemotherapy regimen over the standard period of time). This concept is paramount, since standard chemotherapy dosing is determined through the results of adequately designed and executed clinical trials that reliably estimate a cancer patient population's response and/or survival rate, as well as risk of toxicity. In clinical practice the dose intensity of chemotherapy can be diminished by either the reduction in dose of one or more regimen agents or through time delay of administering the agents (in subsequent cycles of chemotherapy). Cancer patients receiving treatment should be given the initial opportunity to benefit from the effects of recognised standard chemotherapy regimens that reduce tumour burden, lengthen the time of progression-free survival or increase overall survival. The administration of lesser, unproven doses or delayed dosing over longer unproven time periods should only be employed in the palliative setting when, and if, the treating clinician determines the risks of full-dosing outweigh the potential benefits in a given patient	prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose. The exclusion of the effect of neutropenic sepsis on subsequent chemotherapy scheduling and doses, has been made explicit in the guideline.

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					(i.e. unpreventable toxicity). Significantly reduced RDI does not afford any patient their best chance to achieve a clinical benefit from their treatment and potentially introduces only the accompanying toxicity. The restrictions imposed by the guideline scope to exclude consideration of chemotherapy RDI and its implications for longer term outcomes *(see guideline scope section 4.3.2.e - Effect of neutropenic sepsis on subsequent chemotherapy scheduling and doses),* significantly limit the cancer patient population to whom these guidelines are applicable and specifically exclude patients for whom longer term survival is the primary consideration and who would most benefit from receiving full-dose chemotherapy (medium-high NS risk). RDI and potential for longer term survival should have been included in the scope and considered in the draft guideline, in order to appropriately evaluate the clinical and cost-effectiveness of NS prophylaxis. Therefore, patients for whom longer term survival due to chemotherapy treatment is an important consideration, by definition have been excluded from the draft guideline. The final guideline therefore must make the exclusion of these patients from the prevention recommendation clear and explicit. In addition, the exclusion of RDI and its	

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					implications for longer term outcomes serves to exclude consideration of the longer term benefits of G-CSFs from the assessment of clinical and cost-effectiveness of NS prophylaxis strategies. G-CSFs are the only available agents that significantly decrease the incidence, severity and duration of CIN, which not only reduces the risk of FN and its associated morbidity and mortality, but also reduces NS as well as neutropenia-related chemotherapy dose delays and dose reductions. G-CSF prophylaxis therefore has the ability both to reduce short term NS and in turn facilitate achievement of optimal chemotherapy RDI and improve patient outcomes (Kuderer 2007, Lyman 2008, Bohlius 2008). The draft guideline incorrectly assumes that all prophylactic strategies can indirectly improve patient's longer term survival by maintaining RDI (full version page 203 line 3). Antibiotics cannot affect the incidence, severity or duration of neutropenia or its impact on subsequent chemotherapy RDI and are only a short term measure to reduce febrile events. The final guideline should recognise that G-CSFs, through decreasing the incidence, severity and duration of CIN, by definition also decrease NS, which facilitates optimal chemotherapy RDI and improves patient outcomes, whilst antibiotics do not; and that the short term time frame imposed by the scope does not allow these longer term benefits to be captured. 2. <u>Lack of draft guideline alignment with UK clinical practice</u>	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. We agree that the evidence for this recommendation has been drawn from

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					The methodology employed in the draft guideline ignored documented NS risk factors and pooled patient data regardless of chemotherapy risk, tumour type and/or patient characteristics.	heterogeneous populations. We have attempted to reduce the population heterogeneity by excluding paediatric patients, patients receiving inpatient chemotherapy and patients whose regimen includes G-CSF from the model. In addition we have performed sub-group analysis for patients with solid tumours, non-Hodgkin lymphoma and Hodgkin lymphoma. The potential effect of this heterogeneity on the health economic model results has been assessed by sensitivity analysis on the relevant model inputs. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. The results of all one-way sensitivity analyses have been added to the guideline.
					The resulting draft guideline recommendation to use prophylactic quinolone (a wide-spectrum daily oral antibiotic) in all patients regardless of tumour type, NS risk or chemotherapy treatment intent, does not align with current UK standard clinical practice. The survey of clinical practice, presented in the draft guideline, shows it is established UK practice to use G-CSFs to	Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice.

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					support patients receiving medium-high risk chemotherapy in the reduction of severe neutropenia and subsequent reduction of NS; reporting that 95% of Trusts recommend primary prophylaxis with G-CSFs for at risk patients in their local clinical guidelines (full version page 32 line 33). G-CSFs were introduced to UK clinical practice more than 20 years ago and since then have been used according to their approved indication, i.e. to reduce the duration of severe neutropenia and to reduce the incidence of FN. Furthermore, UK clinical practice is aligned with international guidelines such as EORTC (Aapro 2010) which, co-authored by three UK clinicians, was viewed as applicable to the UK population and has subsequently been adopted by UK physicians. Given this clear established practice for use of G-CSFs within the UK, the draft guideline goes against one of its stated objectives, which is to develop recommendations where there is identifiable variation in clinical practice.	The GDG agreed that there was enough variation in practice in the prophylaxis of neutropenic sepsis to warrant investigating this topic, particularly with regard to cost-effectiveness.
					3. <u>Use of inappropriate scientific methodologies for evidence selection, weighting and synthesis</u> Clinical estimates of efficacy for G-CSFs were based on a meta-analysis which included studies using interventions and populations outside the UK licence for some G-CSFs, whilst the most relevant meta-analysis, Kuderer 2007, was not identified or used in the draft guideline. The final guideline should use Kurderer 2007 to generate efficacy estimates, since it is the only meta-analysis that is aligned with the licensed	The Sung et al (2007) review included the trials in the Kurderer et al meta-analysis. Subgroup analyses were done separately for paediatric, SCT, solid tumour and lymphoma patients and for GM-CSF studies.

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					indication of all G-CSFs and which focuses on all the relevant outcomes of interest The clinical efficacy of antibiotics was over-estimated, based on inappropriate pooling of data from a set of heterogeneous studies; using a range of different antibiotic treatments, with different populations, which did not take into account the NS risk or chemotherapy treatment intent (Gafter-Gvili 2005). All four studies used to estimate efficacy for the cost-utility model reported outcomes in terms of febrile episodes, which was used by the guideline as a proxy for NS. Importantly, three of the four antibiotic studies were underpowered with very small patient numbers, which individually did not report statistically significant findings for a quinolone on febrile episodes or mortality. A more appropriate relative risk would be the efficacy observed in the only large randomised clinical trial (RCT) in solid tumour patients from Cullen 2005 (relative risk = 0.72), although this still reports febrile episodes rather than NS. The clinical efficacy of antibiotics is over-estimated, based on inappropriate pooling of heterogeneous studies. The final guideline should use results from Cullen 2005 which are the most appropriate estimate of efficacy.	We agree that the evidence for this recommendation has been drawn from heterogeneous populations. We have attempted to reduce the population heterogeneity by excluding paediatric patients, patients receiving inpatient chemotherapy and patients whose regimen includes G-CSF from the model. In addition we have performed sub-group analysis for patients with solid tumours, non-Hodgkin lymphoma and Hodgkin lymphoma. The potential effect of this heterogeneity on the health economic model results has been assessed by sensitivity analysis on the relevant model inputs. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. The results of all one-way sensitivity analyses have been added to the guideline. The Gafter-Gvili (2005) systematic review,

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						which was appraised as part of the evidence review for this guideline, included data from Cullen (2005). Data from Gafter-Gvili (2005) was used in the analysis and hence the realtive risk cited by Cullen (2005) was not used.
					In comparing the effectiveness of G-CSFs and antibiotics, the final guideline should recognise; i) The substantial and significant differences in the quality and quantity of evidence available; with a high level of evidence in G-CSFs compared to sparse, low quality evidence in antibiotics. ii) The estimates of effectiveness presented in the guideline for antibiotics and G-CSFs versus no treatment are not comparable. They are based on very different sets of evidence in different patient populations and settings, with interventions given at different times and assessed using different outcomes (e.g. febrile events versus NS). As a consequence it is not possible to conduct a formal indirect comparison of G-CSFs versus antibiotics (using placebo/no treatment as the common comparator) because the evidence is too heterogeneous. The final guideline should recognise the high quantity and quality of evidence in G-CSFs compared to sparse, low quality evidence in antibiotics and also that the efficacy estimates for G-CSFs and antibiotics are not comparable because the evidence is too heterogeneous.	The quality of the evidence appraised for this topic has been acknowledged in the evidence summary and GRADE tables and linking evidence to recommendations section. We agree that the evidence for this recommendation has been drawn from heterogeneous populations. We have attempted to reduce the population heterogeneity by excluding paediatric patients, patients receiving inpatient chemotherapy and patients whose regimen includes G-CSF from the model. In addition we have performed sub-group analysis for patients with solid tumours, non-Hodgkin lymphoma and Hodgkin lymphoma. The potential effect of this heterogeneity on the health economic model results has been assessed by sensitivity analysis on the relevant model inputs. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not

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					4. <u>Antibiotic resistance is an important public health issue which has not been adequately addressed in the draft guideline</u> The recommendation to give wide-spectrum oral antibiotics to all cancer patients, would significantly increase the use of antibiotics in this patient group versus current practice, whilst at the same time increasing the incidence, duration and severity of neutropenia (since the draft guideline seeks to replace UK standard clinical practice in the use of G-CSF with antibiotics). There are serious concerns about the use of prophylactic antibiotics in a neutropenic, immune compromised setting including; i) the resulting limitations around the ability to culture and identify the infectious pathogens in septic events which emerged during prophylaxis and are likely resistant to those agents, ii) the potential masking of early septic symptoms serving to delay appropriate treatment, iii) accompanying toxicity in this fragile patient population, iv) potential non-compliance with a daily oral agent and v) development of microbial resistance, as recognised by all other international NS guidelines. Additionally, antibiotic prophylaxis goes against recent Department of Health (DH) advice ("Start smart	cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. The results of all one-way sensitivity analyses have been added to the guideline. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group.

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					– then focus" published by DH advisory committee on antimicrobial resistance and healthcare associated infection in Nov 11) on indiscriminate use of antibiotics, which states 'Do not start antibiotics in the absence of clinical evidence of bacterial infection'. Further, it is reasonably presumed that the use of prophylactic antibiotics in a neutropenic, immune compromised group would not be supported by clinical microbiologists due to the public epidemiologic health risks. The draft guideline does recognise that prophylactic antibiotics contribute to antibiotic resistance, but conclude that in patients receiving anti-cancer treatment the evidence suggests the benefits out-weigh the risks (full version page 112 line 47). However, this is an inappropriate conclusion, since the draft guideline looked only at the weak and sparse evidence of resistance effects in the population being treated (chemotherapy patients). Moreover, resistance in the wider populations of the chemotherapy unit, the hospital and in the general public was not considered. The final guideline should recognise that there are serious concerns about the widespread and indiscriminate use of prophylactic antibiotics in an immune compromised setting and the development of antibiotic resistance, also that there is insufficient clinical evidence to quantify the degree of risk for antibiotic resistance in the chemotherapy population and to the public at large. 5. <u>The cost utility analysis does not adhere to</u>	The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis. NICE have been liaising with the Department of Health and the Health Protection Agency about the implementation of these recommendations.

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					the NICE reference case In the cost-utility analysis, the time horizon is not modelled over the lifetime of the patient as specified in the NICE reference case.	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations. Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.

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					Additionally, the costs of a septic event appears to be significantly underestimated; the cost is derived by assuming a split in high and low risk of adverse event rates, which is not based on evidence or current clinical practice. The cost excludes many of the elements of treating NS, such as the cost of IV antibiotics, ITU beds and nursing support, anti fungal treatments, blood tests, and outpatient follow up. The cost of treating NS in the model (£712 - £766) is therefore significantly lower than the published HRG cost for 'Febrile neutropenia associated with malignancy' (£5,959).	The GDG agreed it would be more appropriate to use costs based on the clinical pathway represented by the guideline recommendations, rather than the HRG cost you cite. This was because the economic analysis only considered adult patients (solid tumour, NHL and HL) who are receiving outpatient chemotherapy. In contrast to those patients who are receiving inpatient chemotherapy, our target population rarely use ICU (ITU) or antifungal drugs (both of which are very expensive). This means the treatment cost for our target population (outpatient) will be much lower than it is for the inpatient group. Consequently the GDG agreed it would be inappropriate to use the HRG cost (which is also likely to cover all cancer patients).
					The model also excludes RDI and its implications for longer term outcomes since it is out of scope. In addition, the costs and wider public health effects associated with antibiotic resistance have not been addressed in the model. Finally, the relative risk estimate for NS (0.437) used in the solid tumour model for quinolones (versus no prophylaxis) is overstated; it uses neutropenic events as a proxy for NS and involves a meta-analysis with inappropriate pooling of heterogeneous studies. A more appropriate relative risk would be the efficacy observed in the only large RCT in solid tumour patients from Cullen 2005 (0.72), although this still reports febrile episodes rather	In order to investigate RDI we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy

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					than NS. The combination of these factors bias the cost-utility analysis against G-CSFs, as the model ignores significant costs, benefits and the key clinical rationale (RDI) for G-CSF use in medium-high NS risk patients in UK clinical practice. The guideline should recognize that this cost utility analysis does not adhere to the NICE reference case and therefore should not be used as the basis for a recommendation on prevention.	regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline Although our systematic review of cost-effectiveness studies did identify several studies trying to model the impact of using G-CSF on patients long-term survival (by maintaining chemotherapy dose) (see cost effective section in chapter 5); none of these studies used any direct clinical data. Instead, these studies were trying to build an indirect relationship between use of G-CSF and long-term survival. They stated that G-CSF could prevent neutropenic sepsis; neutropenic sepsis is a risk factor of receiving dose-reduction chemotherapy and dose-reduction chemotherapy is a risk factor for patient long-term survival. Then based on this hypothesis, the authors claimed that G-CSF could improve patients long-term survival. Furthermore, a recent meta-analysis (Shitara et al., 2011) shows that neutropenia experienced during chemotherapy is actually associated with improved survival in patients with advanced cancer or haematological

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						malignancies undergoing chemotherapy. This implies that experiencing side effects of chemotherapy might not be associated with impaired long term survival. Therefore the GDG were very unsure about the validity of the indirect logic used in these published cost-effectiveness studies and the derived conclusion and did not consider it appropriate to use the methodology from the existing studies to model the impact of using G-CSF on patients long-term survival for this guideline.
					Summary The draft guidelines as currently written recommend use of prophylactic antibiotics in all acute leukaemia, stem cell transplants or solid tumour adult cancer patients receiving chemotherapy, which is contrary to well-established UK clinical practice and UK clinician co-authored international guidelines on the prevention of NS. We strongly believe that the recommendation of antibiotic prophylaxis represents a backwards step in terms of patient care and could have damaging implications in terms of reducing the longer term survival of cancer patients, as well as for wider public health through increased morbid septic events, antibiotic toxicity and resistance in the UK. Anti-cancer treatment and potential for increased survival are the foundation of oncology care. Since the scope excluded consideration of RDI and its implications for longer term outcomes, it limits the cancer patient population to whom these guidelines are applicable.	We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant neutropenia ($\leq 0.5 \times 10^9$/litre) is an anticipated consequence of chemotherapy. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians

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					The final guideline should explicitly state that patients at medium-high NS risk are excluded from the prevention recommendation and that it is expected that these patients will continue to be treated as per current UK clinical practice (as reflected by the guideline survey). References: Kuderer N.M., Dale, D.C., Crawford J.et al. *J Clin Oncol.* 2007 Vol25 pp3158-67 Lyman, G.H., Kuderer N.M., Crawford, J. et al. *J Clin Oncol.* 26: 2008 (May 20 suppl; abstr 6552) Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. *Cochrane Database Syst Rev*. 2008;(4): Art. No.: CD003189 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131062 Aapro MS, Bohlius J, Cameron DA, et al. *Eur J Cancer.* 2011;47:8-32. Gafter-Gvili, A., Fraser, A., Paul, M., van de Wetering, M., Kremer, L., & Leibovici, L. (2005). Cochrane Database of Systematic Reviews.(4):CD004386, 2005, CD004386. Cullen M. D., Steven N., Billingham L., et al. *N Engl J Med* .(2005) 353; 10 988-998	in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg).. However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
Amgen UK	26.06	Full	4	8	Although the guideline aims to relate to the whole of the patient pathway this is clearly not possible, when, by excluding CIN, FN and resultant RDI and longer term outcomes, medium-high NS risk patients cannot be considered.	The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was

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						developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose.
					The guideline prevention recommendation also does not include patients of all ages (patients who are less than 18 year of age are excluded).	A research recommendation has been made for patients who are less than 18 years of age – see chapter 5
Amgen UK	26.07	Full	5	27	<u>The draft guideline as it currently stands would reduce longer term survival of cancer patients in the UK</u> The draft guidelines as currently written, recommending the use of antibiotics in all patients regardless of NS risk, could impact longer term survival for cancer patients in the UK: More patients receiving medium and high risk chemotherapy pre-treated with antibiotics in this way would remain neutropenic for longer or experience severe neutropenia and therefore would not maintain their chemotherapy RDI – impacting their longer term survival. Physicians may also be reluctant to give medium and high	A recent meta-analysis (Shitara et al., 2011) shows that neutropenia experienced during chemotherapy is actually associated with improved survival in patients with advanced cancer or haematological malignancies undergoing chemotherapy. This implies that experiencing side effects of chemotherapy might not be associated with impaired long term survival.

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					risk chemotherapy with only antibiotics as support and therefore could elect to use less aggressive, less effective chemotherapy. This would also impact patient's survival, particularly in the elderly who are at higher risk of NS (Aapro 2010). This also raises an important equality consideration in the elderly who are at higher NS risk. The impact of these guidelines to reduce longer term survival clearly would not support the 'Improving outcomes a strategy for cancer 2011 (DH 2011), which states the need to save an additional 5,000 lives by 2015. <u>Recommendation:</u> The final guideline should recognise the potential longer term negative impact on survival of cancer patients with the current prevention recommendation. References: Aapro MS, Bohlius J, Cameron DA, et al. *Eur J Cancer.* 2011;47:8-32. Improving Outcomes: A Strategy for Cancer (January 2011) DH	
Amgen UK	26.42	Full	7	15	<u>Key Research Recommendations</u> The recommendation for '*A prospective national cohort study to assess the incidence of suspected and proven neutropenic sepsis in patients having anti-cancer treatment'* seems to have missed published literature by Hershman	Data on the incidence of suspected and proven neutropenic sepsis in the UK is not available. The paper quoted in your comment is based in the USA. Consequently we feel this recommendation for research is still valid.

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					2009. Reference: Hershman et al Journal of Medical Economics, 2009; 12(3): 203–210	
Amgen UK	26.43	Full	7	29	The recommendation for '*A prospective study should be carried out to determine which signs and symptoms experienced by patients in the community predict neutropenic sepsis and the outcomes of these episodes'* suggests no awareness of the substantial quantity of evidence on prediction of NS and NS risk.	This research recommendation relates to a need for greater understanding of the signs and symptoms, experienced by patients in the community, which predict for episodes of neutropenic sepsis. We have amended the wording of the recommendation to clarify this.
Amgen UK	26.48	Full	10	49	Process The omission of the effects of NS on subsequent chemotherapy scheduling and doses was raised as a concern by a total of seven commentators during consultation on the draft scope. Despite the level of concern raised, the impact of NS on subsequent chemotherapy scheduling and doses remained outside the final scope.	As stated in our responses to stakeholder comments on the draft 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 was specifically excluded. All stakeholder comments were extensively considered by the GDG following consultation and changes have been made to the recommendations where appropriate.
Amgen UK	26.12	Full	12	5	Comments the same as comments made for Order Number 13 (for page 32, row 33)	Please see our response to order number 13
Amgen UK	26.45	Full	18	1	The guideline states '*Registered stakeholders (Appendix E.2) had one opportunity to comment on the draft guideline which was posted on the NICE website between 16 February 2012 and 12 April 2012 in line with NICE methodology*	Thank you for your comment. We have amended this statement to reflect the changes made by NICE to reduce the stakeholder consultation period from 8 weeks to 6 weeks.

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					(NICE 2012).' The date for return of comments is the 28 March, allowing 6 weeks for consultation, not 8 weeks.	
Amgen UK	26.04	Full	22	14	The guideline recognises that NS causes chemotherapy delay and dose reductions and that alterations to cytotoxic regimens (RDI) are used as a prophylactic strategy, even though considerations of CIN, FN and resultant RDI are excluded from the scope.	This text is from the needs assessment which describes current practice in the UK. It does not examine the evidence nor does it make recommendations for future practice. As such we feel it is appropriate to include this sentence here.
Amgen UK	26.07	Full	22	19	<u>It is inappropriate to use FN and NS interchangeably</u> The draft guidelines state that *'in clinical practice the terms febrile neutropenia and neutropenic sepsis are used interchangeably in this patient group and recommendations in this guideline use the term 'neutropenic sepsis' to indicate the full range of severity of illness'.* Chemotherapy induced neutropenia (CIN) as a preceding condition causing NS is almost completely ignored within the guideline. The assumption that FN and NS are interchangeable definitions has effectively moved the focus of the guideline to preventing/managing sepsis (infection) rather than preventing/managing neutropenia. This is of critical importance because only G-CSF prophylaxis significantly decreases the incidence, severity and duration of CIN, which not only decreases the risk of FN	The remit from the Department of Health was to develop a guideline on the prevention and management of neutropenic sepsis in cancer patients. As such we are required to use this term. However we agree there can be confusion in terminology and so have clarified the terminology used by this guideline in section 1.1, first paragraph. We have consistently used the term "neutropenic sepsis" throughout the guideline.

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					but also reduces the incidence of resulting NS, as well as CIN-related dose delays and dose reductions. This in turn facilitates achievement of optimal relative dose intensity (RDI), yielding expected patient outcomes as observed in clinical trials. Antibiotics do not alter the incidence, severity or duration of CIN or the impact on subsequent chemotherapy RDI. Instead, prophylactic antibiotics may actually increase the severity of NS through elicitation of resistant pathogen selection that may emerge as a result of treatment. Recommendation: We consider it inappropriate to use the terms FN and NS interchangeably and would recommend that wording in the guideline be modified to more accurately reflect medical terminology used.	
Amgen UK	26.05	Full	23	6	Comments the same as comments made for Order Number 5 (for page 22, row 14)	Thank you for your comment.
Amgen UK	26.08	Full	28	24	The draft guideline approach does not align with UK clinical practice *NS risk factors, neutropenic complications, and RDI are ignored:* Although the draft guideline recognises and summarises the relevant risk factors, the guideline evaluated the efficacy of prophylactic NS strategies without consideration of NS risk (patient characteristics, tumour type or chemotherapy) or impact on RDI and longer	This text is from the needs assessment which describes current practice in the UK. It does not examine the evidence nor does it make recommendations for future practice. This table provides concise examples of risk of neutropenic sepsis from differing chemotherapy regimens. It is not intended as an exhaustive list.

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					term survival. This does not reflect current UK clinical practice, where physicians consider both NS risk as well as longer term outcomes when reviewing prophylaxis options.	
Amgen UK	26.11	Full	32	33	The draft guideline recommendations do not align with UK clinical practice The draft guideline recommends use of prophylactic quinolone (an antibiotic) in all patients (with acute leukaemias, SCT and solid tumours) regardless of tumour type, NS risk or chemotherapy treatment intent. This does not align with UK clinical practice i.e. to use G-CSFs to support patients receiving medium and high risk chemotherapy. The survey of clinical practice presented in the draft guideline shows it is established UK practice to use G-CSFs to support patients receiving medium-high risk chemotherapy in the reduction of severe neutropenia and subsequent reduction of NS; reporting that 95% of Trusts recommend primary prophylaxis with G-CSFs for at risk patients in their local clinical guidelines. UK clinical practice is also in alignment with the EORTC international guidelines (Aapro et al 2010) which define medium risk patients as those receiving chemotherapy with an FN risk of 10-20% and high risk patients as those receiving chemotherapy with an FN risk ≥ 20% or those receiving chemotherapy with an FN risk	The recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance. The GDG agreed that there was enough variation in practice in the prophylaxis of neutropenic sepsis to warrant investigating this topic, particularly with regard to cost-effectiveness.

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					of 10-20% who have additional patient risk factors (such as age, history of prior FN). These guidelines, co-authored by three UK clinicians, have been widely adopted by UK physicians (as evidenced by the survey presented in the draft guidelines) and as such are viewed as being applicable to the UK population. Given the clear established practice for use of G-CSFs within the UK, the draft guideline goes against one of its stated objectives, which is to develop recommendations where there is identifiable variation in clinical practice. Reference: Aapro MS, Bohlius J, Cameron DA, et al. Eur J Cancer. 2011;47:8-32.	
Amgen UK	26.10	Full	42	29	*Different definition of NS is used*: A new, narrower definition of NS is used within the guideline which is not aligned with UK clinical practice: The definition - *'a temperature higher than 38 ^{0}C and a neutrophil count lower than 0.5 x 10^{9}/litre'* - describes NS with severe neutropenia, whereas current clinical practice is to review/treat patients with moderate neutropenia and fever. As acknowledged in the draft guideline, setting a narrow definition of NS could result in some patients with sepsis being missed and going on to develop life threatening infection. The draft guideline estimates that there are currently two deaths a day due to NS. The NCEPOD report stated that between 16-	The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of

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					23% of patients were assessed to have had FN within 30 days of their last cycle of chemotherapy. The exact number that died due to NS is not stated within the report, but if this restricted NS definition were to be used in future, the death rate due to NS is likely to increase.	≤0.5. The evidence also showed that increased temperature was associated with an increase in infection. The lowest value for fever studied in the evidence was 38°C and the GDG decided to adopt this value in their definition for neutropenic sepsis.
Amgen UK	26.14	Full	70	11	Antibiotics and G-CSFs are different in their impact on CIN, NS, RDI and longer term survival 1. *Antibiotics and G-CSFs are different interventions with different mechanisms of action (MOAs):* It is recognised in the draft guideline that there are two separate approaches to reducing the risk of life-threatening NS; one to prevent or reduce the likelihood of infection through prophylactic use of antibiotics and another is to prevent or moderate the degree of neutropenia through prophylactic use of G-CSF and therefore reduce the risk of infection. Despite recognising the different MOAs, the draft guideline incorrectly assumes that all prophylactic strategies could indirectly improve patient's longer term survival by maintaining RDI. This is an incorrect assumption: G-CSF primary prophylaxis significantly decreases the	Both neutropenic sepsis (Shayne 2006; Lyman 2001) and neutropenia are indications for patients to receive dose-reduction chemotherapy. So by preventing neutropenic sepsis, antibiotics and other prophylactic strategies of neutropenic sepsis could indirectly improve patient's long term survival by maintaining RDI. It is acknowledged that besides preventing neutropenic sepsis, G-CSF might have another MOA to improve patient's long term survival; which is preventing neutropenia. However without data from high-quality evidence (relative risk of having dose-reduction chemotherapy for patients with and without neutropenia), this MOA of G-CSF could not be modelled. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline.

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					incidence, severity and duration of chemotherapy induced neutropenia (CIN) which, in addition to decreasing the risk of NS, also reduces neutropenia-related chemotherapy dose delays and dose reductions, thereby facilitating achievement of optimal RDI and improving patient outcomes. Antibiotics do not affect the incidence, severity or duration of neutropenia nor the impact on subsequent chemotherapy RDI, but instead target potential pathogens that may emerge as a result of the CIN, while introducing additional toxicities to patients (e.g. Achilles tendon rupture in those receiving quinolones), and the potential development and spread of multidrug resistant bacterial strains. <u>Recommendation:</u> The final guideline should recognise that G-CSFs, through decreasing the incidence, severity and duration of chemotherapy-induced neutropenia, impact RDI and longer term survival whereas antibiotics do not. *2. Antibiotics and G-CSFs are used in different patient populations and have different treatment goals* Prophylactic G-CSFs provide the potential for survival benefits beyond the duration of chemotherapy, by prevention of CIN and NS, facilitating optimal RDI and improving longer term survival (Kuderer 2007, Lyman 2008 and	The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. Reference: 1. Shayne M, Crawford J, Dale DC, et al. Predictors of reduced dose intensity in patients with early-stage breast cancer receiving adjuvant chemotherapy. Breast Cancer Res Treat. 2006 Dec;100(3):255-62. 2. Lyman G, Crawford J, Dale D, et al. Clinical Prediction Models for Febrile Neutropenia (FN) and Relative Dose Intensity (RDI) in Patients Receiving Adjuvant Breast Cancer Chemotherapy (Abstract). Proc Am Soc Clin Onclo 2001; abstr 1571. It is acknowledged that many drugs have more than one clinical indication, and could be used on different patient populations for different purposes. However the aim of our literature review and economic analysis was to find out the most clinically and cost-effective strategy for preventing neutropenic sepsis. Preventing neutropenia or maintaining chemotherapy dose were not investigated and so recommendations cannot be made on

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					Wilders 2011) and are used by physicians primarily in patients receiving chemotherapy with medium to high NS risk. Goals of treatment include reduction in neutropenia, NS, and maintenance of chemotherapy RDI. Prophylactic antibiotics are a short term measure and can only be used to prevent infection during chemotherapy, primarily in patients with neutropenia, with treatment goals to reduce rates of infection and febrile episodes. <u>Recommendation:</u> The final guideline should recognise that G-CSFs and antibiotics are used in different patient populations, with different treatment goals and different clinical outcomes. References: Kuderer N.M., Dale, D.C., Crawford J.et al. *J Clin Oncol.* 2007 Vol25 pp3158-67 Lyman, G.H., Kuderer N.M., Crawford, J. et al. *J Clin Oncol.* 26: 2008 (May 20 suppl; abstr 6552) Wildiers H. & Reiser M. *Crit Rev Onc Hem.* 77: 2011 221-240	these issues.
Amgen UK	26.46	Full	70	18	The guideline states that antibiotics cause '*diarrhoea, vomiting or allergic reaction'.* It is suggested that the guideline should also mention the rare but debilitating side effect with quinolones of tendon rupture. This is particularly increased in the elderly and those on concomitant steroids (e.g. NHL patients), i.e. the patient population to whom this guideline refers.	The list of side effects given in line 18 is meant to be illustrative rather than exhaustive. The potential side effects of using quinolones were discussed by the GDG when making their recommendations. This has been documented in the linking evidence to recommendations section for chapter 5.

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Amgen UK	26.23	Full	70	19	The draft guideline acknowledges that '*There are concerns that the use of prophylactic antibiotics may lead to antibiotic resistance in the local community'*. However, this issue was not considered a significant factor in making its prevention recommendation and no evidence evaluating or modelling the impact of prophylactic antibiotics on the wider community was considered by the draft guideline.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (in the linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only

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						be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Amgen UK	26.47	Full	70	24	The guideline states that the side effects for G-CSFs include '*diarrhoea, weakness and a flu-like syndrome'*. These are side effects very commonly related to the chemotherapy treatment itself and do not reflect the side effects listed in the SPCs for G-CSFs, namely bone pain, headache, nausea and injection site pain. The guideline also states that the side effects for G-CSFs include *'rarely more serious complications such as clotting disorders and capillary leak syndrome',* these are not side effects listed on the SPC for G-CSFs. Rare complications listed in the SPC include splenomegaly and pulmonary effects.	We have amended the guideline to include both common and rarer side effects specific to G-CSFs.
Amgen UK	26.49	Full	70	26	The guidelines state that '*Long acting formulations which are given infrequently are available but are more* expensive'. According to the NICE Methods guide cost effectiveness, not cost alone, is the appropriate economic	This text is background to why the topic was investigated. You are correct that cost-effectiveness is the most appropriate economic consideration which is why we have developed an economic model to assess this.

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					consideration.	
Amgen UK	26.19	Full	70	35	<u>Use of inappropriate scientific methodologies for evidence selection, weighting and synthesis – comparison of G-CSFs versus antibiotics</u> Efficacy of G-CSFs has been evaluated in studies treating a total of 19,622 patients with demonstrated efficacy in the reduction in incidence of NS in a wide range of tumour types, compared to antibiotic studies treating a total of 4,645 patients, in a limited range of tumour types. Effectiveness estimates used for antibiotics and G-CSFs versus no treatment are based on studies in different patient populations, in different settings, with interventions given at different times, using different outcomes: • Different patient populations, in different settings, with different NS risks Efficacy of antibiotics is evaluated in adult patients, predominantly with haematological cancers, treated in an in-patient setting. In contrast to the G-CSFs studies which are in adults and children, treated in an out-patient setting and receiving chemotherapy with medium-high NS risk • Different outcomes Antibiotic studies evaluate infection rates and	We agree that the evidence for this clinical question has been drawn from heterogeneous populations. We have attempted to reduce the population heterogeneity by excluding paediatric patients, patients receiving inpatient chemotherapy and patients whose regimen includes G-CSF from the model. In addition we have performed sub-group analysis for patients with solid tumours, non-Hodgkin lymphoma and Hodgkin lymphoma. The potential effect of this heterogeneity on the health economic model results has been assessed by sensitivity analysis on the relevant model inputs. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. The results of all one-way sensitivity analyses have been added to the guideline.

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					rates of febrile episodes and short term mortality, whilst G-CSF studies evaluate incidence, severity and duration of neutropenia, NS and long term mortality. Outcomes relating to febrile episodes and NS are used interchangeably to evaluate efficacy of G-CSFs and antibiotics. • Treatments are administered at different points in the chemotherapy cycle Antibiotics are given up to 14 days after chemotherapy (sometimes after patients have become neutropenic), whilst G-CSFs are given 24 hours after chemotherapy prior to neutropenia. Although evidence exists for both G-CSFs and antibiotics versus placebo/no treatment it is not possible to conduct a formal indirect comparison of evidence, because evidence is too heterogeneous. No conclusions about relative efficacy can be conducted because of a lack of appropriate comparable evidence in similar patient populations. A comparison of the most relevant evidence showing effectiveness for G-CSFs and antibiotics on NS would be to use estimates from Kuderer 2007 and Cullen 2005 respectively although this is still a comparison of different outcomes (NS versus febrile	The Sung et al (2007) review included the trials in the Kuderer et al (2007) meta-analysis, therefore this data has been used. The Gafter-Gvili (2005) systematic review, which was appraised as part of the evidence review for this guideline, included data from

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					episodes). Recommendation: In comparing the effectiveness of G-CSFs, the final guideline should recognise the substantial and significant differences in the quality and quantity of evidence available for G-CSFs and antibiotics, with high quantity and quality of evidence in G-CSFs compared to sparse evidence in antibiotics. Also that the efficacy estimates for G-CSFs and antibiotics are not comparable because the evidence is too heterogeneous. References: Kuderer N.M., Dale, D.C., Crawford J.et al. *J Clin Oncol*. 2007 Vol25 pp3158-67 Cullen M. D., Steven N., Billingham L., et al. *N Engl J Med*. (2005) 353; 10 988-998	Cullen (2005). The quality of the underlying evidence for all recommendations, and any associated limitations, have been documented in the evidence sections and taken into account when making decisions as a GDG (as documented in the linking evidence to recommendations section).
Amgen UK	26.16	Full	70	39	Use of inappropriate scientific methodologies for evidence selection, weighting and synthesis – G-CSFs versus no treatment Clinical efficacy estimates of G-CSF versus no treatment presented in the guideline are based on inappropriate meta-analyses, which included studies of unlicensed treatments (GM-CSFs) and in patient populations outside the label for some G-CSFs (paediatrics and patients receiving SCTs). This means that the efficacy estimates in the guideline are not generalisable to the UK population. The most relevant meta-analysis, Kuderer 2007, (which focused on the primary outcomes of interest – i.e. FN, short	The Sung et al (2007) review included the trials in the Kuderer et al (2007) meta-analysis, therefore this data has been used. Subgroup analyses were done separately for paediatric, SCT, solid tumour and lymphoma patients and for GM-CSF studies to account for the heterogeneous nature of the data.

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					term mortality and hospitalisation) was not identified or used in the draft guideline. The meta-analyses identified in the draft guideline were Sung (which included paediatric patients, patients receiving SCTs and GM-CSFs), Bohlius 2008 (which was performed only in NHL) and Cooper 2011 (which only focused on NS). Of the 148 studies identified; 29 included bone marrow or peripheral-blood stem-cell transplantation and 31 were studies of children or children and adults. These efficacy estimates are therefore not generalisable to current UK clinical practice. The most relevant meta-analysis, and not considered in the draft guideline, is Kuderer 2007 which reported a meta-analysis of randomised clinical trials (RCTs) comparing G-CSF primary prophylaxis with placebo or untreated controls, which excluded studies if; they used GM-CSFs, were in children or leukaemia or multiple myeloma patients or included bone marrow or peripheral-blood stem-cell transplantation. Seventeen studies were identified, including a total of 3,493 patients; 65% of patients had solid tumours and 35% had non-Hodgkin lymphoma (NHL); 10 studies used filgrastim (59%), 6 used lenograstim (35%) and	

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					1 used pegfilgrastim (6%). The results of the Kuderer 2007 meta-analysis showed that infection-related mortality (reported in 12 of the RCTs consisting of 2917 patients) occurred in 2.8% of controls and 1.5% of G-CSF-treated patients, resulting in a weighted overall relative risk (RR) of 0.55 (95% CI, 0.34-0.90; *P* = 0.018). Early mortality was reported in 13 of the 17 RCTs reported, consisting of 3,122 patients. Overall, early mortality occurred in 5.7% of control patients and 3.4% of G-CSF-treated patients, resulting in a weighted summary RR of 0.60 (95% CI, 0.43-0.83; *P* = 0.002). <u>Recommendation:</u> The final guideline should reference studies that are aligned with the licensed indication of all G-CSFs to generate efficacy estimates and that are focused on all of the outcomes of interest, i.e. the meta-analysis conducted by Kuderer 2007. Reference: Kuderer N.M., Dale, D.C., Crawford J.et al. *J Clin Oncol*. 2007 Vol25 pp3158-67 Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. *Cochrane Database Syst Rev*. 2008;(4): Art. No.: CD003189 Sung, L., et al. *Annals of Internal Medicine*, 2007 147, 400-411 Cooper N., Madan J., Whyte S. *BMC Cancer.* 2011, 11: 404	

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Amgen UK	26.18	Full	79	1	Use of inappropriate scientific methodologies for evidence selection, weighting and synthesis – antibiotics versus no treatment Efficacy estimates of antibiotics versus no treatment are overestimated, based on sparse, poor quality evidence with inappropriate pooling of heterogeneous studies. The draft guideline efficacy estimates showing a mortality benefit for antibiotics are based on meta-analysis from Gafter-Gvili 2005. The meta-analysis was a comparison of heterogeneous populations and underpowered studies, which used a diverse class of antibiotic agents and combinations of agents with a very different range of bacterial coverage (gram positive/negative) and non-absorbable to absorbable characteristics making some useful only for gut decontamination regimens. Most of the studies were in haematological cancer patients, within an in-patient setting, from older studies with very small patient numbers and included patients in a transplant setting. Importantly, the outcomes reported in these antibiotic studies were rates of infection or febrile episodes rather than FN as reported in G-CSF studies. None of the individual studies included in the meta-analysis reported significant findings for quinolone agents on NS or mortality, with the exception of one study	We selected only relevant quinolone studies (ciprofloxacin, levofloxacin or ofloxacin) from the Gafter-Gvili et al review, which included Cullen 2005. Methodological quality was taken into account using the GRADE methodology (see GRADE profile, table 5.1). Only studies in patients with solid tumours or lymphomas were included in the effectiveness estimates for the economics model. The effectiveness estimates for antibiotics were derived from a meta-analysis of relevant studies. Larger studies with more events, such as Cullen et al 2005, therefore had greater weight in our estimates. However, our conclusions were robust when using reduced effectiveness estimates, such as the suggested relative risk of 0.72 for NS events from Cullen et al, 2005. We agree that the evidence for this clinical question has been drawn from heterogeneous populations. We have attempted to reduce the population heterogeneity by excluding paediatric patients, patients receiving inpatient chemotherapy and patients whose regimen includes G-CSF from the model. In addition we have performed sub-group analysis for patients with solid tumours, non-Hodgkin lymphoma and Hodgkin lymphoma. The potential effect of this heterogeneity on the health economic model results has been assessed by sensitivity analysis on the

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					(which comprised only 33 and 36 patients per group respectively - Nenova 2001). The authors of Gafter-Gvili 2005 stated that '*most of the studies present were of uncertain methodological quality'*, also stating that '*a RCT powered to demonstrate a difference in mortality due to prophylaxis is probably not feasible, since it would require an inordinately large sample size*.' The Cullen 2005 study is the largest study evaluating the efficacy of quinolones as prophylaxis for preventing febrile events. It is the only solid tumour RCT of quinolone and includes a mix of tumour types, however it reports febrile episodes not NS. Therefore, the relative risk estimate of 0.720 from Cullen is the best quality available estimate for the relative risk for NS events comparing quinolones to placebo, although even here efficacy may be overestimated as it does not report NS as an endpoint. <u>Recommendation:</u> The clinical efficacy of antibiotics is over estimated, based on inappropriate pooling of heterogeneous studies. The final guideline should use results from Cullen 2005 which are the most appropriate estimate of efficacy. References: Gafter-Gvili, A., Fraser, A., Paul, M., van de	relevant model inputs. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. The results of all one-way sensitivity analyses have been added to the guideline.

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					Wetering, M., Kremer, L., & Leibovici, L. (2005). Cochrane Database of Systematic Reviews.(4):CD004386, 2005., CD004386. Cullen M. D., Steven N., Billingham L., et al. *N Engl J Med* .(2005) 353; 10 988-998	
Amgen UK	26.21	Full	79	35	Comments the same as comments made for Order Number 22 (for page 112, row 44)	Thank you for your comment.
Amgen UK	26.17	Full	89	16	Use of inappropriate scientific methodologies for evidence selection, weighting and synthesis - PEG versus filgrastim For pegylated (PEG) versus filgrastim Cooper 2011 is deemed to be low quality evidence in the draft guideline, as defined by "Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate" Within the draft guideline the GRADE profile tables of evidence describe evidence from Cooper 2011 as having *'Serious Limitations i.e. 2/5 trials had double blinding, 2/5 were open label and 3/5 trials were phase II studies'* with '*Serious imprecision i.e. Low number of events and 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm'.* Despite the evidence grading, the data in the Cooper 2011 meta-analysis comparing PEG versus daily G-CSF represents a large body of evidence taken from 5 RCTs (including key	The evidence for pegfilgrastim versus filgrastim was limited to a single outcome, febrile neutropenia. There was uncertainty about the effect of pegfilgrastim on overall mortality which the GDG considered a more important outcome than febrile neutropenia.

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					registrational studies), in the highly relevant patient populations of breast cancer and NHL and treating a total of 606 patients. It should be noted that the breadth and quality of this evidence is considerably more robust than the smaller and more heterogeneous antibiotics evidence base. Reference: Cooper N., Madan J., Whyte S. *BMC Cancer.* 2011, 11: 404	
Amgen UK	26.32	Full	97	5	<u>Cost effectiveness publications identified in the draft guideline</u> As part of the draft guideline development a review of the published literature regarding cost utility was conducted; this review found 10 studies. Eight out of the ten publications are for tumours and chemotherapies with an NS risk greater than 20%: • Borget 2009, Danova 2009, Liu 2009, Ramsey 2008, Lyman 2009b, and Whyte 2011 all consider early stage breast cancer receiving chemotherapy ≥ 20% risk of NS • Lathia 2010 and Lyman 2009 consider NHL patients being treated with CHOP 21 which has a risk greater than 20% of NS • The two papers by Timmer Bonte 2006, 2008 look at G-CSF in combination	

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					with antibiotics for patients with SCLC. The therapeutic intent for this group of patients is different to that of the medium – high risk breast and NHL cancer patients. The draft guideline states that it was surprised there were no studies looking at the cost utility of antibiotics. The draft guideline concludes that this is because the analysis has not been conducted and not because it would have been inappropriate to include antibiotics in this group of 'high risk' patients. The draft guideline states that they had to create a de novo model as none of the previous studies answered this question directly. It is true that antibiotics were not considered in the above publications however it does not mean that the methodology of these papers is not valid. In particular, two papers, Liu 2009 and Whyte 2011, were conducted from a UK perspective and have been undertaken in accordance with the NICE methods guide. It should also be noted that these two publications model G-CSF over an appropriately long time horizon and do consider RDI. As such it is disappointing that the methodology published by Liu 2009 and Whyte 2011 were not adopted in the draft guideline and adapted to include an antibiotic arm. This is particularly relevant of the Whyte 2011 model as it was developed by authors affiliated to an esteemed health economics department at a leading UK university. In fact two of the authors have acted	The GDG agreed that it would be appropriate to use antibiotics for target patients (as described in section A2.1) who are at high-risk of neutropenic sepsis. Both Liu 2009 and Whyte 2011 were designed to model multiple clinical indications of G-CSF: • Reducing incidence of FN. • Reducing short-term mortality (by preventing FN). • Reducing long-term mortality (by maintaining chemotherapy dose). However for this guideline, the GDG were only interested in G-CSF's efficacy in preventing neutropenic sepsis. Neither paper included all interventions considered relevant for the topic in the guideline (e.g. quinolones). Liu 2009 looked at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counted the cost of G(M)-CSF without counting the cost of chemotherapy. No costs were modelled beyond 1 year; whilst the

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					as members of technology appraisal committees at NICE and are very familiar with conducting cost utility analysis aligned with the NICE reference case. The draft guideline compares the results from its model to those found in the systematic review of cost utility studies considering G-CSF versus nothing/placebo (Lathia 2010 and Whyte 2011). The draft guideline states that the Lathia 2010 paper compares well to the de novo model results; however this comparison is not valid as the Lathia 2010 cohort were Canadian and the patients who experienced NS received secondary G-CSF prophylaxis for their remaining chemotherapy cycles.	effectiveness was modelled for lifetime. This study also had conflicts of interest. Whyte et al 2011 modelled three functions of G-CSF: • Reducing incidence of febrile neutropenia • Reducing short-term mortality (by preventing febrile neutropenia) • Reducing long-term mortality (by maintaining chemotherapy dose). Only the efficacy data for the first function of G-CSF (reducing incidence of febrile neutropenia) was obtained from a systematic review. Efficacy data for the other two functions of G-CSF was estimated based on unproven assumptions and indirect evidence. <u>Assumption 1</u> Whyte et al (2011) assumed there is a linear positive correlation between incidence of febrile neutropenia and short-term mortality (although this assumption was not reported in the full-text). For example if the probability of dying from an febrile neutropenia event is 0.036 (Kuderer et al. 2006) and G-CSF has prevented 100 episodes of febrile neutropenia; then the number of lives saved by G-CSF is calculated as 100*0.036=3.6. The GDG strongly disagree with this assumption, as a recent systematic review (Sung et al 2007) shows that although G-CSF is effective in reducing incidence of febrile

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						neutropenia, it has little or no impact on short-term mortality. This implies that there is no direct correlation between incidence of febrile neutropenia and short-term mortality. Therefore the GDG felt that Whyte et al 2011 may significantly overestimate the efficacy of G-CSF in reducing patient short-term mortality. <u>Assumption 2</u> Whyte et al (2011) assumed that febrile neutropenia could be used as a surrogate for patients impaired long-term survival (febrile neutropenia is a risk factor for patients receiving low relative dose intensity chemotherapy; and low relative dose intensity chemotherapy is a risk factor of long-term mortality). Therefore by preventing febrile neutropenia episodes, the authors stated that G-CSF could facilitate chemotherapy administration, and indirectly improve patients long-term survival. However the GDG were very unsure about the validity of this indirect logic and its derived conclusion, especially after considering the results of more direct evidence: Correlation between use of G-CSF and RDI (relative dose intensity) for breast cancer patients • Papaldo et al (2005) shows that the addition of varying intensity schedules of open-label G-CSF to high-dose epirubicin/cyclophosphamide chemotherapy in patients with stage I and II breast cancer had

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						no significant impact on the delivered dose-intensity compared with the non-G-CSF arms. • Results from the Impact of Neutropenia in Chemotherapy European study group (INC-EU) prospective observational study shows that the impact of primary prophylaxis with G-CSF on RDI is not significant (Pettengell 2008). Correlation between neutropenia and patient long-term survival • A recent meta-analysis (Shitara, et al., 2011) shows that neutropenia experienced during chemotherapy is actually associated with improved survival in patients with advanced cancer or haematological malignancies undergoing chemotherapy. This implies that experiencing side effects of chemotherapy might not be associated with impaired long term survival. Consequently the GDG decided not to adopt the methodology used by Whyte et al (2011).
					The draft guideline also compares its results to those of Whyte 2011 but does not present the full findings of the Whyte 2011 study. The draft guideline implies that this paper only shows that secondary prophylaxis with PEG G-CSF is cost effective at a willingness to pay threshold of £20,000. The draft guideline has missed the critical point of the paper which states that the most cost effective strategy for preventing NS is dependent on the baseline NS risk, patient age,	Due to limited space, it was not possible for us to discuss the detailed results (base case analysis and sensitivity analysis results) of each study included in the systematic review of published cost utility analyses. However, a more detailed summary of each included study can be found in Table 5.10. In Table 5.10 it is stated that the results of Whyte et al (2011) are highly sensitive to baseline febrile neutropenia risk.

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					and drug acquisition cost. In fact the base case results at a willingness to pay threshold of £20K are as follows; • For a patient with a baseline NS risk greater than 38% primary prophylaxis with PEG G-CSF is the only cost effective strategy • For patients with a baseline FN risk of between 11% and 37% PEG G-CSF secondary prophylaxis is the only cost effective strategy • Below a baseline risk of 11% no treatment is the most cost effective strategy The Whyte 2011 paper also shows that the results are dependent on drug acquisition cost and that if the G-CSF acquisition cost were reduced by 50% then primary prophylaxis with PEG G-CSF is the most cost effective strategy at a baseline NS risk of 22% or more and secondary prophylaxis with PEG G-CSF is the most cost effective strategy at a baseline NS risk of between 5-21%. The cost-effectiveness of PEG G-CSF would be improved if the HRG cost of 'FN with malignancy' had been available for inclusion in the model at the time of the analysis.	In our economic model a range of different baseline risks were tested in one-way sensitivity analysis (5-100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested, G-CSF is still not cost effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. The GDG agreed it would be more appropriate to use costs based on the clinical pathway represented by the guideline recommendations, rather than the HRG cost you cite. This was because the economic analysis only considered adult patients (solid tumour, NHL and HL) who are receiving outpatient chemotherapy. In contrast to those patients who are receiving inpatient chemotherapy, our target population rarely use ICU (ITU) or antifungal drugs (both of which are very expensive). This means the treatment cost for our target population (outpatient) will be much lower than it is for the inpatient group. Consequently the GDG agreed it would be inappropriate to use the HRG cost (which is also likely to cover all cancer patients).

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					Lastly the draft guideline critiques the Whyte 2011 model for two reasons. Firstly, the draft guideline states that *"the analyses considered the combined effectiveness of chemotherapy and G(M)-CSF, but did not count the cost of chemotherapy properly*". In this patient population G-CSF is only given to support chemotherapy and the Whyte 2011 analysis did account for the cost of chemotherapy, hence this criticism of the Whyte 2011 paper is erroneous. Secondly, the draft guideline notes that Whyte 2011 analysis is likely to overestimate the clinical effectiveness of chemotherapy plus G-CSF by using longer term survival rates reported by Cancer Research UK. This limitation of the analysis was identified by the authors and could easily have been changed by the health economist if the methodology had been adopted. In conclusion, it is surprising that instead of adopting a peer reviewed methodology,	One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.50 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). We have amended the text to clarify the limitations of the Whyte 2011 analysis. References: Papaldo P, Lopez M, Marolla P, et al. Impact of five prophylactic filgrastim schedules on hematologic toxicity in early breast cancer patients treated with epirubicin and cyclophosphamide. J Clin Oncol 2005;23:6908–18. 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.

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					conducted from a UK perspective, constructed according to NICE reference case, and published by academics at a leading UK health economic institute, that the draft guideline chose to develop a de novo model which does not conform to the NICE reference case. If the draft guideline had adopted the approach of Whyte 2011 but updated it with an antibiotic arm then the ICERs of PEG G-CSF versus either antibiotics and no treatment would have been significantly different to those published in the draft guideline and would have resulted in different conclusions regarding the cost-effectiveness of PEG G-CSF. References: Borget I, Di Palma M. *EJHP Practise*. 2009, 15, 58-61 Danova Tumori 2009 Vol95 pp219-226 Liu Z., Doan Q.V., Malin J., Leonard, R. *Appl Health Econ Health Policy* 2009 Vol7 pp193-205 Ramsey S et al *Value in Health 2008* 12(2):217-25# Lyman et al. *Current Med Research & Opinions* 2009 Vol25 pp401-411 Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. *Value in Health* 2011;14(4):465-474. Lathia N, *Cancer*, 2010, 116, 3, 742-8 Timmer-Bonte, J. N. H., et al. *Journal of Clinical Oncology* 24.19 31 (2006): 2991-97. 32-33 Timmer-Bonte, J. N. H., *et al.Journal of Clinical Oncology* 26.2 (2008): 290-96.	Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
Amgen UK	26.25	Full	106	8	A de novo model was created to inform the prevention recommendations of the draft	

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					guideline The de novo model does not fully assess the costs and benefits of the different prophylaxis strategies considered in the draft guideline for the following reasons; • The time horizon is too short to fully account for all the costs and benefits of the different prophylaxis strategies. The time horizon should be the lifetime of the patient, as specified in the NICE reference case.	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations.

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						Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
					• The costs associated with NS are significantly underestimated and the cost of NS quoted in the NHS reference costs has been ignored. The cost of NS in the draft guideline model is £766.30 for patients not receiving a G-CSF and £712.49 for patients that do receive a G-CSF. These figures are very low compared to the NHS reference cost of 'FN associated with malignancy' which is £5,959 (NHS reference costs 2009-2010).	The GDG agreed it would be more appropriate to use costs based on the clinical pathway represented by the guideline recommendations, rather than the HRG cost you cite. This was because the economic analysis only considered adult patients (solid tumour, NHL and HL) who are receiving outpatient chemotherapy. In contrast to those patients who are receiving inpatient chemotherapy, our target population rarely use ICU (ITU) or antifungal drugs (both of which are very expensive). This means the treatment cost for our target population (outpatient) will be much lower than it is for the inpatient group. Consequently the GDG agreed it would be inappropriate to use the HRG cost (which is also likely to cover all cancer patients). In order to test the robustness of the health economic model, the following scenarios about resource use were explored in sensitivity analysis: • The probability of using an ambulance for patients with neutropenic sepsis (0-100%)

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						• The probability of patients with neutropenic sepsis who are at high risk of serious adverse events (Solid tumour: 5-20%; Non-Hodgkin lymphoma: 10-35%; Hodgkin lymphoma: 5-15%) • Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events (1-6 days) • Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events (6-14 days) • Cost per hospital bed day (£100 - £1000). The results of one-way sensitivity analysis showed that the model results were robust to all the above scenarios.
					• The efficacy of antibiotics for solid tumours is derived from evidence that is weak and inappropriately analysed, consequently the de novo model uses a significant over estimate of their effectiveness	One way sensitivity analysis of the relative risk of neutropenic sepsis with prophylaxis showed quinolones were cost effective up to a relative risk of 0.79.
					• Chemotherapy RDI and the associated survival benefits are not included	In order to investigate this effect we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be

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						needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline Although our systematic review of cost-effectiveness studies did identify several studies trying to model the impact of using G-CSF on patients long-term survival (by maintaining chemotherapy dose) (see cost effectiveness section of chapter 5); none of these studies used any direct clinical data. Instead, these studies were trying to build an indirect relationship between use of G-CSF and long-term survival. They stated that G-CSF could prevent neutropenic sepsis; neutropenic sepsis is a risk factor of receiving dose-reduction chemotherapy and dose-reduction chemotherapy is a risk factor for patient long-term survival. Then based on this hypothesis, the authors claimed that G-CSF

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						could improve patients long-term survival. Furthermore, a recent meta-analysis (Shitara et al., 2011) shows that neutropenia experienced during chemotherapy is actually associated with improved survival in patients with advanced cancer or haematological malignancies undergoing chemotherapy. This implies that experiencing side effects of chemotherapy might not be associated with impaired long term survival. Therefore the GDG were very unsure about the validity of the indirect logic used in these published cost-effectiveness studies and the derived conclusion and did not consider it appropriate to use the methodology from the existing studies to model the impact of using G-CSF on patients long-term survival for this guideline.
					• The long term costs and health outcomes associated with antibiotic resistance to cancer patients, patients in the hospital, and the general public have not been considered.	The best available evidence identified to address the issue of antibiotic resistance caused by use of quinolones was derived from two systematic reviews: one was a review conducted for this guideline, (see clinical evidence section of chapter 5); and the other was a Cochrane review undertaken by Gafter-Gvili, et al., (2005). The conclusions of these two reviews were very similar. After use of quinolones, although there was an increase in colonisation with bacteria resistant to quinolones, there was no statistically significant increase in the number of infections caused by pathogens resistant to quinolones. The GDG were aware of the potential limitations of these two reviews but could not

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						find any better evidence to answer the clinical question. In addition, to model the effect of antibiotic resistance, data would be needed on how likely it is for a patient to get another infection in future, which was caused by the resistant pathogen. The GDG considered that it would be difficult to obtain such data and that it was unlikely that antibiotic resistance would occur during the time-horizon of the economic model (one course of chemotherapy). They therefore agreed not to model antibiotic resistance. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5).

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						The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
					• An incorrect dose of antibiotics has been used	Thank you, we have corrected this. One-way sensitivity analysis has been conducted on the effect of changing dose of G-CSF. The results show that our conclusion

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					• An incorrect dose of daily G-CSF has been used • The draft guideline dismisses existing UK peer reviewed cost utility studies which have been developed in line with the NICE reference case <u>Recommendation:</u> We strongly request that the quality of this analysis is reviewed, particularly as was the basis for the recommendation on prevention that is in opposition to current UK standard clinical practice, international guideline recommendations and peer-reviewed published cost-utility analyses. Reference: NHS reference costs 2009-2010: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459	is robust to changes in G-CSF dose. The existing UK studies have been included in the evidence review. However, none of the studies found directly addressed our question (the adaptability problems and limitations of the UK studies can be found in the cost effectiveness section of chapter 5). As a result, de novo models have been built to inform the recommendations.
Amgen UK	26.36	Full	106	41	<u>Antibiotic resistance cost and consequences are explicitly excluded from the model</u> The evidence reporting antibiotic resistance in chemotherapy patients receiving quinolones is weak. In the systematic review by Gafter Gvili 2005 the authors point out that: • Length of follow-up too short to detect the emergence of resistant bacteria and resistance data were not routinely collected in these studies.	The best available evidence identified to address the issue of antibiotic resistance caused by use of quinolones was derived from two systematic reviews : one was a review conducted for this guideline, (see clinical evidence section of chapter 5); and the other was a Cochrane review undertaken by Gafter-Gvili, et al., (2005),. The conclusions of these two reviews were very similar. After use of quinolones, although there is an increase in colonisation with bacteria resistant to quinolones, there was no statistically

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					• To actually assess the risk for resistance development, studies must perform surveillance cultures prior to and following antibiotic treatment. • None of these studies assessed resistance development. This systematic review should therefore not be used in the draft guideline as definitive evidence that prophylactic use of antibiotics in chemotherapy patients is not associated with antibiotic resistance. Furthermore, this study does not provide strong enough evidence for costs and health outcomes associated with antibiotic to be removed from the analysis. In addition, the draft guideline does not consider the potential impact of antibiotic resistance on the wider community as well as on cancer patients. Using prophylactic treatment in cancer patients is likely to affect resistance in other patients treated in the chemotherapy suite, hospital trust, and general public. There is no evidence presented in the guideline which assesses how the use of prophylactic antibiotics in large numbers of cancer patients could impact the development of antibiotic resistance in the chemotherapy suite, the wider hospital and the general public. <u>Recommendation:</u> The final guideline should acknowledge that by not including the longer	significant increase in the number of infections caused by pathogens resistant to quinolones. The GDG were aware of the potential limitations of these two reviews but could not find any better evidence to answer the clinical question. In addition, to model the effect of antibiotic resistance, data would be needed on how likely it is for a patient to get another infection in future, which was caused by the resistant pathogen. The GDG considered that it would be difficult to obtain such data and that it was unlikely that antibiotic resistance would occur during the time-horizon of the economic model (one course of chemotherapy). They therefore agreed not to model antibiotic resistance. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($<0.5 \times 10^9$/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall

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					term costs and consequences of antibiotics they are biasing the cost-utility results in favour of quinolones.	mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Amgen UK	26.38	Full	108	30	<u>Comments on the cost-utility results</u> The very high ICERs which are clearly greater than a willing to pay threshold range of £20,000 to £30,000 per QALY gained are a direct result	

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					of the inappropriate modelling approach outlined by the draft guideline. The ICERs between PEG G-CSF and antibiotics for solid tumours and the ICER between PEG G-CSF and no treatment for NHL and HD patients would significantly change if; • The time horizon in the model was increased to the life time of the patient	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations.

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						Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
					• The cost of NS from the HRG code to be used for all patients with NS, that is do not include the estimate of NS patients that can be treated as an out-patient with oral antibiotics until this becomes clinical practice following the recommendations in this draft guideline	The GDG agreed it would be more appropriate to use costs based on the clinical pathway represented by the guideline recommendations, rather than the HRG cost you cite. This was because the economic analysis only considered adult patients (solid tumour, NHL and HL) who are receiving outpatient chemotherapy. In contrast to those patients who are receiving inpatient chemotherapy, our target population rarely use ICU (ITU) or antifungal drugs (both of which are very expensive). This means the treatment cost for our target population (outpatient) will be much lower than it is for the inpatient group. Consequently the GDG agreed it would be inappropriate to use the HRG cost (which is also likely to cover all cancer patients).
					• Acknowledgement that the Cullen 2005 paper is the most appropriate source for antibiotic efficacy data or remove antibiotic from solid tumours model	Cullen 2005 was included in the review by Gafter Gvilli

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					• Adapt the model so it accommodates risk factor for NS so that treatment strategies for high and medium risk patients can be separately assessed and not assumed all the same • Use the correct dose for antibiotic which link to the efficacy inputs • Use the correct dose for G-CSF which are linked to the efficacy inputs and licensed indication • Inclusion of RDI and its implications for long term outcomes <u>Recommendation:</u> We strongly request that the quality of this analysis is reviewed, particularly as was the basis for the recommendation on prevention that is in opposition to current UK standard clinical practice, international guideline recommendations and peer-reviewed published cost-utility analyses.	We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant neutropenia ($\leq 0.5 \times 10^9$/litre) is an anticipated consequence of chemotherapy. Thank you, we have corrected this. One-way sensitivity analysis has been conducted on the effect of changing dose of G-CSF. The results show that our conclusion is robust to changes in G-CSF dose. In order to investigate this effect we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time.

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						The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline
Amgen UK	26.09	Full	112	6	*Chemotherapy dose-intensity definitions are confused:* The draft guideline uses definitions of dose-intense and dose-dense chemotherapies that are unclear and not aligned with clinical practice terminology, resulting in potential confusion over which patients the guidelines apply to.	We have not used the phrase dose-dense within the guideline. We have used the term dose intensity which is felt widely used in clinical practice. However, we have clarified the term dose intensity in the glossary of the guideline.
Amgen UK	26.02	Full	112	41	Comments the same as comments made for Order Number 2 (for page 114, row 18)	Thank you for your comment.
Amgen UK	26.20	Full	112	44	<u>Antibiotic resistance is an important public health issue which has not been adequately addressed in the draft guideline</u> The draft guideline states that *'prophylactic antibiotics contribute to antibiotic resistance but concluded that in patients receiving anti-cancer treatment the evidence suggests the benefits outweigh the risk'.* The recommendation to give antibiotics to all	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was

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					cancer patients, would significantly increase the use of antibiotics in this patient group versus current UK standard clinical practice, whilst at the same time increasing the incidence, duration and severity of neutropenia (since the draft guideline seeks to replace use of G-CSF with antibiotics). There are serious concerns about the use of prophylactic antibiotics in an immune compromised setting and; i) the resulting limitations around the ability to identify the infecting pathogen in septic events, ii) the potential masking of early septic symptoms delaying appropriate treatment, iii) accompanying toxicity in this fragile patient population, iv) potential non-compliance and v) development of microbial resistance, as recognised by other international NS guidelines. The documented public health threat of quinolone resistance should not be ignored by the guideline. Studies have consistently shown the dangers of indiscriminate exposure of immune-suppressed cancer patients, who have no active infection, to quinolones (Kern 1994, Oppenheim 1989, Bucaneve 2005, Kern 2005, Carralata 1995, Crucian 2003, Tacconelli 2008, Muto 2003, Wade 1994, Molbak 1999, Strahilevitz 2009). A recent review focused on the relationship between fluoroquinolone use and the rising	considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.

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					prevalence in neutropenic cancer patients of multidrug resistant pathogens (Bow 2011): This concluded that widespread use of antibacterial agents of one class can encourage multiclass drug resistance, which reduces prophylaxis and treatment efficacy in neutropenic cancer patients. There is also longitudinal data linking indiscriminate quinolone use with resistant E. coli and Staphylococcus species, which jeopardize the effectiveness in treating patients who have *"documented infections due to the emergence of multidrug resistant organisms".* In addition, the most significant treatment-related risk for the development of MRSA is quinolone exposure (Tacconelli et al 2008). Finally, administration of fluoroquinolones was identified as the most important risk factor during an epidemic caused by a hypervirulent strain of C. difficile (CDAD, Quebec). Recent Department of Health (DH) advice ("Start smart – then focus" Nov 11) was published by the DH advisory committee on antimicrobial resistance and healthcare associated infection on indiscriminate use of antibiotics, and stated *'Do not start antibiotics in the absence of clinical evidence of bacterial infection'*. The National Centre for Policy Analysis (NCPA) produced a report on unnecessary deaths in the UK and concluded that *"Widespread use, prolonged use, or both of*	

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					decolonization therapies should be avoided, because this has been associated with the evolution and spread of antibiotic resistant strains,. undermining the effectiveness of the control effort." There are serious concerns about the use of prophylactic antibiotics used in an immune compromised setting and the development of microbial resistance, as recognised by other international NS guidelines. The recommendation to give antibiotics to all cancer patients, regardless of NS risk, goes against the DH advice on use of antibiotics and the use of prophylactic antibiotics in an immune compromised group would not be supported by clinical microbiologists. <u>Recommendation:</u> The final guideline should recognise that there are serious concerns about the widespread and indiscriminate use of prophylactic antibiotics in an immune compromised setting and the development of antibiotic resistance. Evidence presented in the draft guideline on the impact of antibiotic resistance in patients receiving antibiotics for prevention of NS was inadequate: In studies reporting outcomes of bacterial resistance, the length of follow up was too short to detect the emergence of resistant bacteria. In addition, none of the studies	

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					adequately assessed resistance development by conducting surveillance cultures both prior to and following antibiotic treatment. In addition the draft guideline ignores the conclusion from Gafter Gvili 2005 which stated *"When compared to placebo patients given quinolones and TMP/SMZ were found to be at increased risk of harbouring bacilli resistant to the specific drug than patients receiving placebo (RR=1.47)*". Recommendation: The final guideline should recognise that there is insufficient clinical evidence to quantify the degree of risk for antibiotic resistance in the chemotherapy population and to the public at large. References: Gafter-Gvili, Cochrane Database of Systematic Reviews.(4):CD004386, 2005., CD00438 Kern et al. *Anrimicrob Chemother*. 1994 38 681-687 Oppenheim et al. *BMJ* 1989 vol 299 294-297 Bucaneve et al. *NEJM* 2005 353 10 Kern et al. *Eur J Clin Micro.* 2005, 24, 111-118 Carratala et al. *Clin Infect Dis.* 1995 vol 20 557-560 Cruciani et al. *JCO*. 2003 4127-4137 Tacconelli et al. J *Antimicrob Chemother*. 2008 Jan;61(1):26-38 Muto CA, et al Infect Control Hosp Epidemiol. 2003;24(5):362-86. Review. Wade et al Clinical approach to infection in the compromised host 1994 Plenum publishing 3rd ed	

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					Strahilevitz et al. *Clin Microbiol Rev.* 2009 Oct;22(4):664-89 Molbak et al *N Engl J Med.* 1999 Nov 4;341(19):1420-5. Bow et al. *Curr Opin Infect Dis*. 2011 Dec;24(6):545-53	
Amgen UK	26.24	Full	113	2	The guideline states '*that changing anti-microbial resistance patterns meant the cotrimoxazole trials may no longer be applicable'.* The draft guideline therefore recognises that antibiotic resistance is a concern in the use of cotrimoxazole, although it does not currently consider it to be an issue in the use of quninolones. However, given the draft prevention recommendation this is likely to change over time.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendation section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All

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						antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Amgen UK	26.13	Full	113	10	<u>International clinical guidelines</u> The draft guideline appears to dismiss other international guidelines as not relevant, noting that guidelines had been developed in non UK healthcare settings. However, the EORTC guidelines (Aapro 2010) were co-authored by three UK clinicians and have subsequently been adopted by UK physicians and as such are viewed as being applicable to the UK population Reference: Aapro MS, Bohlius J, Cameron DA, et al. *Eur J Cancer.* 2011;47:8-32.	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
Amgen UK	26.39	Full	113	30	Comments the same as comments made for	Thank you for your comments.

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					Order Number 40 (for page 108, row 30)	
Amgen UK	26.22	Full	114	6	Comments the same as comments made for Order Number 22 (for page 112, row 44)	Thank you for your comments.
Amgen UK	26.01	Full	114	18	<u>NS complications, Chemotherapy Relative Dose Intensity (RDI) and implication for longer term outcomes</u> RDI is the ratio of standard chemotherapy regimen dose to the actual delivered dose over a specific time period. RDI is commonly calculated over all chemotherapy cycles delivered during a course of chemotherapy as a percentage (e.g. RDI of 85% would indicate that a patient received 85% of a standard chemotherapy regimen over the standard period of time). This concept is paramount, since standard chemotherapy dosing is determined through the results of adequately designed and executed clinical trials that reliably estimate a cancer patient population's response and/or survival rate, as well as risk of toxicity. In clinical practice the dose intensity of chemotherapy can be diminished by either the reduction in dose of one or more regimen agents or through time delay of administering the agents (in subsequent cycles of chemotherapy). Cancer patients receiving treatment should be given the initial opportunity to benefit from the	The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not

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					effects of recognised standard chemotherapy regimens that reduce tumour burden, lengthen the time of progression-free survival or increase overall survival. The administration of lesser, unproven doses or delayed dosing over longer unproven time periods should only be employed in the palliative setting when, and if, the treating clinician determines the risk of full-dosing out-weighs the potential benefits in a given patient (i.e. unpreventable toxicity). Significantly reduced RDI does not afford any patient their best chance to achieve a clinical benefit from their treatment and potentially introduces only the accompanying toxicity. The exclusion of RDI and its implications for longer term outcomes from the scope has a significant impact on the remit of the guidelines: 1. *Excludes patients for whom longer term survival is the primary consideration and who would most benefit from receiving full-dose chemotherapy (medium-high NS risk).* RDI and longer term survival must be considered in order to adequately assess the effectiveness of NS prophylaxis strategies in patients for whom survival is a consideration i.e. patients who would benefit from receiving full-dose chemotherapy (medium-high NS risk) (Pettengell 2008, Bonadonna 2005, Fauci 2011, Bosly 2008, Chang 2000). The need to consider	been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices.

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					the impact on RDI and longer term survival was flagged by seven commentators during the scoping process. This was acknowledged by the Institute as a very important issue but was excluded from the final scope as it was *"felt that it was not possible to investigate such a vast and complicated area"* (http://www.nice.org.uk/nicemedia/live/12349/50684/50684.pdf). This issue was also acknowledged within the clinical guidelines (full version page 114 line 18). <u>Recommendation:</u> Anti-cancer treatment and potential for increased survival are the foundation of oncology care. Therefore, the final guideline should recognise that RDI and longer term survival are needed to assess the effectiveness of NS prophylaxis strategies in patients who would benefit from receiving full-dose chemotherapy (medium-high NS risk), and as this is excluded from the scope, then this patient group should be explicitly excluded from the guideline recommendations on prevention. 2. *Excludes consideration of the longer term benefits of G-CSFs from the assessment of effectiveness of prophylaxis NS strategies.* G-CSFs significantly decrease the incidence, severity and duration of chemotherapy induced neutropenia (CIN) which; i) reduces the risk of NS and its associated morbidity and mortality and ii) reduces neutropenia-related	

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					chemotherapy dose delays and dose reductions, which facilitates the achievement of optimal chemotherapy RDI and improves patient outcomes (Kuderer 2007, Lyman 2008, Bohlius 2008, Leonard 2009). Antibiotics do not affect the incidence, severity or duration of neutropenia or its impact on subsequent chemotherapy RDI, but instead target potential pathogens that may emerge as a result of the CIN and as such are only a short term measure to reduce febrile events. The draft guideline incorrectly assumes that all prophylactic strategies can indirectly improve patient's longer term survival by maintaining RDI (full version page 203 line 3). <u>Recommendation:</u> The final guideline should recognise that G-CSFs facilitate optimal chemotherapy RDI and improve patient outcomes, whilst antibiotics do not, and that the short term time frame imposed by the scope does not allow these longer term benefits to be captured. References: Kuderer N.M., Dale, D.C., Crawford J.et al. *J Clin Oncol.* 2007 Vol25 pp3158-67 Lyman, G.H., Kuderer N.M., Crawford, J. et al. *J Clin Oncol.* 26: 2008 (May 20 suppl; abstr 6552) Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. *Cochrane Database Syst Rev*. 2008;(4): Art. No.: CD003189.	

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					Pettengell R, et al. *Ann Hematol.* 2008; 87: 429-430 Bonadonna, *BMJ.* 2005, 29, 330, 217 Fauci J., Whitowrth J.N., Schneider et al. *Gynecologic Oncology.* 122 (2011) 532–535 Leonard R et al. *Eur J Cancer.* Suppl 2009; 7(2): 270. Abstract 5033	
Amgen UK	26.44	Full	169	36	Factual Inaccuracies The guideline states that *'Depot formulations (for example pegylated G-CSF) are available',* however pegylated G-CSF is not a depot formulation.	Thank you for your comment, we have amended the sentence for accuracy.
Amgen UK	26.37	Full	170	42	Comments the same as comments made for Order Number 38 (for page 106, row 41)	Thank you for your comment.
Amgen UK	26.26	Full	172	20	The time horizon for the models was inappropriately short The time horizon considered in the de novo model was; 63 days for solid tumour patients, 126 days for NHL patients, and 196 days for HD patients. The use of such a short time horizon conflicts with the NICE methods guide, which states that '*the time horizon should be sufficiently long to reflect all important differences between costs and outcomes between the technologies being compared'* (Section 5.2.13 of the NICE guide to methods for technology appraisal). As a consequence of the short time horizon, the	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to

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					model accounts for all costs incurred during the chemotherapy cycle, but not all QALY losses due to death, which should be appropriately accounted over the lifetime of the patient. If the time horizon in the de novo model was lengthened to the lifetime of the patient, as is standard practice for cost utility analysis, then there would be a significant reduction in the ICER for PEG G-CSF versus no treatment, daily G-CSF or quinolones. Furthermore, if the chemotherapy RDI were included in the model then there would be further QALY gains due to longer term survival gains, which would further reduce the ICER of PEG versus no treatment, daily G-CSF or quinolones. Finally, the short term nature of the model means that costs and health outcomes associated with the development of antibiotic resistance (in cancer patients, the chemotherapy suite, the hospital trust, or the wider general population) are not included. The exclusion of these costs and health outcomes biases the model in favour of the quinolones and essentially ignores the primary reason cancer treatment is given in the first place. <u>Recommendation:</u> The time horizon of the model should be lengthened to be the lifetime of the patient Reference:	rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations. Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.

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					NICE guide to methods for technology appraisal http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459	
Amgen UK	26.28	Full	174	6	<u>The relative risk of NS for antibiotics is overstated in Table A4.</u> The relative risk estimate for NS for quinolones versus no prophylaxis provided for solid tumour patients in the guidelines (0.437) is overstated; it uses neutropenic events as a proxy for NS and involves a meta-analysis with inappropriate pooling of heterogeneous studies. In the absence of any data reporting the efficacy of antibiotics in prevention of NS, the guideline uses neutropenic events (febrile episodes) as a proxy to calculate the relative risk for antibiotics. The estimate appears to be derived from a meta-analysis using data from only 4 studies (from Table A4.1: Hartlapp 1987, RR = 0.188, n = 42; Schroeder 1992, n = 75, RR = 0.159; Carlson 1997, RR = 0.800, n = 90; and Cullen 2005, RR = 0.720, n = 1565). However there is high heterogeneity between Carlson 1997 and Cullen 2005 versus Hartlapp 1987 and Schroeder 1992 (I^2 = 0.701), which indicates that that there are potentially large differences in data collection, study management, and definitions across studies, differences in efficacy across patient populations, or important	One way sensitivity analysis of the relative risk of neutropenic sepsis with prophylaxis showed quinolones were cost effective up to a relative risk of 0.79 (greater than the suggested value of 0.72 from Cullen 2005). The relative risk of 0.72 from Cullen et al (2005) refers to probable infections (not just febrile episodes but ones with other clinical signs). In fact the relative risk is lower for patients with solid tumours in this study (if patients with non-Hodgkin lymphomas are excluded, see Cullen et al, 2007). The effectiveness estimates for antibiotics were derived from a meta-analysis of relevant studies. Larger studies with more events, such as Cullen et al 2005, therefore had greater weight in our estimates. However, our conclusions were robust when using reduced effectiveness estimates, such as the suggested relative risk of 0.72 for NS events from Cullen et al, 2005. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is

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					changes in cancer treatment over time. Therefore the meta-analysis appears to be based on inappropriate pooling of heterogeneous studies. However, even using these four studies, it is not clear from the draft guideline exactly how the estimate of 0.437 was derived. Of the studies included, the Cullen 2005 study comprises the largest source of relevant information about the efficacy of quinolones as prophylaxis for neutropenic events; it includes a mix of tumour types, unlike Hartlapp 1987 (testicular cancer only) and Carlson 1997 (ovarian cancer only) and contains more recently collected data than the other studies. It is also the only solid tumour, quinolone-only study identified in Table A4.1, with both clear adequate concealment of treatment allocation and double blinding. Therefore, the relative risk estimate of 0.72 from Cullen 2005 is the most robust available estimate for the relative risk for neutropenic events comparing quinolones to placebo. Despite this, the applicability of this efficacy estimate to solid tumour patients in the model can be challenged for the following reasons: • Cullen 2005 measured febrile episodes and not NS. • The baseline risk of NS for breast	still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. The results of all one-way sensitivity analyses have been added to the guideline.

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					cancer patients was 11.5% as such it is not appropriate to infer that the same relative risk applies to chemotherapies with a higher NS risk profile. • Cullen 2005 states that patients who 'planned to have G-CSF' were excluded from the study however it is unclear whether in practice any patients did have G-CSF. The inclusion of G-CSF would obviously alter the results In conclusion, there is no evidence reporting the efficacy of antibiotics to reduce the risk of NS in patients who have solid tumours. There is only one robust study (Cullen 2005), reporting RR of febrile episodes, this reports the relative risk is 0.72, which is almost half the efficacy of the 0.437 used in the de novo model. <u>Recommendation:</u> The quinolone relative risk of NS should be changed to 0.72 or antibiotics should be removed as a comparator in the solid tumour model References: Carlson JW, Fowler JM, Mitchell SK, Carson LF, Mayer AR, Copelands LJ. *Gynecologic Oncology*. 1997;65:325–9. Cullen M, Steven N, Billingham L, Gaunt C, Hastings M, Simmonds P, et al. *New England Journal of Medicine*. 2005;353(10):988–98. Hartlapp JH. *Drugs* 1987;34(Suppl 1): 131–3. Schroeder M, Schadeck-Gressel C, Selbach J, Westerhausen M. *Onkologie*.1992;15:476–9.	

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Amgen UK	26.31	Full	177	10	<u>The incorrect dose of daily G-CSF used as inputs in the de novo model</u> In the de novo model the daily G-CSF dose is 300mcg for 8 days. This is in contrast to the SPC dosing, and the dosing in the randomised clinical trials, which state that they should be dosed at 5mcg/kg/day until the neutrophil count recovers. The dosing of daily G-CSF considered in the model should be as follows: a. Dosing by weight – Patient's weights were reported in three studies (Green 2003, Romieu 2007, Gigg 2003) and a weighted mean was calculated to be 72.3kg (SD 14.7kg). Using this patient weight distribution, the following syringe sizes were calculated; 20% of patients weight < 60kgand require a single 300mcg syringe, 74% of patients weigh 61kg-96kg and require a single 480mcg syringe, and 5% of patients weigh at least 97kg and require two 300mcg syringes. b. Dosing duration – The length of dosing in the clinical trials that derive the efficacy for daily G-CSF is between 9 and 11 days. By not dosing by weight for only 8 days the draft guideline is assuming the daily G-CSF dose is	Thanks for your comment. The daily dose of G-CSF has been changed to the BNF recommend dose, which is 5mcg/kg/day.The cost of G-CSF has been recalculated based on patient weight distribution. The new drug cost for G-CSF (per day) is £98.57.

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					only 55% of the dose used in the G-CSF RCT evidence. As the draft guideline derives the relative risk of NS from RCT evidence it is inconsistent and inappropriate to reduce the dosing assumptions in the model whilst leaving the relative risk of NS unchanged. There are no RCT data looking at the effect of reduced dosing as quoted in the draft guideline on the reduction of NS. However the best available data is a cohort study by von Minckvitz 2008, which shows that at a dose similar to that being proposed by the draft guideline the efficacy (relative risk) in reducing NS is approximately 0.75 (if it is assumed TAC patients have a 24% baseline risk of NS) compared to the 0.56 quoted in the Cooper 2005 meta analysis. <u>Recommendation:</u> The dosing of daily G-CSF should be aligned to the licensed dosing and the RCTs from which the relative risk of NS were derived References Green MD, Koelbl H, Baselga J, et al. *Ann Oncol.* 2003;14:29-35 Romieu G, Clemens M, Mahlberg R, et al. *Crit Rev Oncol Hematol.* 2007;64:64-72 Grigg A, Solal-Celigny P, Hoskin P, et al. *Leuk Lymphoma.* 2003;44:1503-1508 von Minckwitz G, Kümmel S, Du Bois A, et al. *Ann Oncol.* 2008;19:292-298. Cooper N., Madan J., Whyte S. *BMC Cancer.* 2011, 11: 404	

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Amgen UK	26.30	Full	177	26	<u>The incorrect dose and dosing schedule of antibiotics are used</u> Table A11 bases the drug acquisition cost of antibiotics on 3 days of antibiotic use. In contrast, the model uses a relative risk of NS for quinolones from 4 trials with the following antibiotic treatment durations; • Cullen 2005 - dosed for 7 days at 500mg per day, • Schroeder 1992 - two types of antibiotics were given in combination - dosed on day 3-14, • Carlson 1997 - 500mg twice daily antibiotics were started on day 6 and continued until ANC increased above 1 x 10^9/litre Mean duration of prophylaxis was 7.7 days per cycle • Harlapp 1987 - 200mg twice daily was for 7-16 days (mean = 10 days) The duration of antibiotic treatment used in the model is therefore not consistent with the duration used in the clinical trials, on which the relative risk of NS for antibiotics was estimated. It must also be noted that 3 days antibiotic prophylaxis has no published evidence to recommend it as a preventative measure. Furthermore, it is difficult to see how 3 days could be implemented in clinical practice since the timing and duration of neutropenia varies by	Thanks for your comment. The dose and dosing schedule of antibiotics used in the original report have been replaced by the dose and dosing schedule reported by Cullen 2005; because the GDG felt that this paper is most applicable to our clinical setting. References Cullen M, Steven N, Billingham L, Gaunt C, Hastings M, Simmonds P, et al. New England Journal of Medicine. 2005;353(10):988–98.

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					patient hence it is unclear how physicians could determine the neutropenic nadir and know when to start antibiotics (without daily blood tests). Furthermore, such a short dose of antibiotics is likely to increase the risk of antibiotic resistance. <u>Recommendation:</u> The correct dose and dosing schedule of antibiotics should be used in the cost utility analysis References Carlson JW, Fowler JM, Mitchell SK, Carson LF, Mayer AR, Copelands LJ. *Gynecologic Oncology.* 1997;65:325–9. Cullen M, Steven N, Billingham L, Gaunt C, Hastings M, Simmonds P, et al. *New England Journal of Medicine*. 2005;353(10):988–98. Hartlapp JH. *Drugs.* 1987;34(Suppl 1): 131–3. Schroeder M, Schadeck-Gressel C, Selbach J, Westerhausen M. *Onkologie*. 1992;15:476–9.	
Amgen UK	26.27	Full	178	13	<u>The costs associated with NS are significantly underestimated in the de novo model</u> The cost of treating a neutropenic event has been calculated in the guideline by assuming that; • 90% of neutropenic patients have a low risk of adverse events and can be discharged from hospital after 2 days • 10% of neutropenic patients have a high risk of adverse events and will require a hospital stay for 7 days. These assumptions mean the draft guideline	The GDG agreed it would be more appropriate to use costs based on the clinical pathway represented by the guideline recommendations, rather than the HRG cost you cite. This was because the economic analysis only considered adult patients (solid tumour, NHL and HL) who are receiving outpatient chemotherapy. In contrast to those patients who are receiving inpatient chemotherapy, our target population rarely use ICU (ITU) or antifungal drugs (both of which are very expensive). This means the treatment cost for our target population (outpatient) will be much lower than it is for the inpatient group. Consequently the GDG

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					assumes that an average solid tumour patient with confirmed NS will be in hospital for 2.5 days, 3.25 days for NHL, and 2.5 days for HL. There is no evidence to support the split between patients with a high and low risk of adverse events and their length of stay in hospital, instead the input parameters used in the model were estimated by clinical opinion. These estimates contradict the average length of stay reported in both HRG costing data and in peer reviewed publications: • The NHS reference cost data states the average length of stay for an elective in-patient is 8.78 days and non elective of 5.8 days • Kuderer 2007 shows that the length of stay for solid tumours is 8.13 days for solid tumours and 10.17 days for lymphoma. • Schelenz 2011 found that the mean length of stay was 9.2 days in a study looking at the epidemiology, management, and economic impact of febrile neutropenia in oncology patients receiving routine care at a regional UK cancer centre (Norwich) which considered 1,700 adult patients This low estimate of the number of days in hospital for the treatment of NS results in an underestimate of the cost for treating NS when	agreed it would be inappropriate to use the HRG cost (which is also likely to cover all cancer patients). According to the NHS reference cost (2009-10), the average cost of an excess bed day is £255, which includes the cost of staff, medication, routine examination and treatment. Since the cost of excess bed days has been included in the economic model, the costs of any routine tests or intravenous antibiotic were not added in separately to avoid double counting. Data based on HRGs may not be appropriate in all circumstances (for example, when the definition of the HRG is broad or the mean cost probably does not reflect resource use in relation to the technology under appraisal). In such cases, other sources of evidence, such as micro-costing studies, may be more appropriate.

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					compared to other cost utility publications and the HRG cost. The cost of NS is further under-estimated by not considering the following important costs in the model; • The cost of IV antibiotics to treat the NS • The cost of bloods and other inpatient investigations • The cost per bed day quoted in the guideline is for a standard hospital bed and not ITU which is where some sepsis patients are treated • The cost of anti fungals In the analysis described in the draft guideline only the cost of standard bed days, the cost of oral antibiotics, and the cost of telephone support for outpatients is included. The draft guideline itself does not explicitly state the cost of treating NS and it is only possible to review this figure by examining the Treeage model. By conducting this analysis we found that the draft guideline assumes the cost of treating NS is £766.30 for a patient not receiving G-CSF and £712.49 for a patient receiving G-CSF. These figures are significantly lower than assumed in other published cost utility studies (Liu assumed £3,095 and Whyte assumed approximately £2,100). The cost of treating NS is also significantly	

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					lower than the HRG cost for 'Febrile neutropenia associated with malignancy' which is £5,959. This is a new HRG code that was published in 2011 hence it was not available when Liu 2009 or Whyte 2011 conducted their analysis. In order to adhere to the NICE methods guide, HRG costs should be used as a primary cost source in cost utility analysis as it is derived from activity within the NHS itself: Section 5.5.5 of the NICE methods guide states that *'national data based on HRGs are a valuable source of information and should be used when appropriate and available'*. In summary the draft guidelines significantly underestimates the cost of treating NS in the NHS at between £712 and £766. • The percentage of people at risk of an adverse event is not based on evidence or current clinical practice • Many of the elements which inform the cost of treating NS including; cost of IV antibiotics, cost of ITU beds and nursing support, cost of anti fungals treatments, cost of blood tests, and outpatient follow up have been omitted from the analysis. • The HRG cost 'FN associated with malignancy which is £5,959 has been ignored <u>Recommendation:</u> The NHS reference cost for	

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					NS should be included in the model References: NHS reference costs 2009-2010: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459 Kuderer N.M., Dale, D.C., Crawford J.et al. *J Clin Oncol.* 2007 Vol25 pp3158-67 Schelenz 2011: *Annals of oncology advance access.* November 2011 Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. *Value in Health.* 2011;14(4):465-474. Liu Z., Doan Q.V., Malin J., Leonard, R. *Appl Health Econ Health Policy.* 2009 Vol7 pp193-205	
Amgen UK	26.40	Full	185	1	Comments the same as comments made for Order Number 40 (for page 108, row 30)	Thank you for your comment
Amgen UK	26.41	Full	201	26	Comments the same as comments made for Order Number 40 (for page 108, row 30)	Responses are the same as for order number 40
Amgen UK	26.03	Full	202	49	Comments the same as comments made for Order Number 2 (for page 114, row 18)	Thank you for your comment
Amgen UK	26.15	Full	202	49	Comments the same as comments made for Order Number 16 (for page 70, row 11)	Thank you for your comment
Amgen UK	26.29	Full	202	49	The draft guideline de novo model ignores chemotherapy RDI impact on longer term survival The draft guideline acknowledges that	In order to investigate this effect we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for

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					neutropenia and NS are indications for chemotherapy dose reduction and dose delay. They also state that it is generally considered that a reduction in chemotherapy dose is likely to be detrimental to a patient's longer term survival and reference Bonadonna 2005. However they justify excluding RDI due to: • Lack of evidence – There are several peer-reviewed papers with evidence on this for example Chirivella 2008 • easibility problems – This should not be a reason to not include RDI in the model, particularly as at least two peer-reviewed publications, Liu 2009 and Whyte 2011 have successfully conducted analysis which includes RDI. The draft guideline states that RDI is equally maintained by G-CSF and quinolones. This is an incorrect assumption: G-CSFs, by reducing neutropenia, facilitate optimal RDI and provide the potential for longer term survival benefits in patients who would benefit from receiving full dose chemotherapy (i.e. medium-high risk patients). In contrast antibiotics do not facilitate optimal chemotherapy RDI, and therefore have no impact on survival beyond the immediate period of chemotherapy. The exclusion of RDI in the de novo modelling therefore significantly biases the results towards antibiotics, by not allowing the longer term benefits of G-CSFs to	and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline Although our systematic review of cost-effectiveness studies did identify several studies trying to model the impact of using G-CSF on patients long-term survival (by maintaining chemotherapy dose) (see cost effectiveness evidence section for chapter 5); none of these studies used any direct clinical data. Instead, these studies were trying to build an indirect relationship between use of G-CSF and long-term survival. They stated that G-CSF could prevent neutropenic sepsis; neutropenic sepsis is a risk factor of receiving dose-reduction chemotherapy and dose-

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					be captured and alters the conclusion for patients who have a medium to high risk of NS where the longer term survival is the treatment goal. Recommendation: If the draft guideline is to include medium and high risk patients in its recommendations then RDI must be included in the cost utility analysis References: Bonadonna. *BMJ*. 2005, 29, 330, 217 Chirivella, I. et al. Breast Cancer Res Treat. 2008 Liu Z., Doan Q.V., Malin J., Leonard, R. *Appl Health Econ Health Policy* 2009 Vol7 pp193-205 Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. *Value in Health* 2011;14(4):465-474.	reduction chemotherapy is a risk factor for patient long-term survival. Then based on this hypothesis, the authors claimed that G-CSF could improve patients long-term survival. Furthermore, a recent meta-analysis (Shitara et al., 2011) shows that neutropenia experienced during chemotherapy is actually associated with improved survival in patients with advanced cancer or haematological malignancies undergoing chemotherapy. This implies that experiencing side effects of chemotherapy might not be associated with impaired long term survival. Therefore the GDG were very unsure about the validity of the indirect logic used in these published cost-effectiveness studies and the derived conclusion and did not consider it appropriate to use the methodology from the existing studies to model the impact of using G-CSF on patients long-term survival for this guideline.
Amgen UK	26.33	Full	204	6	Comments the same as comments made for Order Number 34 (for page 97, row 5)	Thank you for your comment
Amgen UK	26.34	Full	204	14	Comments the same as comments made for Order Number 34 (for page 97, row 5)	Thank you for your comment
Amgen UK	26.35	Full	204	25	Comments the same as comments made for Order Number 34 (for page 97, row 5)	Thank you for your comment
Anglo Celtic Collaborative Oncology Group	36.00	Full	General		This guideline disagrees with International Guidelines of EORTC,NCCN and ASCO) Also London Cancer New Drugs Group Guidance	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no

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						prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
Anglo Celtic Collaborative Oncology Group	36.03	Full	93	1-19	(and table) This is the only RCT to test value of GCSF prophylaxis. Main aim was to test impact on achieved dose-intensity for 'standard dose' chemotherapy of early breast cancer. The difference was very marked and for control patients fewer than 50% of patients achieved as good as 85% or higher planned dose intensity- this could be interpreted as saying that more than half the patients may have had not only reduced benefit but possibly no benefit despite toxicity. Admissions to hospital attributable to infection post -randomisation occurred in 54 cases in the control arm against 34 in the GCSF arm (not major endpoints-see above).	Thank you for this information
Anglo Celtic Collaborative Oncology Group	36.04	Full	93	1-19	The trial was supported by an education grant from Amgen UK but was sponsored by Swansea University, and currently by Imperial College London and managed by the Scottish Cancer Trials Office in Edinburgh (now designated part of CACTUS)	Thank you for this information
Anglo Celtic Collaborative Oncology Group	36.02	Full	107	2,3	Oncologists assess neutropenic sepsis risk based on patient and chemotherapy regimen characteristics.	We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant

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					It seems inappropriate to ignore this important issue. Algorithms for risk are published-See Kuderer ,N et al It is also important to recognise the strategic purpose of treatment where maintenance of dose intensity is very likely to be critical and has only been demonstrated in a randomised trial for GCSF intervention using standard doses of chemotherapy in early stage breast cancer. Generally achievement of a critical dose-intensity is very likely to be important in the curative treatment of lymphomas and early stage breast cancer.	neutropenia ($\leq$0.5 x 10^9/litre) is an anticipated consequence of chemotherapy. The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be

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						acknowledged in the recommendation.
Anglo Celtic Collaborative Oncology Group	36.01	Full	108	49	We understand that costings now are based on actual drug price which for GCSFs is much reduced with the advent of biosimilars	All G-CSFs are biosimilars that in terms of regulation aren't treated as generics. Therefore, whilst each PCT probably has its own agreement, there is no nationally negotiated discount as normally found on the CMU website. Given this the GDG decided to use the BNF price since there is no other reliable NHS source. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A).
Arden Cancer Network	38.00	Full	General		Monotherapy with pip/tazo in the septic patient- if you are going to give an aminoglycoside makes more sense to give it up front when it may have an impact, can always discontinue once patient settled or have pathogens.	The recommendations made were based on the evidence appraised for this topic which did not support addition of aminoglycosides to any group as initial empiric therapy.
Arden Cancer Network	38.01	Full	General		What microbiological considerations would change monotherapy- no guidance	Such decisions need to be based on local microbiological resistance patterns and can't be specified in the recommendation
Arden Cancer Network	38.02	Full	General		No mention in algorithm of reviewing an individuals previous microbiology	The algorithm has been updated in line with changes made to recommendations
Arden Cancer Network	38.03	Full	General		Quinolone prophylaxis- not just C. diff risk but potent selective agent for ESBLs etc. Needs to	The issues of infection and resistance patterns, and Clostridium difficile (C. diff)

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					be a risk assessment as to overall benefit.	rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider

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						that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Arden Cancer Network	38.04	Full	General		The prevention component of the draft guideline is basic at best due to narrow scope	The Guideline scope was to consider the prevention and management of neutropenic sepsis in all cancer patients. In line with NICE processes, the scope and key questions were set in consultation with stakeholders.
Arden Cancer Network	38.05	Full	General		The draft covers multi-disease, multi chemotherapies and multi risks and needs to be more specific in each of these areas, using available evidence or becomes too dilute	The Guideline scope was to consider the prevention and management of neutropenic sepsis in all cancer patients. In line with NICE processes, the scope and key questions were set in consultation with stakeholders.
Arden Cancer Network	38.06	Full	General		many gaps in the management of patients with curative intent e.g. value of relative dose intensity	Due to time constraints it is not possible for a clinical guideline to make recommendations on all aspects of care. Those areas which were prioritised for investigation in the neutropenic sepsis guideline are clearly defined in the guideline scope. Those areas not in the scope, have not had the evidence appraised and we are unable to make recommendations on them.
Arden Cancer Network	38.07	Full	General		Short term mortality is not always the most important outcome	Within the scope of this guideline, the GDG considered that patients and clinicians would value short term mortality as the most important outcome. This is because, within the setting of the prevention and management of neutropenic sepsis, it is survival from these

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						brief episodes (around 5 days) which is of major concern to patients.
Arden Cancer Network	38.08	Full	General		not in line with current clinical practice using growth factors (e.g. EORTC guidelines including UK input)	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
Arden Cancer Network	38.09	Full	General		Omission of gentamicin from up front therapy suggests experience of a less sick group of patients than ACN see in haematology practice	The recommendations made were based on the evidence appraised for this topic which did not support addition of aminoglycosides to any group as initial empiric therapy.
Arden Cancer Network	38.10	Full	General		Haematology guidelines (National) indicate that haematology patients with neutropenic sepsis should be reviewed by a senior haematologist within 24 hours of presentation (not 48 as mentioned in draft)	The GDG have reviewed this recommendation, and felt that to improve the patient experience and clinical management, a patients risk of septic complications should be assessed within a maximum of 24 hours of presentation. They have also clarified that a healthcare professional with competence in managing complications of anti-cancer treatment should assess the patient's risk of septic complications.
Arden Cancer Network	38.11	Full	Page 20 flowchart		Refers to a member of the oncology team (as opposed to a member of the oncology / haematology team) assessing the patient.	Thank you for your comment. For clarity, the GDG have amended the recommendation to "a healthcare professional with competence in managing complications of anti-cancer treatment"

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Beating Bowel Cancer	34.18	Full	General		Overall, I am disappointed in the conclusions and recommendations of this guideline. I do not feel that it adequately addresses the bio-psychosocial needs of any cancer patient in general, or of bowel cancer patients in particular. Nor does it present me with any clear insight into how I might advise my patients to become proactive partners in their own treatment pathway, to prevent and reduce their individual risk of sepsis. Nor does it address the important short term consequences, or minimise the impact of the long term outcomes for patients receiving sub-optimal dosages of chemo or facing early cessation of treatment as a result of chemo induced neutropenia. I am deeply concerned about the recommendation to treat with 3 days of broad spectrum antibiotics regardless of individual need or circumstances. I am not convinced by the findings of the CGC which have discounted the potential negative impact this is likely to have on the long term health of the patient, or the risk of developing antibiotic resistance in an already vulnerable group of people who may have multiple lines of chemotherapy during the lifetime of their cancer journey. In addition, having chosen to use a biomedical model based on secondary healthcare exclusively, focusing only on the short term management of symptoms to reduce mortality associated with FNS during chemotherapy, it	NICE have recently published a guideline on patient experience in adult NHS services (CG138) which will hopefully address the issues you have raised. We consider that advising patients on these issues should form a corner stone of good clinical practice and does not need to be specified in a recommendation. The long term outcomes for patients receiving sub-optimal dosages of chemotherapy was outside the scope of the guideline. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it. It is unclear where the Guideline recommends three days of antibiotics for every patient. Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills. These issues are outside the scope of this guideline and consequently we are unable to make recommendations on them.

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					fails to consider the importance of prevention, self-management and the consequences of missed, reduced or discontinued treatments caused by neutropenia. Consequently, I believe that NICE are at risk of creating a document that will lead to wider variance in practice and inequality of service provision across England and Wales as the guidance is interpreted and considered in different ways by local commissioning groups and healthcare providers. This potential to create greater inequality in the way patients are able to access the most appropriate treatment and support for their own individual need, will undermine their ability to live as well as possible, for as long as possible with cancer as a chronic disease, and is contrary to the aspirations of the IOSC, 2012.	We believe the clear statements in this guideline will harmonise treatments to a much greater degree than is currently undertaken.
Beating Bowel Cancer	34.16	Full	46-49	General	Training in the identification and management of neutropenic sepsis should be a pre-requisite part of professional development and practice competence for all staff working with patients who may be affected by the condition – in both hospital and community settings, in the same way that other mandatory training modules are currently. It is not enough only to train the staff working in the specialist units, as the incidence of patients who seek help for sepsis related events is not restricted to the times when these specialist staff are available in the units where patients may traditionally present – A&E, GP out of hours services, NHS Direct helplines, acute	Thank you for your comments, we agree.

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					medical admission and elderly admission wards and hospices where patients may end up if they become unwell out of normal surgery/consulting hours. Since early diagnosis and intervention is likely to lead to less intensive treatment, more successful outcomes and shorter overall stays in hospital with fewer related complications, there must be some economic benefit to be gained from investing in basic information skills as part of an ongoing mandatory training programme, and perhaps models from other areas priority areas – eg. DVT prevention - could be used to demonstrate potential savings.	As stated in the linking evidence to recommendations section, it is possible that there may be cost savings resulting from this recommendation. However it is not possible to quantify what these are.
Beating Bowel Cancer	34.15	Full	44-46	General	The evidence available on the quality and timing of giving of health information resources and key contact details may be of poor quality and limited in quality for neutropenia and sepsis in particular, but the focus of healthcare policy is currently to improve the overall provision of the most appropriate information delivered in the right way, at the right time to ensure comprehension and engagement with the messages. Recommendations should therefore include establishing local solutions which meet the Information Standard Criteria as defined by DH to ensure evidence based information is provided at a consistently high level, and peer reviewed by both patients and clinicians to ensure quality and content of resources. Charities are ideally placed to support healthcare providers with (often free copies) of	We agree. This is why we have recommended research in this area. We agree but setting this up will be a matter for local implementation.

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					tumour or disease specific health information resources to this high specification across the UK. This potentially represents a significantly cost effective means of ensuring equality and reducing variance, while encouraging partnership and collaboration between health service providers and patient groups.	
Beating Bowel Cancer	34.04	Full	5 - 6	45-47 1-2	Implies that the patient will be offered outpatient treatment when considered to be at low risk of developing septic complications and able to self-care at home with support from family/carer. How will this be monitored in practice, and how can community healthcare teams support these patients to ensure safety? Also, who will make this assessment, if they do not have the appropriate clinical experience or the responsibility to discharge – especially during out- of-hours periods (evenings and weekends) where there is no acute oncology team on call.	We have amended the recommendations to clarify that a patients' social circumstances should taken into account when determining if they are suitable for discharge. This will be a matter for local implementation. This decision would be made by someone competent to do so. We do not feel it is necessary to specify this in the recommendation as it is part of good clinical practice.
Beating Bowel Cancer	34.01	Full	5	8-13	Information and support for patients – it is not enough to say "provide information", but guidance must also highlight the importance of timing for information giving, in stages, so that messages don't get "lost" in the pile of paperwork the patient is given, and thus never read or remembered. It is vital to check understanding of information given, and ensure continued concordance at each visit /contact. The measures should be intrinsic to the governance of chemotherapy services, enabling shared decisions and informed consent as part of the preparation for	The information required will be different for individual patients. We have no evidence to specify the timing of such information. Therefore it is not possible to specify this in the recommendation. We have recommended further research in this area.

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					each cycle of treatment.	
Beating Bowel Cancer	34.02	Full	5	15 - 19	Investigations and risk stratification - holistic needs assessment and validated scoring system for personal risk stratification can support the implementation of successful prevention strategies & minimise the impact of complications arising from the chemo induced neutropenia at pre-treatment appointment and then at each visit.	Thank you for this information.
Beating Bowel Cancer	34.03	Full	5	27-30	Preventing the septic complications of therapy – Should state "offer appropriate prophylactic intervention as determined by results of validated scoring system and individual needs assessment….to reduce risk of infection associated with neutropenia". The word "offer" also implies choice, but there is no reference as to how this informed choice is assured, or how concordance/compliance will/should be measured. Anti-biotic therapy will not prevent neutropenia, nor will it protect patients against viral or fungal infections. It may in fact undermine the body's natural defences to cope with such challenges. Overuse and sub-optimal clinical doses of antibiotics has also led to resistant strains of bacteria in the past, and this should also be a significant concern for patients and clinicians following this guidance.	We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where neutropenia ($\leq$0.5 x 10^9/ litre) is an anticipated consequence of chemotherapy. Whilst the word "offer" in this context denotes the strength of the evidence underling the recommendation (in accordance with NICE style), patients always have choice in what treatments they have. Thank you for your comments. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of

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						expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff

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						rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
					Where there is a demonstrated clinical need, other prophylactic interventions such as GCSF therapy should be offered to ensure safe completion and overall cost effectiveness of treatment based on both quality of life and overall survival, in line with the aims of the IOSC, 2012.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-

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						CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
Beating Bowel Cancer	34.05	Full	9	40	While the guideline is aimed at all healthcare professionals and commissioners who may come into contact with patients/carers concerned about or affected by neutropenic sepsis, it frequently refers to ambiguity and uncertainty arising from a lack of data, or sub-optimal clinical studies which produce ambiguous results. It does not provide enough clinically appropriate detail and guidance to help them make clinically effective decisions. Nor does it help patients engage in shared decision making processes regarding their own personal risks on their individual treatment pathway. This is likely to lead to variance in access to appropriate services and support and undermine equity in access to prophylactic treatments for patients who have been	Whilst we acknowledge that there is ambiguity and uncertainty arising from a lack of data, the guideline has attempted to reduce this uncertainty by providing recommendations for clinical practice, without being overly prescriptive in areas where the evidence is sparse. The wording of the recommendations has been carefully considered to engage patients in shared decision making. The patient members of the group were fully involved in the development and wording of all recommendations and they considered them appropriate. NICE have recently published a guideline on patient experience in adult NHS services (CG138) which will hopefully address the

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					consciously excluded from the guidance – those undergoing multiple lines of treatment and with increasing risk of concurrent complications.	issues you have raised.
Beating Bowel Cancer	34.06	Full	15	17-24	Incorporating health economics evidence – There is no mention of the intrinsic value of pro-active approach to preventative intervention strategies as a cost effective means of improving the efficiency of resource allocation or improving the health outcomes of the population. Instead the focus is exclusively on the diagnosis and management of septic episodes.	The text you are referring to describes the methodology behind incorporating health economic evidence. We have changed "diagnosis" to "prevention" for clarity.
Beating Bowel Cancer	34.07	Full	20	Algorithm	There is no indication of who is responsible for identifying when the patient may be unwell in box 2 or the time frames for this, given that there is also the parallel box where prophylactic antibiotics have been offered for a specific group of patients, where we are told that there is a specific window between days 5-7. In box 3, there is no indication of who is responsible for making the referral, or which assessment tool they will have used for making their diagnosis, given that they cannot determine the platelet count in the community setting, and that pyrexia may not be a symptom exhibited by the patient. I am also conscious that pyrexia may be masked by the steroids being taken to manage the nausea, or by the paracetamol being taken to manage the pain associated with healing	We have deliberately not recommended who should be responsible for identifying when a patient is unwell because this recommendation applies to everyone involved in a patients' health care. This guideline recommends giving prophylactic antibiotics during the expected period of neutropenia which may vary from patient to patient. We have deliberately not recommended who should be responsible for referral when a patient is unwell because this recommendation applies to everyone involved in a patients' health care. At this stage the patient has not been assessed or diagnosed – the recommendation indicates the need to be seen in secondary or tertiary care. We agree that patients with neutropenic sepsis may not present with fever but have other symptoms and signs consistent with significant infection. We have amended the

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					surgical wounds, in addition to the joint pains and muscle cramps, and flu like symptoms associated with most chemo regimen. The community healthcare team and GPs therefore need clear lines of communication and access to accurate clinical records to help support their patient care practice 24/7/365 in order to be able to fully support and comply with this guideline. Patients/Carers can (and do) also self–refer direct to secondary healthcare, where there are robust protocols in place to support this. We are aware however, that there are significant barriers to appropriate self-referral where access to reliable transport is limited - especially when there is such varied access to services out of hours across the country. There is however potential to build on existing models of service provision todevelop a much more effective, cost-efficient model of support for vulnerable patients in the future, with free or low cost access to a national dedicated tele-health/ tele-medicine helpline, expanding the model currently used by several private providers of chemotherapy in the community. In box 5, should it not also be recommended that patients with suspected neutropenic sepsis should be reverse barrier nursed in a controlled environment, rather than in an open ward as an acute emergency?	recommendations and algorithm to reflect this. We agree but setting this up will be a matter for local implementation, so it is not possible for the guideline to make recommendations on this issue. We agree but setting this up will be a matter for local implementation, so it is not possible for the guideline to make recommendations on this issue. We agree but setting this up will be a matter for local implementation, so it is not possible for the guideline to make recommendations on this issue. . Barrier nursing was not identified as a priority for investigation in the guideline because the GDG did not consider this to be commonly used. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it.

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					Throughout the algorithm, education for healthcare professionals is indicated (although there is no guidance as to how that should be achieved, or what should be covered). There is however, no reference to the information and education requirement for the patient and their carers during the same episode, which is arguably just as important, if they are to be partners in their own treatment.	Education of healthcare professionals will be a matter for local implementation, so it is not possible for the guideline to make recommendations on this issue. We have recommended that patients are provided with information and support. This is represented by the left hand arrow in the algorithm.
Beating Bowel Cancer	34.08	Full	21	Agorithm	Last line- clinical outcome boxes: Discharging patients re-assessed as low risk carries risk of unplanned readmission due to failure to cope at home and may discriminate against patients who are elderly and frail, living alone or in isolated rural communities where the local transport and community healthcare services are fragmented and insubstantial. Communication between secondary and primary care providers must therefore be of an excellent quality to assure continuity of care and support for these patients, who may still be very debilitated physically and emotionally following an acute infection.	We have amended the recommendations and algorithm to clarify that a patients' social circumstances should take into account when determining if they are suitable for discharge. We agree
Beating Bowel Cancer	34.09	Full	22	38 - 40	The description of the most vulnerable point in the chemotherapy cycle is approximately 5 – 7 days after administration of the chemo, but it can take 2 – 4 weeks to recover, when surely the patient remains at a moderate to high risk, especially if facing repeated treatments sustained over many weeks/months?	We agree but feel that the current text is clear.
Beating Bowel Cancer	34.10	Full	24	5-7	We strongly support the call for accurate coding of neutropenic sepsis episodes as sequelae of cancer treatments, and reporting as such of as	Thank you for your comment.

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					part of a national cancer data set	
Beating Bowel Cancer	34.11	Full	25	28	*"The majority of deaths from neutropenic sepsis occur in the 65-79 yrs age bracket".* The incidence of bowel cancer is increasing, and patients are still commonly diagnosed with advanced disease (>50% of cases), predominantly in this same age bracket. In the light of chronological age no longer being used as a barrier to active treatment, increasing numbers of patients are being treated with chemotherapy regimen considered to be of "moderate" cytotoxic risk to health, and as a result may not be considered for proactive preventative management strategies for sepsis. Is this one explanation contributing to the increase in number of deaths from neutropenic sepsis in all age groups from 65+?	We have not investigated this issue and are therefore unable to comment.
Beating Bowel Cancer	34.12	Full	29	Table 1.2	The explanation of the likelihood of sepsis occurring from treatment does not indicate how this risk is changed by a second or multiple treatment with cytotoxics, which may be clinically significant for the patient and the clinician prescribing subsequent treatments and managing risk of unwanted side effects.	This table provides concise examples of risk of neutropenic sepsis from differing chemotherapy regimens. It is not intended as an exhaustive list.
Beating Bowel Cancer	34.13	Full	32	13	Prevention of neutropenic sepsis: Active treatment options considered – The definition of the group of patients to be offered the prophylactic antibiotics is very prescriptive, but seems to underestimate the significant variance in the sub-groups of patients likely to be included within the catch all	This text is from the needs assessment which describes current practice in the UK. It does not examine the evidence nor does it make recommendations for future practice. We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant neutropenia ($\leq 0.5 \times 10^9$/litre) is an anticipated consequence of chemotherapy.

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					description of "acute leukaemia, stem cell transplants or solid tumours". From the expertise of the representatives on the panel, leukaemia; breast; lung and reproductive organ tumours were considered, but there was no one representing bowel cancer or any of the rarer cancers. As I understand it, neither was there any micro-biology or gastroenterology representation on the CGC, and I wonder if this might have produced a different understanding of the challenges and potential solutions. Antibiotics given prophylactically will not reduce the risk of neutropenia, or treat existing neutropenia, and so therefore cannot be compared directly with the GCSF preparations which do. I feel that this is an important point which has been misunderstood, or at least significantly misrepresented in the document – especially since the evidence suggests that there is very little clinical support for this practice currently. It is inferred that days 5, 6 and 7 are therefore the optimum time to take a 3 day course of prophylactic antibiotics so that it has the best clinical effect to prevent septic episodes. However, this is often the period when secondary nausea and vomiting become an issue which leads to questions around the effect of the combined medications on the bowel, potential for reduced tolerance and absorption of the oral antibiotics. How can clinicians ensure that this prophylaxis does not end up doing	A microbiologist was a member of the GDG. A gastroentereologist was not identified as a core member of the GDG during the scoping phase and consequently was not advertised for. We have acknowledged that prophylaxis with G-CSF (as recommended by ASCO and EORTC) reduced the rate of febrile neutropenia in the clinical evidence section of section 5.1. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG do not intend this inference, but instead support the recommendation "during the expected period of neutropenia".

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					more harm than good – especially as it is something that may have to be repeated for several cycles, depending on the circumstances?	
					This guidance raises several questions for me: How can clinicians ensure that the patient complies with the instructions for the correct timing and completion of the treatment?	This will be a matter for local implementation, so it is not possible for the guideline to make recommendations on this issue.
					How will patients be able to reconcile the benefits of the treatment with the unwanted side effects and iatrogenic conditions associated with this repeated antibiotic therapy, especially as it is likely to be exacerbated by concurrent symptoms from the other side effects of the cytotoxic therapy.	The issues of adherence to treatment and side effects were examined by the individual studies appraised, and found that mortality was still reduced.
					Is there not also a danger of a false sense of security if antibiotics have been taken and a viral infection or a fungal infection is the cause of the fever?	We do not believe so. Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills.
					In the case of GCSF medications, if these are given prior to commencing treatment, that decision should be based on the clinical need established from investigation and examination of the individual patient. Any decision to treat should include due consideration of the circumstances of the treatment, combined with the relative risks as calculated for the individual.	Thank you for this information.
					Side effects of GCSF are often manageable with anti-histamine therapy and the option for oral antibiotics as a secondary prophylaxis or	Thank you for this information.

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					treatment remains intact for those who have the highest risk of sepsis. Since 91% of the surveyed acute trusts already have GCSF protocols in place, in response to the EORTC definitions of high risk patients, then it seems contradictory of NICE to now be suggesting that their use is inappropriate and "making recommendations on topics where there is already agreed clinical practice". Those with the confirmed lowest risk of sepsis can safely be managed with conservative, self – help techniques that can be taught effectively and efficiently and reinforced by primary healthcare professionals supporting patients at home/in the community.	Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance. The GDG agreed that there was enough variation in practice in the prophylaxis of neutropenic sepsis to warrant investigating this topic, particularly with regard to cost-effectiveness. Thank you for this information.
Beating Bowel Cancer	34.14	Full	43	18-21	These two sentences seem to contradict each other, and perhaps the balance of the argument should be that sepsis should be considered as a possible diagnosis when based on the findings of an individual holistic assessment with a validated scoring tool. This would consider not only the blood counts, and the presence of fever, but also other circumstances (co-morbidity/medications, etc) and presenting features displayed by the patient in the absence of fever or a blood count of less than 1 x 10 to the 9th /litre, which more accurately reflects what	We have amended this text for clarity. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of $\leq$0.5.

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					is known from all the published evidence, and seems(from the supporting evidence provided by NICE) to be the basis for the majority of clinical practice in the UK currently.	
Beating Bowel Cancer	34.17	Full	70	13-20	The direction to use an antibiotic which may or may not be clinically appropriate or effective for the individual patient is a concern, particular when the side effects of this particular group of antibiotics could be of significant risk to bowel cancer patients who will already have impaired/compromised gastrointestinal function. Quinalones also carry a risk of peripheral nerve changes, and neurological complications, and respiratory symptoms which could be further amplified by the well documented cytotoxic effects of their chemotherapy (Oxaliplatin).	This text is from the background which describes why this topic needed to be investigated. It does not examine the evidence nor does it make recommendations for future practice. The potential side effects of using quinolones were discussed by the GDG when making their recommendations. This has been documented in the linking evidence to recommendation section for chapter 5.
Beating Bowel Cancer	34.00	NICE Short	General		Neutropenia and the risk of overwhelming infection and hospitalisation is something that frequently evokes a great deal of fear and anxiety for the patients and their families who contact the charity. We also regularly hear from patients who have become very anxious and distressed because they are unable to tolerate the prescribed doses or complete the recommended cycles of chemotherapy as a consequence of their cytotoxic regimen. We empathise with just how frightening this must be for them and their families. We therefore welcome NICE's recognition of the need to develop clear clinical guidelines for the prevention and management of neutropenic	Thank you for this information Thank you

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					sepsis. Our feeling is, however, that that the short summary document – while often the reading of choice for busy clinicians and healthcare providers - is unhelpfully generalist in trying to cover the needs of so many different patient groups, tumour types and clinical specialities under one overarching heading, determined only by a need to reduce short term mortality. Specifically, we believe that it does not provide enough clinically relevant detail to adequately differentiate the potential needs and risks associated with each of the sub-groups (e.g. blood cancers as distinct from individual solid tumours; the chemo- naïve patients from those having subsequent/multiple lines of chemotherapy; patients with underlying co-morbidities, and the increased risk for adults with increasing age) which will help clinicians and patients make effective, safe decisions regarding the best practice for them as individuals - and especially where the focus for the outcomes of treatment is on quality of life and increased overall survival, (as per IOSC, 2012). As such, we believe that this guideline may increase the risk of variance in practice across the country, resulting in potential discrimination against individuals who are perhaps the most vulnerable and at greatest risk of significant harm from the unintended consequences of their cancer treatments.	The short version of the guideline only contains the recommendations from the full version. However the wording of the recommendations in both versions is identical. These recommendations were developed based upon the evidence appraised – which is documented in the full guideline. The Guideline has produced recommendations which guide clinicians in their management of individual patients. Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills. Quality of life was explicitly considered in each of the recommendations. Unfortunately, very few studies had addressed this robustly. We believe the clear statements in this guideline will harmonise treatments to a much greater degree than is currently undertaken.

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					This group includes many bowel cancer patients whom we know to be elderly, and often with a low level of health literacy or living with challenging bio-psychosocial and economic constraints. In addition, the focus of the short document gives no substantial guidance or recommendations on strategies for prevention, nor recognition of the risks inherent in a prophylactic administration of a quinolone antibiotic know to have what could be significant side effects for immune-compromised bowel cancer patients. Neither does the short guideline recommend the introduction of a standard risk assessment tool to accurately identify and support those patients most at risk of developing neutropenic sepsis. To produce a robust clinical guideline that is going to be effective for such a diverse range of individuals, we believe that it is fundamental that clinicians and commissioners recognise and address the specific patient's individual need. This need is unlikely to be safely or efficiently met but the - currently poorly differentiated - high, medium and low risk groups currently being described in the guidance We also believe that this short guideline - if used by non-specialist commissioners without reference to the full guidance - will increase variance and inequity in service provision, undermining the efficiency of current clinical practice, and potentially putting individual lives	The short version of the guideline only contains the recommendations from the full version. However the wording of the recommendations in both versions is identical. These recommendations were developed based upon the evidence appraised – which is documented in the full guideline. We have recommended research into the signs and symptoms, experienced by patients in the community, which predict for episodes of neutropenic sepsis. We are unclear which risk groups you are referring to. We believe the clear statements in this guideline will harmonise treatments to a much greater degree than is currently undertaken.

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					at risk. The overall impression of the document is that it has been written entirely from the perspective of a secondary care clinician following a "traditional" biomedical model for intervention in patients who are otherwise relatively healthy and chemo-naïve. This, however, potentially excludes a great number of cancer patients currently being treated with both curative and palliative intent in the 65+ age bracket, common to many solid tumour cancer patients, including bowel cancer. The guidelines also seem to disregard the potential for greater responsibility and integration of care pathways for primary healthcare providers, by failing to address the role of community healthcare professionals in supporting cancer patients with chemotherapy induced neutropenia. This is especially true in many cancers which are now being considered "chronic" healthcare conditions, and for which patients are likely to have many lines of cytotoxic and radiological treatment in their ongoing treatment pathway, and is likely to have far reaching consequences in the future as GP commissioning becomes established. Effective prevention and management of personal risk should therefore be based on a	The GDG comprised a multidisciplinary group of clinicians and 3 patients, all of whom inputted into writing the recommendations. The guideline recommendations make no distinction about age (other than for paediatrics and teenage/young adults) nor between curative or palliative chemotherapy because the guideline group acknowledged the potential risk of neutropenic sepsis for all people receiving chemotherapy. The majority of the guideline deals with secondary care because neutropenic sepsis is a medical emergency that requires urgent secondary care. However a significant part of the guideline deals with the identification of neutropenic sepsis and the training of healthcare professionals who interact with people at risk of chemotherapy related neutropenic sepsis in a community setting. All the recommendations in Chapter 3 apply equally to primary and secondary care. Section 4.1 in Chapter 4 was specifically developed for primary care asking the question "Which symptoms and/or signs experienced by patients in the community predict neutropenic sepsis? Recommendations in guidelines are designed to assist the practice of healthcare

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					bio-psychosocial model of individual holistic needs assessment, rather than a "one size fits all", biomedical approach to which it is difficult for patients and their carers to relate to, or to engage with. We would therefore ask that any future guidance document also recognises the need to provide additional information and education resources that will increase awareness of the condition amongst community and primary healthcare teams, and facilitate increased personal responsibility and independence for patients – and their carers.	professionals, however, they do not replace their clinical knowledge and skills. We have recommended further research in this area.
British Infection Association	37.00	Full	5	27	The recommendation for widespread use of ciprofloxacin is a concern from an antibiotic resistance point of view – although the evidence review didn't find good quality evidence specific to neutropenic patients, there is now good evidence in the UK (as well as elsewhere in the world) that quinolones including ciprofloxacin contribute to selection of multi-resistant organisms including MRSA, *C difficile* and multi-resistant Gram negative organisms such as extended-spectrum beta lactamase producing coliforms. The Department of Health Guidance on *C difficile* 2009 states use of quinolones should be minimised (http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/ClostridiumDifficile/) and most centres have moved away from using quinolones outside of a very limited list of restricted indications. I would be reluctant to go back to widespread use of ciprofloxacin in this patient group without definitive evidence of	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendation section for chapter 5).

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					benefit *as well as definitive of evidence of lack of harm from selection of increasingly resistant organisms.*	The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
British Infection Association	37.01	Full	61	28	Obtaining peripheral cultures should be done at the same time as central line cultures in patients with central lines in order to be able to be useful in terms of determining differential time to positivity. If as the draft guidance suggests, central line cultures are done initially then after completing initial assessment peripheral cultures are done, the delay between taking the two sets of blood cultures may render the	The evidence comparing paired versus unpaired blood culture samples was not appraised and therefore we are unable to make recommendations on this issue. Blood cultures should be performed in accordance with national standard operating procedures.

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					differential time to positivity un-interpretable.	
British Infection Association	37.03	Full NICE summary	131 8	1 6-8	There is evidence that prior use of ciprofloxacin is a risk for selection of resistant organisms. In such patients I would recommend that initial treatment of sepsis even in non neutropenic patients should include an aminoglycoside as part of dual therapy to reduce the risk that the organism causing the sepsis is resistant to the therapy chosen. This is particularly important in severe sepsis.	We agree that local resistance patterns may affect whether this recommendation can be implemented. This is why we have stated this in the recommendation.
British Infection Association	37.02	Full	137	1	The recommendation not to offer empiric glycopeptide antibiotics to patients with suspected neutropenic sepsis who have central venous access devices seems to be based on no clear evidence of benefit but also on limited poor quality evidence of harm. This requires further clarification: is this also applicable to patients who have neutropenic sepsis with central lines who have specific features of line infection e.g. erythema/pus at line site or rigors on flushing line – if so piperacillin/tazobactam alone is unlikely to provide sufficient cover against Gram positive organisms. In addition, a significant number of patients with Gram positive line infections do not have specific clinical features (*e.g.* erythema at the line site/rigors on line flushing *etc*) and present with 'neutropenic sepsis' with no clear focus until the diagnosis is confirmed on blood cultures. Therefore it would be prudent to cover all patients with central lines presenting with neutropenic sepsis with a glycopeptide at least until the blood culture results are reviewed *e.g.*	Management of specific infections is explicitly excluded from the scope of this guideline - the treatment is not, by definition, empiric. Therefore this recommendation is not intended to cover the situation you have cited. We acknowledge that patients with Gram positive infections may not have specific signs suggesting line infection. The evidence appraised suggests in this group, there is no positive benefit for empiric glycopeptides whilst there is evidence of harm. This is covered the clinical evidence section for section 6.3.

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					in 48 hours or until an alternative focus of infection has been confirmed.	
British Nuclear Medicine Society	7.00	Full	General		BNMS have no comments to make.	Thank you for your comment.
British Society for Antimicrobial Chemotherapy	29.11	Appendices	General		We recommend the use of frequencies instead of percentages when referring to incidences or prevalence hence Instead of 5% cases stating 1 in 20	We agree that frequency is more appropriate than percentage, from the research point of view. However it is acknowledged that in clinical practice most clinicians will use percentages, rather than frequencies to assess patients risk of neutropenic sepsis. So the GDG felt it was more appropriate to use percentage as this would be easier for clinicians to understand.
British Society for Antimicrobial Chemotherapy	29.12	Appendices	General		There is a danger in combining haematology and oncology patients because the former have profound prolonged neutropenic and the latter shorter periods.	Thank you for your comment. Sub-group analyses were conducted for patients with solid tumours, non-Hodgkin lymphoma and Hodgkin lymphoma, to account for these differences.
British Society for Antimicrobial Chemotherapy	29.13	Appendices	General		There is a wide variation in defining fever, also different devices are used and different sites.	Thank you for your comments. Unfortunately we are unclear what section of the appendices you are referring to.
British Society for Antimicrobial Chemotherapy	29.14	Appendices	General		Strictly speaking it is empirical antibacterial therapy as not all antibacterials are antibiotics nor are all antibiotics antibacterial	We have chosen to use the term antibiotics because this is the most commonly used term in clinical practice.
British Society for Antimicrobial Chemotherapy	29.00	Appendices	1	1	The term "neutropenic sepsis" is odd for two reasons 1) it is inconsistent with the common understanding of fever that occurs during neutropenia and is more usually referred to as "neutropenic fever". Moreover "neutropenic sepsis" suggests there is a causal link between neutropenia and sepsis which there isn't. Also,	The remit from the Department of Health was to develop a guideline on the prevention and management of neutropenic sepsis in cancer patients. As such we are required to use this term. However we agree there can be confusion in terminology and so have clarified the terminology used by this guideline in

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					sepsis suggests fever plus other signs and symptoms of severe illness none of which is defined. Hence if the term is to be used it should be understood to be colloquial and not a scientific term and should be rendered it should be in quotes "neutropenic sepsis" Besides I doubt whether it is helpful to introduce a new term in an area where there is already confusion.	section 1.1, first paragraph.
British Society for Antimicrobial Chemotherapy	29.04	Appendices	7	24	What constitutes a blood culture? How much blood, which site, via a CVC and peripheral vein or exclusively peripheral?	We are unclear which text you are referring to in your comment. However the guideline defines both blood culture and peripheral blood culture in the glossary. Blood cultures should be performed in accordance with national standard operating procedures.
British Society for Antimicrobial Chemotherapy	29.01	Full Appendices	111 7	1 12	The recommendation for universal prophylaxis for the period of neutropenia is likely to be controversial and at odds with practice in our Unit. It is inconsistent with the national drive to limit use of this class of antibiotics given their association with Clostridium-difficile-associated disease, acquisition/selection of meticillin-resistant Staphylococcus aureus and selection of resistance in Gram-negative organisms, which we have seen with these agents. Perhaps a more suitable approach would be a local risk-assessment based on clinical outcomes and local microbiology surveillance?	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5).

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						The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
British Society for Antimicrobial Chemotherapy	29.07	Full Appendices	112 10	1 26	Quinolone prophylaxis for solid tumours. Evidence for this reducing mortality is mainly in high-risk (haematology) patients. Patients with solid tumours are at lower risk of infection and the Society would be concerned about increased risk of problems such as C.difficile and increased Gram-negative resistance if quinolone prophylaxis were adopted for all	We disagree, the largest single trial relates to patients with solid tumours. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision

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					neutropenia.	of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard.

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						The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
British Society for Antimicrobial Chemotherapy	29.03	Full Appendices	112 7	1 12-15	My colleagues and I are extremely concerned about the requirement to offer all patients with neutropenia following chemotherapy/transplant fluoroquinolone prophylaxis. While we are aware of the body of evidence showing reductions in gram negative infections and other parameters when prophylaxis is used, we feel that there has not been sufficient consideration given to the evidence of fluoroquinolones as drivers for Clostridium difficile infection and other antimicrobial resistance. We feel that the recommendation should allow units to undertake their own risk assessments and make decisions on whether to use this approach based on local factors.	The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($\leq$0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key

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					The implication that it should be for the patient to decide whether to accept prophylaxis is not acceptable.	element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in resistance patterns and C difficile rates. We strongly believe that a patient is able to make an informed decision regarding their care and choice in treatment.
British Society for Antimicrobial Chemotherapy	29.02	Full Appendices	112 7	1 13	Use of fluoroquinolone for prophylaxis is recommended for all patients (regardless of risk yet there is no risk-benefit assessment provided. Also, not all fluoroquinolones are the same. Indeed only two appear to be reliable for this indication ciprofloxacin 500 mg bd and levofloxacin 500 mg o.d.	The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($\leq$0.5 x 10^9/litre) and only during the period of expected neutropenia. We are not able to recommend particular risk thresholds as we do not have enough evidence to do this.
British Society for Antimicrobial Chemotherapy	29.05	Full Appendices	133 8	1 3	There are other effective regimens besides piperacillin-tazobactam including ceftazidime, meropenem. Would it not be better to state :broad-spectrum antibacterial dugs shown to be effective as monotherapy such as piperacillin-tazobactam. Surely this will also depend upon institutional circumstances including especially	While other regimes are effective, the evidence appraisal concluded that where feasible, the use of piperacillin-tazobactam was the most effective antibiotic treatment (see clinical evidence for section 6.2).

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					the local epidemiology. Should not the empirical regimen be predicated on prior prophylaxis?	
British Society for Antimicrobial Chemotherapy	29.06	Full Appendices	133 8	1 3	We recommend that consideration is given to including information on differentiated approach(es) to treatment, such as complementing the "core" empirical regimen with aminoglycosides or glycopeptides, or identification and management of severe sepsis/septic shock, suspected CVC infection, high local incidence of MR Staphylococcus aureus etc.	The management of severe infection/septic shock and the management of specific infections were specifically excluded from the scope of this guideline. Hence we are not able to make recommendations in these areas. We agree that local resistance patterns may affect whether this recommendation can be implemented. This is why we have stated this in the recommendation.
British Society for Antimicrobial Chemotherapy	29.08	Full Appendices	137 12	1 3	We recommend this section includes reference to penicillin allergic patients and treatment option for them.	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.
British Society for Antimicrobial	29.09	Full	137	3	We recommend identifying when empiric glycopeptides antibiotics are indicated e.g. The	Management of specific infections is explicitly excluded from the scope of this guideline - the

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Chemotherapy		Appendices	12	11	central line looks infected and the patient is known to be colonised with MRSA.	treatment is not, by definition, empiric. Therefore this recommendation is not intended to cover the first situation you have cited. We have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern.
British Society for Antimicrobial Chemotherapy	29.10	Full Appendices	166 14	1	We applaud the clear statement about discontinuing empirical therapy.	Thank you for your comment.
British Society for Haematology & Royal College of Pathologists	17.18	Full	General		There is no discussion within this document of the use of G-CSF in the treatment of patients with neutropenic sepsis, this is established practice for many clinicians, and the drug is probably overused in this regard, but in patients with severe sepsis it may be desirable to give treatment that may speed up neutrophil recovery, so not to discuss this issue is a major omission.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. However, the use of G-CSF in the treatment of neutropenic sepsis was not identified as a priority for investigation in the guideline because the GDG did not consider this to be commonly used. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it.
British Society for Haematology & Royal College of Pathologists	17.19	Full	General		It would be helpful if there was more emphasis on the importance of patients infective history and local antibiotic resistance patterns. Where a patient has had culture positive results with resistant organisms then different antibiotics would be used first time. It is important for the patient to carry this information. We have had patients treated at other hospitals (commonly occurs with Centres/Units) arriving septic in Emergency Department and known to have multiresistant organism. It is of critical importance this information is available	We agree that this may be important but this topic was not identified as a priority for investigation in the guideline because the GDG considered there would only be a small proportion of patients for whom their infective history would significantly alter treatment. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it.

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					wherever the patient is being treated.	
British Society for Haematology & Royal College of Pathologists	17.21	Full	General		Another general point is that this guidance is too broad – the authors do state in several places within the document that they could not include leukaemia and SCT patients in some of the cost-effectiveness analyses. Clearly patients being treated entirely as in-patients are different and this should be reflected more obviously especially in the choice of antibiotics for prophylaxis and treatment as they face greater risks of hospital acquired infections eg *C.difficile* and MRSA. The authors also do not discuss the possibilty that using ciprofloxacin as prophylaxis may create a greated risk of resistant organisms making dual therapy with aminoglycosides more desirable.	We agree that inpatients have very different prophylaxis costs to those patients receiving outpatient management. This is why patients with stem cell transplants and leukaemia were excluded from the cost effectiveness analysis. However the GDG agreed that the improvement in short term mortality outweighed the potential additional costs and decided to recommend prophylaxis with quinolones for adults with stem cell transplants and acute leukaemias. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($<0.5 \times 10^9$/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common

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						in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
British Society for Haematology & Royal College of Pathologists	17.25	Full	General		It is unfortunate that economic modelling could not be based on the cheaper costs of biosimilar G-CSF which would clearly have altered the cost per QALY assessment for G-CSF use, clearly the guideline group recognise this limitation.	All G-CSFs are biosimilars that in terms of regulation aren't treated as generics. Therefore, whilst each PCT probably has its own agreement, there is no nationally negotiated discount as normally found on the CMU website. Given this the GDG decided to use the BNF price since there is no other reliable NHS source. One-way sensitivity analysis has shown that

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						the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A).
British Society for Haematology & Royal College of Pathologists	17.27	Full	Appendix A		We have great concerns at some of the assumptions made in the cost-utility analysis of G-CSF's presented, specifically the short-time frames used in the modelling, which will not take account of longer term benefits,	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on

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						short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations. Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
					the failure to take into account the issue of maintaining dose-intensity,	In order to investigate maintaining dose intensity we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent

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						chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline Although our systematic review of cost-effectiveness studies did identify several studies trying to model the impact of using G-CSF on patients long-term survival (by maintaining chemotherapy dose) (see cost effective section in chapter 5); none of these studies used any direct clinical data. Instead, these studies were trying to build an indirect relationship between use of G-CSF and long-term survival. They stated that G-CSF could prevent neutropenic sepsis; neutropenic sepsis is a risk factor of receiving dose-reduction chemotherapy and dose-reduction chemotherapy is a risk factor for patient long-term survival. Then based on this hypothesis, the authors claimed that G-CSF could improve patients long-term survival. Furthermore, a recent meta-analysis (Shitara et al., 2011) shows that neutropenia experienced during chemotherapy is actually associated with improved survival in patients with advanced cancer or haematological malignancies undergoing chemotherapy. This implies that experiencing side effects of chemotherapy might not be associated with impaired long term survival. Therefore the GDG were very unsure about the validity of the indirect logic used in these published cost-effectiveness studies and the derived conclusion and did not consider it appropriate

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						to use the methodology from the existing studies to model the impact of using G-CSF on patients long-term survival for this guideline.
					and the broad-brush approach which fails to consider differences in patient performance status or regimen intensity.	We agree that the evidence for this recommendation has been drawn from heterogeneous populations. We have attempted to reduce the population heterogeneity by excluding paediatric patients, patients receiving inpatient chemotherapy and patients whose regimen includes G-CSF from the model. In addition we have performed sub-group analysis for patients with solid tumours, non-Hodgkin lymphoma and Hodgkin lymphoma. The potential effect of this heterogeneity on the health economic model results has been assessed by sensitivity analysis on the relevant model inputs. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. The results of all one-way sensitivity analyses have been added to the guideline.

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British Society for Haematology & Royal College of Pathologists	17.04	Full	4 and 9		In the Introduction part 'Who is the guideline intended for?' – it is stated that it is to prevent febrile neutropenia in cancer patients but in this day and age with increasing numbers of rheumatology pts on MTX and ulcerative colitis patients on 6-MP this really should be broadened to include all patients being treated with cytotoxic agents	The remit for this guideline was to develop recommendations on the prevention and management of neutropenic sepsis in cancer patients. Consequently we have not looked at any other patient groups.
British Society for Haematology & Royal College of Pathologists	17.00	Full	20		It is not only patients on anti-cancer treatments that develop neutropenic sepsis, this may also occur in patients with other inherited or acquired defects in neutrophil number/function e.g. MDS, aplastic anaemia.	The remit for this guideline was to develop recommendations on the prevention and management of neutropenic sepsis in cancer patients. Consequently we have not looked at any other patient groups.
British Society for Haematology & Royal College of Pathologists	17.01	Full	20		This is a restrictive definition of neutropenic sepsis, e.g. patients on steroids may not develop fever. Firstly there is the definition of febrile neutropenia stating that the neutrophil count has to be < 0.5. The evidence given does not support this and from Figure 1.7 it is clear that the majority of centres use a neutrophil count of < 1.0. We all know that a neutrophil count of 0.6 on admission may be 0.1 within 24 hours after chemotherapy and using 0.5 as a cut off point is potentially dangerous and may well lead to additional deaths. The national Acute Oncology Service triage is suggesting patients with temperature >37.5C should be phoning in, there should be consistency across the board.	We agree that patients with neutropenic sepsis may not present with fever but have other symptoms and signs consistent with significant infection. We have amended the recommendations and algorithm to reflect this. The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs

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						with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of $\leq$0.5. The evidence also showed that increased temperature was associated with an increase in infection. The lowest value for fever studied in the evidence was 38^{o}C and the GDG decided to adopt this value in their definition for neutropenic sepsis.
British Society for Haematology & Royal College of Pathologists	17.02	Full	21		Confused by boxes at bottom of flowchart, especially the 3rd and 4th ones, which appear in conflict, are we discharging patients, stepping down to oral antibiotics or both?	The recommendations allow for discharge of patients and/or stepping down to oral antibiotics. This is because while most patients who could be discharged early are able to tolerate oral antibiotics, some may have a specific contraindication which requires IV antibiotics. However, these patients can be discharged if facilities exist to deliver outpatient IV antibiotics. The social circumstances of some patients may mean they are not able to be discharged but are still able to step down to less resource intensive regimens for example oral antibiotics. We have added to the linking evidence to recommendations section to clarify this..
British Society for Haematology & Royal College of Pathologists	17.03	Full	23	28	We feel that the one hour door to needle time is now well established in most hospitals as a target for patient with suspected neutropenic sepsis, it is disappointing that the recommendations in this document are so vague, the door to needle time concept should be preserved	This text is from the needs assessment which describes current practice in the UK. It does not examine the evidence nor does it make recommendations for future practice. We acknowledge that this is an important clinical issue and was debated at length by the GDG. However the evidence was not clear enough to recommend a specific time or

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						specific clinical group where time to antibiotic delivery altered the patients outcome. Hence the recommendation does not define a specific time period or limit its indication to a specific clinical presentation.
British Society for Haematology & Royal College of Pathologists	17.05	Full	37	11	Welcome idea of national prospective audit	Thank you for your comment.
British Society for Haematology & Royal College of Pathologists	17.06	Full	42	6-7	Believe that this should read "A single study in 102 patients (Apostolopoulou, *et al.,* 2010) reported that ANC >0.5 x 10^9/litre has high negative predictive value for bacteraemia"	We believe the original statement is correct. In the Apostolopoulou study if a person did not have ANC<0.5 x 6 10^9 /litre (if their was ANC≥0.5 x 6 10^9 /litre) there was a high probability that they did not have bacteraemia.
British Society for Haematology & Royal College of Pathologists	17.07	Full	42	29	Would like to see some reminder about caveats in diagnosing suspected neutropenic sepsis e.g. effects of steroids in masking pyrexia. Also risk of severe and overwhelming sepsis exist in patients with some haematological conditions, or treated with certain agents e.g. purine analogues, even when not neutropenic. This section would benefit from stronger cross-linking with section 4	We agree that patients with neutropenic sepsis may not present with fever but have other symptoms and signs consistent with significant infection. We have amended the recommendations and algorithm to reflect this. The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment.
British Society for	17.23	Full	61		Most centres would include urine culture rather	Urine culture was not identified as a priority

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Haematology & Royal College of Pathologists					than urinalysis as an additional investigation for all patients presenting with neutropenic sepsis – not just blood cultures.	for investigation in the guideline as the question focussed on investigations that would influence emergency empiric assessment. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it. However the existing recommendation does not preclude the use of urine or any other targeted culture if it is deemed clinically necessary.
British Society for Haematology & Royal College of Pathologists	17.08	Full	61	28	Although this is discussed in the text, it is not clear from this recommendation box whether peripheral blood culture is being recommended instead of, or as well as, central cultures in patients with CVC	We have added "additional" to this recommendation for clarity.
British Society for Haematology & Royal College of Pathologists	17.09	Full	65	1	This should read "oncology or haematology team", puzzled as to where 48 hours has come from – this will not be achievable in many DGH's where oncologists may only visit, would within "one working day" be better?	For clarity, the GDG have amended the recommendation to "a healthcare professional with competence in managing complications of anti-cancer treatment". The GDG have reviewed this recommendation and felt that to improve the patient experience and clinical management a patients risk of septic complications should be assessed within a maximum of 24 hours of presentation.
British Society for Haematology & Royal College of Pathologists	17.22	Full	112		We are very concerned at the proposal that quinolones should be used widely in this population as prophylaxis against febrile neutropenia. We do not feel that sufficient weight has been given to the potential negative consequences of such a strategy. It seems to be accepted by the guideline group that there are relatively poor data available regarding: - infections with resistant organisms	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia.

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					- colonisation with resistant organisms - *C.difficile* rates in patients treated prophylactically - MRSA colonisation / infection rates in the treated groups. We do not believe that large-scale data exist to allow us to accurately predict the effect of such a strategy in this population and are particularly concerned about rates of hospital-acquired *C.difficile* and MRSA. This would be likely to have greatest impact on larger cancer centres where these patients are concentrated. We have significant concerns about implementing such a policy when one considers population health in addition to that of the treated individual. If such a strategy were mandated there would need to be considerable upward revision of 'targets/limits' for hospital acquired infections. This would be a terrific backward step after all of the efforts nationwide to reduce this risk.	The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section of chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is

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						done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
					The authors only appear to have compared to cotrimoxazole whereas many centres use colistin orally as prophylaxis	As stated in the linking evidence to recommendations section, whilst the evidence on cotrimoxazole was appraised the GDG decided to focus on the evidence related to quinolones because of concerns that changing anti-microbial resistance patterns meant the cotrimoxazole trials may no longer be applicable.
British Society for Haematology & Royal College of Pathologists	17.24	Full	112		The lack of recommendation of G-CSF for any patients due to cost is highly contentious and is out of line with the EORTC updated guidelines 2010 and indeed most of the rest of the developed world. The authors say that this does not matter as the EORTC guidelines are based on G-CSF vs no prophylaxis and that they were not based on UK studies. This is nonsense – our reading of the EORTC guidelines does not exclude patients on antibiotic prophylaxis and it is unlikely that the UK will differ from Europe in the prevalence of febrile neutropenia.	Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
					Also there is no mention of the need for G-CSF to maintain dose intensity of treatment especially in lymphoma treatments.	In order to investigate this effect we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be

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						needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians

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						in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. Not withstanding this, the GDG noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
					Furthermore in the cost effectiveness studies leukaemia and SCT patients were not included so they should be excluded from this recommendation!	Patients with stem cell transplants and leukaemia were excluded from the cost effectiveness analysis because inpatients have very different prophylaxis costs to those

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						patients receiving outpatient management. However the GDG agreed that the improvement in short term mortality outweighed the potential additional costs and decided to recommend prophylaxis with quinolones for adults with stem cell transplants and acute leukaemias.
British Society for Haematology & Royal College of Pathologists	17.10	Full	112	1	Find peculiar that there is a recommendation to offer quinolone prophylaxis, but no specific recommendation to either offer or not to offer growth factor prophylaxis. This is discussed in this rather lengthy text, but most readers will want quick and easy access to recommendations, both positive and negative, and will not want to have to search through some very complex health economic data. There should therefore be a statement of some sort about growth factors.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to

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						discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
					As primary prophylaxis with G-CSF for older patients undergoing CHOP-like chemotherapy is an explicit recommendation of the ASCO guidelines, the differing conclusion reached here would also benefit from being made clearer.	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
					There is also no health economic discussion	In order to investigate this effect we would

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					about the use of growth factors to maintain dose intensity in curable diseases such as diffuse large B-cell lymphoma, nor does the recommendation about quinolone prophylaxis include this group of diseases. R-CHOP carries a febrile neutropenia risk on >20%, to not use G-CSF in this group may be medicolegally indefensible.	need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline
					Many hospitals have stopped using quinolone prophylaxis, especially for inpatients, because of perceived risk of *C.difficile* and other hospital-acquired infections.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic

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						(<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in

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						infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
British Society for Haematology & Royal College of Pathologists	17.11	Full	121	1	Given the NCAG position that antibiotics should be given within 60 minutes, perhaps this should mirror that? There are commonly delays in treating patients with antibiotics when clinicians have to wait for the full blood count result. We have found that delays are avoided by treating before the count is available, making the pathway smoother. Clearly some patients may receive antibiotics inappropriately but it is safer.	We acknowledge that this is an important clinical issue and was debated at length by the GDG. However the evidence was not clear enough to recommend a specific time or specific clinical group where time to antibiotic delivery altered the patients outcome. Hence the recommendation does not define a specific time period or limit its indication to a specific clinical presentation.
British Society for Haematology & Royal College of Pathologists	17.12	Full	133	1	Use of monotherapy is at odds with the Surviving Sepsis Campaign guidelines which state that combination therapy should be considered in neutropenic patients: http://www.survivingsepsis.org/Pages/default.aspx Most clinicians would likely consider combination therapy in neutropenic patients showing signs of severe sepsis. Need also advice about antibiotics for patients	These recommendations are based on a systematic search and appraisal of the clinical evidence. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance. The recommendations made were based on the evidence appraised for this topic which did not support addition of aminoglycosides to any group as initial empiric therapy. Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills. This is explicitly stated in the methodology section of this guideline. The clinical question which generated the

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					with history of penicillin allergy.	recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.
British Society for Haematology & Royal College of Pathologists	17.13	Full	133	1	Insisting on the use of Tazocin monotherapy as first line treatment is also contentious as there are increasing rates of bacterial resistance and no provision for penicillin-allergic patients.	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy,

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					Once again although Tazocin monotherapy may be fine for the majority of out-patients combination with an aminoglycoside may well be far more appropriate for in-patients where there is an additional risk of resistant bacteria and also a significant risk of *S.aureus* (especially if an indwelling catheter is present) which at least will be treated with the gentamicin.	then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this. The recommendation states that there may be specific microbiological contraindications to monotherapy with piperacillin-tazobactam. However, the evidence appraised for this topic did not support addition of aminoglycosides to any group as initial empiric therapy.
British Society for Haematology & Royal College of Pathologists	17.26	Full	148		The authors do not appear to have given consideration to what oral antbiotics should be given, in many of the papers researching use of oral antbiotics for low risk neutropenic sepsis patients, a combination of a quinolone and broad-spectrum penicillin were given, but this combination may not be logical in patients who have been given prior ciprofloxacin prophylaxis.	We have stated in the linking evidence to recommendations section of section 6.5 that local microbiological resistance patterns vary. We have added text to clarify that choice of antibiotic may be influenced by prior prophylaxis. Consequently the GDG were unable to recommend a specific antibiotic strategy.
British Society for Haematology & Royal College of Pathologists	17.14	Full	154	20	Needs to be some discussion about considering other causes of fever, especially in those with prolonged neutropenia.	We acknowledge that persistent fever may be due to viral or fungal causes. However, these are clinical issues which have been explicitly excluded from the scope of the guideline. Consequently the evidence on this has not been appraised and we are unable to make recommendations on this issue.
British Society for Haematology & Royal College of Pathologists	17.15	Full	159	8	Welcome research recommendation on this page.	Thank you for your comment.

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British Society for Haematology & Royal College of Pathologists	17.16	Full	163	1	Find this thoroughly confusing! Presume this means discharge on oral antibiotics? This recommendation needs to be made much clearer.	The recommendations allow for discharge of patients and/or stepping down to oral antibiotics. This is because while most patients who could be discharged early are able to tolerate oral antibiotics, some may have a specific contraindication which requires IV antibiotics. However, these patients can be discharged if facilities exist to deliver outpatient IV antibiotics. The social circumstances of some patients may mean they are not able to be discharged but are still able to step down to less resource intensive regimens for example oral antibiotics. We have added to the linking evidence to recommendations section to clarify this.
British Society for Haematology & Royal College of Pathologists	17.17	Full	166	1	The second part of this recommendation is very vague and hard to reconcile with previous two.	The recommendations allow for discharge of patients and/or stepping down to oral antibiotics. This is because while most patients who could be discharged early are able to tolerate oral antibiotics, some may have a specific contraindication which requires IV antibiotics. However, these patients can be discharged if facilities exist to deliver outpatient IV antibiotics. The social circumstances of some patients may mean they are not able to be discharged but are still able to step down to less resource intensive regimens for example oral antibiotics. We have added to the linking evidence to recommendations section to clarify this.

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						We have amended the wording of the recommendation to clarify that it relates to "all" patients.
British Society for Haematology & Royal College of Pathologists	17.20	Full	199	6	Many haematologists/oncologists are advised not to use ciprofloxacin because of the issue of *C.difficile*, which has become more prevalent in recent years since most of the trial evidence quoted.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme

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						alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Central South Coast Cancer Network	11.17	Full			General – There is no discussion within this document of the use of G-CSF in the treatment of patients with neutropenic sepsis, this is established practice for many clinicians, and the drug is probably overused in this regard, but in patients with severe sepsis it may be desirable to give treatment that may speed up neutrophil recovery, so not to discuss this issue is a major omission.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. However, the management of patients with severe sepsis by intensive/critical care units was specifically excluded from the scope of this guideline. Therefore we have not investigated this issue and cannot make recommendations on it.
Central South Coast Cancer Network	11.18	Full	General		There are commonly delays in treating patients with antibiotics when clinicians wait for the full blood count with the absolute neutrophil count. We have found that delays are avoided by treating before the count is available makes the pathway smoother. Clearly some patients may receive antibiotics inappropriately but it is safer.	We agree. The guideline recommends that patients with suspected neutropenic sepsis should be treated as an acute medical emergency.
Central South Coast Cancer Network	11.19	Full	General		It would be helpful if there was more emphasis on the importance of patients' infective history and local antibiotic resistance patterns. Where a patient has had culture positive results with	We agree that this may be important but this topic was not identified as a priority for investigation in the guideline because the GDG considered there would only be a small

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					resistant organisms then different antibiotics would be used first time. It is important for the patient to carry this information. We have had patients treated at other hospitals (commonly occurs with Centres/Units) arrived septic in ED and were known to have multi-resistant organism. It is of critical importance this information is available wherever the patient in being treated.	proportion of patients for whom their infective history would significantly alter treatment. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it.
Central South Coast Cancer Network	11.00	Full	20		Not only patients on anti-cancer treatments that develop neutropenic sepsis, may also occur in patients with other inherited or acquired defects in neutrophil number/function e.g. MDS, aplastic anaemia	The remit for this guideline was to develop recommendations on the prevention and management of neutropenic sepsis in cancer patients. Consequently we have not looked at any other patient groups.
Central South Coast Cancer Network	11.01	Full	20		This is a restrictive definition of neutropenic sepsis, e.g. patients on steroids may not develop fever	We agree that patients with neutropenic sepsis may not present with fever but have other symptoms and signs consistent with significant infection. We have amended the recommendations and algorithm to reflect this
Central South Coast Cancer Network	11.02	Full	21		Confused by boxes at bottom of flowchart, especially 3rd and 4th ones, which appear in conflict, are we discharging patients, stepping down to oral antibiotics or both?	The recommendations allow for discharge of patients and/or stepping down to oral antibiotics. This is because while most patients who could be discharged early are able to tolerate oral antibiotics, some may have a specific contraindication which requires IV antibiotics. However, these patients can be discharged if facilities exist to deliver outpatient IV antibiotics. The social circumstances of some patients may mean they are not able to be discharged but are still able to step down to less resource intensive regimens for example oral antibiotics. We have added to the linking evidence to recommendations section to clarify this.

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Central South Coast Cancer Network	11.03	Full	23	28	I feel that the one hour door to needle time is now well established in most hospitals as a target for patient with suspected neutropenic sepsis, it is disappointing that the recommendations in this document are so vague, the door to needle time concept should be preserved.	This text is from the needs assessment which describes current practice in the UK. It does not examine the evidence nor does it make recommendations for future practice. We acknowledge that this is an important clinical issue and was debated at length by the GDG. However the evidence was not clear enough to recommend a specific time or specific clinical group where time to antibiotic delivery altered the patients outcome. Hence the recommendation does not define a specific time period or limit its indication to a specific clinical presentation.
Central South Coast Cancer Network	11.04	Full	37	11	Welcome idea of national prospective audit	Thank you for your comment.
Central South Coast Cancer Network	11.05	Full	42	6-7	Believe that this should read "A single study in 102 patients (Apostolopoulou, et al., 2010) reported that ANC >0.5 x 6 10^9 / litre has high negative predictive value for bacteraemia".	We believe the original statement is correct. In the Apostolopoulou study if a person did not have ANC<0.5. x 6 10^9 /litre (if their was ANC≥0.5 x 6 10^9/litre) there was a high probability that they did not have bacteraemia.
Central South Coast Cancer Network	11.06	Full	42	29	Would like some reminder about caveats in diagnosing suspected neutropenic sepsis e.g. effects of steroids in masking pyrexia. Also risk of severe and overwhelming sepsis exist in patients with some haematological conditions, or treated with certain agents e.g. purine analogues, even when not neutropenic. This section would benefit from stronger cross-linking with section 4. It is important to bear in mind that someone with a neutrophil count of 0.6 may have a neutrophil count of 0.1, 24 hours later, and figure 1.7 reveals that the majority of	We agree that patients with neutropenic sepsis may not present with fever but have other symptoms and signs consistent with significant infection. We have amended the recommendations and algorithm to reflect this. The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or

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					centres use neutrophils of <1.0 as a cut off – the NICE definition of neutropenic sepsis may be too restrictive.	unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of ≤0.5.
Central South Coast Cancer Network	11.07	Full	61	28	Although this is discussed in the text, it is not clear from this recommendation box whether peripheral blood culture is being recommended instead of, or as well as, central cultures in patients with CVC.	We have added "additional" to this recommendation for clarity.
Central South Coast Cancer Network	11.08	Full	65	1	This should read "Oncology or Haematology team", puzzled as to where 48 hours has come from – this will not be achievable in many DGH's where oncologist's may only visit, would within "one working day" be better?	For clarity, the GDG have amended the recommendation to "a healthcare professional with competence in managing complications of anti-cancer treatment". The GDG have reviewed this recommendation, and felt that to improve the patient experience and clinical management a patients risk of septic complications should be assessed within a maximum of 24 hours of presentation.
Central South Coast Cancer Network	11.09	Full	112	1	Find it peculiar that there is a recommendation to offer Quinolone prophylaxis, but no specific recommendation to either offer or not to offer growth factor prophylaxis. This is discussed in this rather lengthy text, but most readers will want quick and easy access to recommendations, both positive and negative,	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity.

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					and will not want to have to search through some very complex health economic data. There should therefore be a statement of some sort about growth factors.	Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of

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						G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
					As primary prophylaxis with G-CSF for older patients undergoing CHOP-like chemotherapy is an explicit recommendation of the ASCO guidelines, the differing conclusion reached here would also benefit from being made clearer.	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
					There is also no health economic discussion about the use of growth factors to maintain dose intensity in curable diseases such as diffuse large B-cell lymphoma, nor does the recommendation about Quinolone prophylaxis include this group of diseases. R-CHOP carries a febrile neutropenia risk on >20%, to not use G-CSF in this group may be medicolegally indefensible.	In order to investigate this effect we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in

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						these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline
					Many hospitals have stopped using Quinolone prophylaxis, especially for inpatients, because of perceived risk of *C.difficile* and other hospital-acquired infections.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5).

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						The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Central South Coast Cancer Network	11.10	Full	121	1	Given the NCAG position that antibiotics should be given within 60 minutes, perhaps this should mirror that?	We acknowledge that this is an important clinical issue and it was debated at length by the GDG. However the evidence was not clear enough to recommend a specific time or specific clinical group where time to antibiotic delivery altered the patients outcome. Hence the recommendation does not define a specific time period or limit its indication to a specific clinical presentation.

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Central South Coast Cancer Network	11.11	Full	133	1	Use of monotherapy is at odds with the Surviving Sepsis Campaign guidelines which state that combination therapy should be considered in neutropenic patients: http://www.survivingsepsis.org/Pages/default.aspx Most clinicians would likely consider combination therapy in neutropenic patients showing signs of severe sepsis. Need also advice about antibiotics for patients with history of Penicillin allergy.	These recommendations are based on a systematic search and appraisal of the clinical evidence. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance. The recommendations made were based on the evidence appraised for this topic which did not support addition of aminoglycosides to any group as initial empiric therapy. Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills. This is explicitly stated in the methodology section of this guideline. The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy,

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						then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.
Central South Coast Cancer Network	11.12	Full	148		No consideration given to what oral antibiotics should be given. In many of the papers researching use of oral antibiotics for low risk neutropenic sepsis patients, a combination of Quinolone and broad spectrum Penicillin were given, but this combination may not be logical in patients who have been given prior Ciprofloxacin prophylaxis.	We have stated in the linking evidence to recommendations section of section 6.5 that local microbiological resistance patterns vary. We have added text to clarify that choice of antibiotic may be influenced by prior prophylaxis. Consequently the GDG were unable to recommend a specific antibiotic strategy.
Central South Coast Cancer Network	11.13	Full	154	20	Needs to be some discussion about considering other causes of fever, especially in those with prolonged neutropenia.	We acknowledge that persistent fever may be due to viral or fungal causes. However, these are clinical issues which have been explicitly excluded from the scope of the guideline. Consequently the evidence on this has not been appraised and we are unable to make recommendations on this issue.
Central South Coast Cancer Network	11.14	Full	159	8	Welcome research recommendation on this page.	Thank you for your comment.
Central South Coast Cancer Network	11.15	Full	163	1	Thoroughly confused, presume this means discharge on oral antibiotics? This recommendation needs to be made much clearer.	The recommendations allow for discharge of patients and/or stepping down to oral antibiotics. This is because while most patients who could be discharged early are able to tolerate oral antibiotics, some may have a specific contraindication which requires IV antibiotics. However, these patients can be discharged if facilities exist to deliver outpatient IV antibiotics. The social circumstances of some patients may mean

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						they are not able to be discharged but are still able to step down to less resource intensive regimens for example oral antibiotics. We have added to the linking evidence to recommendations section to clarify this.
Central South Coast Cancer Network	11.16	Full	166	1	The second part of this recommendation is very vague and hard to reconcile with previous two.	The recommendations allow for discharge of patients and/or stepping down to oral antibiotics. This is because while most patients who could be discharged early are able to tolerate oral antibiotics, some may have a specific contraindication which requires IV antibiotics. However, these patients can be discharged if facilities exist to deliver outpatient IV antibiotics. The social circumstances of some patients may mean they are not able to be discharged but are still able to step down to less resource intensive regimens for example oral antibiotics. We have added to the linking evidence to recommendations section to clarify this. We have amended the wording of the recommendation to clarify that it relates to "all" patients.
Central South Coast Cancer Network	11.20	Full	199	6	GCSF antibiotic prophylaxis (full guidance p199, line 6) We are advised not to use Ciprofloxacin because of the issue of C difficile. This has become more prevalent in recent years since most of the trial evidence quoted.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($<0.5 \times 10^9$/litre) and only during the period of expected neutropenia.

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						The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is

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						done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Clatterbridge Centre for Oncology	13.00	Full	General		No guidance in penicillin allergy, common event but only one line of therapy suggested	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.
Clatterbridge Centre for Oncology	13.02	Full	General		Klastersky et al 2000 not used in the original paper as suggested in the NICE document, it was not used as an oral step down tool or a tool to predict discharge. Using a step down approach has given rise to an anecdotal increase in complications in patients with neutropenic sepsis as we have had an increase in the cases of clostridium difficile.	Although Klastersky et al (2000) did not use the MASCC score as a part of a therapeutic strategy, other studies have (see section 7.3 for evidence from studies using MASCC criteria for early discharge: Cerif et al 2006, Girmenia et al 2007, Klatersky et al 2006). Additionally there are published (Dommett 2009) and unpublished data (from Leeds Childrens Hospital) which support the roll-out of a step-down approach without an increase

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						in complication rates.
Clatterbridge Centre for Oncology	13.03	Full	General		Borderline cases were not discussed within the document, this is where the patient doesn't fulfil the actual definition of neutropenic sepsis however has a low grade temperature and a degree of neutropenia. This is a key area when inappropriate antimicrobial stewardship occurs and is an area where clarification would be useful.	Thank you for your comment. The scope of the guideline does not cover borderline cases. The guideline covers the prevention and management of neutropenic sepsis in cancer patients.
Clatterbridge Centre for Oncology	13.04	Full	General		Within the guidance relating to antimicrobial prophylaxis it does not refer to the risks associated with clostridium difficile precipitated by the use of quinolone antibiotics. There has been no consideration as to the enormity of the issue, with a potential 30,000 courses of antimicrobials being given as prophylaxis with the Merseyside and Cheshire network in the course of a year. It is also at odds with key recommendations about stewardship of antimicrobials. Not all patients receiving systemic anticancer therapy will have the same risk of neutropenia thus potentially reducing the amounts of antimicrobials to be given. This is a big cause for concern with a NNT of 11, 10 patients may be at risk of harm. Within the North West region the antimicrobial pharmacists have also raised concerns about this	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($<0.5 \times 10^9$/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a

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						standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Clatterbridge Centre for Oncology	13.05	Full	General		Concerns regarding G-CSF, this is currently funded by the commissioners for high risk regimens. If quinolones are to be used as prophylaxis, concerns are that this funding would no longer be there for primary prophylaxis with G-CSF. This is an important tool to maintain dose intensity for patients who are having adjuvant treatments.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF

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						in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
Clatterbridge Centre for Oncology	13.01	Full	41	29	Worried about the neutrophils being defined as 0.5×10^9 rather than 1×10^9 feel that this has a positive predictive value and would prevent harm to patients	The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-

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						threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of ≤0.5.
Department of Health	22.10	Full	General		Recommendations on the Use of Growth Factors -There has been much voiced concern that the scope for the guidance in relation to the use of GCSF (and GMCSF) was wrong at the outset. The main issues raised are: • The review of GCSF only considers 'survival during anticancer treatment' and does not consider any survival advantage for giving GCSF for maintaining dose intensity which is the key reason for its use in many patients.	The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose. A recommendation on the use of G-CSF for

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						the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation.
					• The review considers giving GCSF to all patients. All international guidelines recommend using GCSF on the basis of the risk of febrile neutropenia. Therefore there is no assessment of the point at which GCSF may become cost effective, based on such risk assessments.	Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with recommendations in other non-NICE guidance. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY.
					• The draft goes against well-established clinical practice. 95% of acute Trusts that were surveyed by the GDG use GCSF as primary prophylaxis in high risk patients, in	The recommendations in this guideline are based on a systematic search and appraisal of the clinical evidence and where relevant the results from a health economic model.

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					line with local clinical guidelines. This is established clinical practice and was not acknowledged.	Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
					• The GDG did not appropriately stratify for risk factors for FN (by taking into account patient or regimen characteristics). Indeed the GDG combined evidence in patients with different types of cancer, receiving different risk of chemotherapies, with different patient factors and with different treatment intent.	We agree that the evidence for this recommendation has been drawn from heterogeneous populations. We have attempted to reduce the population heterogeneity by excluding paediatric patients, patients receiving inpatient chemotherapy and patients whose regimen includes G-CSF from the model. In addition we have performed sub-group analysis for patients with solid tumours, non-Hodgkin lymphoma and Hodgkin lymphoma. The potential effect of this heterogeneity on the health economic model results has been assessed by sensitivity analysis on the relevant model inputs. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. The results of all one-way sensitivity analyses have been added to the guideline.

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					• The guidance implies that no patient should be offered GCSF except with high intensity chemotherapy. However 'high intensity' is not defined and it is not clear whether this would include high risk chemotherapy regimens such as TAC, FEC-T or CHOP 21 where the prescribing of GCSF is routine practice.	The consultation version of the guideline did not make any recommendations on the use of GCSF. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation.
					• GCSF is available at NHS contract prices that are significantly lower than the NHS list price.	As stated in the linking evidence to recommendations section, whilst the GDG acknowledged that clinicians in some settings are able to source G-CSF products at substantially reduced cost, it was noted that these arrangements are fluid and regional and therefore no national recommendations can be based on these discounted costs. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was

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						unlikely that PEG-G-CSF would be available at these levels of discount.
					• There are some concerns about the cost-effectiveness model. It was felt that this was not consistent with the NICE reference case: the time horizon was too short to capture all potential costs and benefits,	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations. Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect

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						of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
					and the model uses an efficacy for antibiotics that is almost double than that demonstrated in the only large scale randomised control trial.	The effectiveness estimates for antibiotics were derived from a meta-analysis of relevant studies. Larger studies with more events, such as Cullen et al 2005, therefore had greater weight in our estimates. However, our conclusions were robust when using reduced effectiveness estimates, such as the suggested relative risk of 0.72 for NS events from Cullen et al, 2005.
					The GDG was limited in its scope and it is recognised that this period 'may be too short to adequately assess the benefits of GCF use in encouraging clinicians to proceed in treatments with greater dose intensity'. The draft guidance also recognises that GCSF products may be sourced at 'substantially reduced prices which could potentially make its use cost effective'. The draft guidance also contains the following statement: 'Balancing these elements of uncertainty against the high ICER described by the economic model led to a strong decision not to recommend the use of GCSF for the prevention of infectious complications and death from neutropenic sepsis but also not to recommend that the use of these agents for other indications is discontinued'.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid

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					Currently, GCSF is prescribed on the basis of a risk assessment with the aim to reduce febrile neutropenia during the chemotherapy cycle and facilitate optimal relative dose intensity by the prevention of chemotherapy induced neutropenia and febrile neutropenia, this improving short term mortality and survival. There are real concerns that as these guidelines are often used by commissioners; the detailed review of the evidence and the extremely high ICER for GCSF in the prevention of neutropenic sepsis may be used as a basis for withdrawing funding for GCSF in this setting. This would have major implications for future treatment and UK survival outcomes: • High and medium risk patients treated with antibiotics may remain neutropenic and therefore the inability to maintain dose intensity will impact on their long term survival.	and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis. A recent meta-analysis (Shitara et al., 2011) shows that neutropenia experienced during chemotherapy is actually associated with improved survival in patients with advanced cancer or haematological malignancies undergoing chemotherapy. This implies that experiencing side effects of chemotherapy

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					• Physicians may be reluctant to give high and medium risk chemotherapy with just antibiotics as support and therefore elect to use a less aggressive and less effective chemotherapy, which would also impact on the patient's long term survival. • The guideline states that a patient's treatment should stop after two neutropenic events.	might not be associated with impaired long term survival.
Department of Health	22.11	Full	General		In conclusion, there is a great deal of concern about the guidance in its current form. The following suggestions have been made: • The scope of the guidance is increased to also cover the use of GCSF to maintain dose intensity.	The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose. It is not possible to amend the scope at this stage.
					• The final guideline should say that the recommendations are not relevant for all patients. Either the prevention	We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant

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					recommendations in the guideline should be removed (i.e. it becomes a guideline on management only) OR the guideline should explicitly state that patients receiving high or medium risk chemotherapy are not included in the prevention recommendations. • The suggested widespread use of quinolone as prophylaxis needs further discussion within the microbiology community.	neutropenia ($\leq$0.5 x 10^9/ litre) is an anticipated consequence of chemotherapy. A microbiologist was appointed to the GDG who was able to advise on prophylaxis and treatment of neutropenic sepsis. Comments have been received from the microbiology community as part of the consultation on the draft guideline. These have all been responded to as part of the consultation process.
Department of Health	22.00	Full	5	5	The definition of neutropenic sepsis is too narrow. There are concerns that a neutropenic patient in septic shock may be missed if they have a 'normal' temperature.	We agree that patients with neutropenic sepsis may not present with fever but have other symptoms and signs consistent with significant infection. We have amended the recommendations and algorithm to reflect this. The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. The evidence also showed that increased temperature was associated with an increase in infection. The lowest value for fever studied

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						in the evidence was 38°C and the GDG decided to adopt this value in their definition for neutropenic sepsis.
Department of Health	22.01	Full	5	19	In general it was felt that this was comprehensive. However, the inclusion of lactate measurement has caused some comment as this is not routine practice. Although it may be useful in determining sick patients, a patient with a high temperature and neutropenia would probably still be treated with antibiotics, even if the lactate was within the normal range.	Thank you for your comment, as documented in the linking evidence to recommendations section of section 4.2.1, the evidence indicated that raised levels of lactate were suggestive of a patient being at increased risk of severe sepsis.
Department of Health	22.02	Full	5	22	Assessing the Patients Risk of Septic Complications - It was agreed that this was good practice and underpins the national developments with the development of Acute Oncology Services, which it may be helpful to refer to, within the guidance. The guidance also recommends that the patients risk of complications should be assessed, 'basing the risk assessment on presentation features and using a validated scoring system'. It is felt that the guidance should incorporate a validated risk scoring system within it, so that that a consistent approach could be adopted.	Examples of validated scoring systems include: • the Multinational Association for Supportive Care in Cancer (MASCC) risk index for adults (aged 18 years and over) (Klastersky J, Paesmans M, Rubenstein EB et al. [2000] The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients (Journal of Clinical Oncology 18: 3038–51) • the modified Alexander rule for children (aged under 18) (Dommett R, Geary J, Freeman S et al. [2009] Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting (European Journal of Cancer 45: 2843–9). These have been included as footnotes within the guideline.

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Department of Health	22.03	Full	5	28	The recommendation in the guidance is to 'offer prophylaxis with a quinolone during the expected period of neutropenia to all adult patients (18 years or over) with acute leukaemia, stem cell transplants or solid tumours. This goes against current practice and many Trusts have restrictive antibiotic guidelines particularly around the use of agents such as fluoroquinolones (ciprofloxacin). It is believed that the microbiology community will refute the proposed benefits outlined in the document and there are some very real concerns about the potential huge increase in antibiotics use within individual hospitals and the general population. As well as the increased risk of C Difficile, there are concerns about the risk of resistance development. In addition, it has been noted that the DH and HPA produced guidance in 2008 that stated that the use of fluoroquinolones should be minimised. It was felt that this single recommendation needed further input from the wider microbiology community. Also, such a blanket recommendation was felt to be inappropriate as it may not be deemed necessary for all chemotherapy regimens.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($<0.5 \times 10^9$/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only

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						be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Department of Health	22.04	Full	5	37	Empiric Intravenous Antibiotic Monotherapy or Intravenous Antibiotic Dual Therapy This has caused significant concern, as many Trusts will have developed local clinical guidance developed on the basis of their local infection rates. Other concerns include: • The recommendation to offer beta lactam monotherapy ignores the huge rise in Extended Spectrum Beta-lactamase (ESBL) producing colifoams over the last few years. ESBL are resistant to the actions of penicillin/beta lactamase combinations such as Tazocin. In addition, prior quinolone use is also a risk factor for subsequent ESBL infection. • Although monotherapy may be appropriate for oncology patients, it is felt less so for haematological patients. • The guidance also does not make any recommendations for the treatment of	Thank you for your comment, we agree that in some areas of the country, resistance to piperacillin-tazobactam will make monotherapy with this agent an inappropriate empiric antibiotic therapy. We have acknowledged this in the current wording of the recommendation and in the linking evidence to recommendations section of section 6.2. In such situations an appropriate empiric antibiotic therapy may be dual therapy including an aminoglycoside, or an alternative monotherapy, for example a carbapenim, but such decisions need to be based on local microbiological resistance patterns and can't be specified in the recommendation The analysis of the trial data did not clearly indicate any group (for example, haematology patients) in whom the data was more or less compelling (see evidence section of section 6.2) The clinical question which generated the recommendation to offer beta lactam

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					patients who have beta lactam hypersensitivity. This is a relatively common occurrence and requires mention.	monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of hypersensitivity as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.
					• It is also felt that the recommendation to 'not offer empiric glycopeptides to patients with neutropenic sepsis who have a central venous access device' requires qualification with the addition of the word 'routinely'. There may be situations for example treating a known MRSA carrier or someone with previous MRSA infections where initial empiric treatment with vancomycin or teicoplanin may be appropriate. It is felt that this needs to be discussed with the wider microbiology community before being adopted.	We have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern. A microbiologist was appointed to the GDG who was able to advise on prophylaxis and treatment of neutropenic sepsis. Comments have been received from the microbiology community as part of the consultation on the draft guideline. These have all been

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						responded to as part of the consultation process.
Department of Health	22.05	Full	5	41	The recommendation to 'not offer empiric glycopeptides to patients with neutropenic sepsis who have a central venous access device' requires qualification with the addition of the word 'routinely'. There may be situations for example treating a known MRSA carrier or someone with previous MRSA infections where initial empiric treatment with vancomycin or teicoplanin may be appropriate. Again, it is felt that this needs to be discussed with the wider microbiology community before being adopted.	Thank you for your comments, we have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern. A microbiologist was appointed to the GDG who was able to advise on prophylaxis and treatment of neutropenic sepsis. Comments have been received from the microbiology community as part of the consultation on the draft guideline. These have all been responded to as part of the consultation process.
Department of Health	22.06	Full	5	46	*Inpatient vs. Outpatient Management Strategies.* Although this is supported it clearly needs to be backed up by the ability to rapidly review and readmit patients. There is also no mention of the oral antibiotics to use in this clinical setting. However, the quinolones are likely to have a role in this setting and again there is a risk of the development of C Difficile. In addition, if a patient develops a bacteraemia while receiving quinolone prophylaxis, it is possible that the isolate would be quinolone resistance and guidelines relating to the management of this should be outlined. It was felt that there should be guidance on the use of a validated tool within	Thank you for your comment, we have stated in the linking evidence to recommendations section of section 6.5 that local microbiological resistance patterns vary and consequently the GDG were unable to recommend a specific antibiotic strategy. We have added text to clarify that choice of antibiotic may be influenced by prior prophylaxis. Decisions on what to use in the event of quinolone resistance would need to be based on local microbiological resistance patterns and cannot be specified in a recommendation.

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					the document, to ensure that it is applicable to all scenarios.	
Department of Health	22.07	Full	10	36	Scope of Guidance - There are concerns that the scope of guidance was inappropriate at the outset. It is understood that these issues were raised in previous consultations. The main concerns are: • In the guidance, all patients are grouped together, regardless of the risk of neutropenic sepsis. The guidance does not take into account the actual aim of treatment, i.e. whether the intent of treatment is curative or palliative. • The review of GCSF only considers 'survival during anti-cancer treatment' and does not consider the survival advantage of giving GCSF to maintain dose intensity which is the key reason for its use in many patients. The GDG felt that this indication was outside of the scope of the guidance.	We believe this comment refers to chapter 5. Different subgroups of patients were investigated. The risk of neutropenic sepsis and the intent of treatment were assessed in the cost-effectiveness model through sensitivity analyses. The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on

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						subsequent chemotherapy scheduling and dose. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for this indication should be acknowledged in the recommendation.
					• It is felt that although the guidance is relatively sound on the identification and treatment of neutropenic sepsis, it is very poor in its discussion of prophylaxis. The emphasis on antibiotic (predominantly quinolone usage) rather than growth factors ignores international guidelines (such as those from EORTC and ASCO), current UK practice and the potential problem of antibiotic resistance.	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations in this guideline are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with recommendations in other non-NICE guidance and current practice. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision

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						of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard.

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						The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Department of Health	22.08	Full	11	10	Membership of Guideline Development Group - The group did not include a Haemato-Oncologist from any of the major units, and therefore the current handling of neutropenic sepsis may not have been understood.	When deciding on the constitution of a GDG, several factors are considered. The specialties on the GDG need to be consistent with the topics in the guideline scope. There also needs to be a balance between the number of individuals from the same specialty who are represented on the GDG so that it is not dominated by one group. It is also important that the individuals on the GDG have a reasonable geographic distribution, so that variations in clinical practice across the UK can be better understood. The total number of people on the group also needs to be limited in order that the group can function effectively. To ensure the correct balance of GDG membership has been achieved, the proposed list of specialties is checked and approved by NICE before it is advertised. It is also discussed at the scoping workshop where stakeholders have an opportunity to comment. The GDG adverts did not preclude haematologists from applying on the group.Appointments to the group were made to the best available candidates and this was in line with NICE's recruitment policies and processes.

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						We have no concerns about the membership or specialist constitution of the GDG. The range of specialists groups represented on the GDG was agreed by the relevant Associate Director. We strongly disagree that the current handling of neutropenic sepsis may not have been understood by the GDG. The consultant haemato-oncologist on the group works in a cancer centre that treats all haematological malignancies including acute leukaemia.
					In addition, the group did not include a cancer pharmacist or an anti-microbial pharmacist. Cancer pharmacists in most centres would be directly involved with the development of guidelines on both prophylaxis and treatment of neutropenic sepsis. Anti-microbial pharmacists would also have a role in the development of guidelines in this in this area.	Thank you for your comment. At the time of scoping this guideline it became clear that the principal issue on antibiotic prescribing would be choosing drugs based on patterns of antibiotic resistance; this would be guided by the microbiologist on the GDG. Although the guideline recommends the classes of drugs that would be appropriate, it does not address the details of individual drugs and their administration, therefore the specific expertise of a pharmacist for these issues was not needed.
Department of Health	22.09	Full	32	34	The draft goes against established UK clinical practice. The GDG's own survey revealed that 95% of acute trusts surveyed use GCSF primary prophylaxis. This is now agreed clinical practice which is not acknowledged.	The recommendations in this guideline are based on a systematic search and appraisal of the clinical evidence and where relevant the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance. The GDG agreed that there was enough variation in practice in the prophylaxis of

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						neutropenic sepsis to warrant investigating this topic, particularly with regard to cost-effectiveness.
East Midlands Cancer Network	42.03	Full	5 and 58	18-19 37	MSU is not mentioned and should be routinely sent in neutropenic patients. Urinalysis may not predict severely septic patients, but a positive MSU culture can help identify what bacterial infection the patient has and help guide a change / step down in antibiotics and so MSU is clinically very useful	MSU was not identified as a priority for investigation in the guideline as the question focussed on investigations that would influence emergency empiric assessment. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it.
East Midlands Cancer Network	42.00	Full	5 and 42	5 29	Definition of neutropenic sepsis should say neutrophils < 1.0 not 0.5. This is the working definition for the majority of hospitals as shown on Fig 1.7 and 1.8 and it is well known that after chemotherapy the neutrophil count can drop rapidly and a level of 0.9 in the morning may well be < 0.5 later that same day and not to treat these patients as neutropenic sepsis will lead to more deaths	The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of $\leq$0.5.
East Midlands Cancer Network	42.17	Full	5 54	19 35	Re. Recommendation to include in the initial clinical assessment of patients with suspected neutropenic sepsis: lactate - The recommendation with regards lactate surprised us. Practically we	This recommendation describes what tests to perform in the initial clinical assessment. This should not influence the clinical decision to treat somebody with suspected neutropenic sepsis as an acute medical emergency.

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					would question the value of this for all patients as we would suspect that we would treat someone with antibiotics if they had a high temperature and neutropenia even if they had a normal lactate.	As documented in the linking evidence to recommendations section of section 4.2.1, the evidence indicated that raised levels of lactate were suggestive of a patient being at increased risk of severe sepsis.
East Midlands Cancer Network	42.04	Full	5 and 65	22 1	This should read oncology / clinical haematology team depending on which specialty the patient is under	Thank you for your comment. For clarity, the GDG have amended the recommendation to "a healthcare professional with competence in managing complications of anti-cancer treatment"
East Midlands Cancer Network	42.02	Full	5 and 9 and 22	27 52 12	This policy should be aimed to prevent neutropenic septic deaths in any neutropenic patients whether or not they have cancer. These days many rheumatoid arthritis patients and ulcerative colitis patients receive cytotoxic chemotherapy drugs eg methotrexate and 6 mercaptopurine and this policy should equally apply to them.	Thank you for your comment. However the scope of the guideline only covers the prevention and management of neutropenic sepsis in cancer patients.
East Midlands Cancer Network	42.05	Full	5	29	Use of quinolone prophylaxis – this is controversial and there is no mention here about the increased risk of hospital acquired infections for patients treated with quinolone prophylaxis which is a major issue eg C difficile and MRSA. A distinction should be made between patients receiving out patient chemotherapy where quinolone prophylaxis may be entirely reasonable and those being treated as in patients where the risk of HAI is too great and we have not used quinolones in this group for many years	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($<0.5 \times 10^9$/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a

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						potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
East Midlands Cancer Network	42.06	Full	5	29	Use of quinolone prophylaxis - The evidence for the proposed benefits of quinolone prophylaxis is disputed by some microbiologists but more	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the

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					importantly we are now living in the era of C. Difficile 027 (CDI) which is a potentially life-threatening infection. Use of antibacterial prophylaxis may promote the development of bacterial resistance and the risk of superinfection with organisms including methicillin resistant S. aureus and CDI. There have been well documented outbreaks of CDI in North America and in the UK at Stoke Mandeville Hospital, Maidstone & Tunbridge Wells NHS Trust and others. There are several hospitals in our region which had excellent records vis-à-vis CDI and have witnessed 027-related deaths. The associated targets for reducing CDI in NHS Trusts could be thrown off track by increased use of quinolones. The DH and HPA produced guidance in 2008 that states: "Restrictive antibiotic guidelines should be developed by trusts, through the AMT, stressing the following recommendations: * Use narrow-spectrum agents for empirical treatment where appropriate. * Avoid use of clindamycin and second- and third-generation cephalosporins, especially in the elderly. * Minimise use of fluoroquinolones, carbapenems and prolonged courses of aminopenicillins." The DH and HPA's recommendations on	GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this

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					fluoroquinolones was a grade B recommendation ie strongly recommended and supported by non-RCT studies and/or by clinical governance reports and/or the Code. As such we would suggest that the recommendation that "all adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours" are offered prophylaxis with a quinolone is discussed and agreed with the Healthcare Associated Infection and Antimicrobial Resistance Group at DH, with the HPA and with the wider microbiology community.	standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis. Comments have been received from the microbiology community, Department of Health and HPA as part of the consultation on the draft guideline.
East Midlands Cancer Network	42.08	Full	5 and 121	34 1	The recommendation for the 'immediate' administration of IV antibiotics should be defined. The NCEPOD recommendations say within 30 minutes although realistically most Trust aim for within 1 hour see table 1.3 pg 34 and one of these time points should be chosen to allow audit	We acknowledge that this is an important clinical issue and was debated at length by the GDG. However the evidence was not clear enough to recommend a specific time or specific clinical group where time to antibiotic delivery altered the patients outcome. Hence the recommendation does not define a specific time period or limit its indication to a specific clinical presentation.
East Midlands Cancer Network	42.15	Full	8 154	14-19 1	Recommendation to switch from IV to oral antibiotic therapy after 48 hours of treatment in patients whose risk of developing septic complications has been re-assessed as low by a healthcare professional with recognised professional competence in managing complications of anti-cancer treatment using a validated risk scoring system. - The GDG do not recommend which oral treatment to use but it is our understanding that the quinolones	We have stated in the linking evidence to recommendations sections that local microbiological resistance patterns vary. We

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					would be most useful in this respect. There are two issues here: the issue of CDI covered already and the fact that if a patient develops a breakthrough bacteraemia while on quinolone prophylaxis, it's not beyond the bounds of probability that the isolate will be quinolone resistant. In this scenario guidance would be required. - We also have concerns with the referenced validated scoring system. We feel that MASCC criteria are very complex particularly for those areas which have not used them previously. We are also aware they were derived in order to assess suitability for, amongst other things, oral treatment in an era (published in 2000) when quinolone resistance was much lower than it is now and there was no 027 CDI	have added text to clarify that choice of antibiotic may be influenced by prior prophylaxis. Consequently the GDG were unable to recommend a specific antibiotic strategy. Decisions on what to use in the event of quinolone resistance would need to be based on local microbiological resistance patterns and cannot be specified in a recommendation. We have specified in the recommendation that the validated risk scoring system should be used by a healthcare professional with recognised professional competence in managing complications of anti-cancer treatment. We have also recommended that training should be provided for these individuals. We have no reason to believe that the risk scoring system has become less discriminatory over time (see Evidence Review, page 158, lines 2-3).
East Midlands Cancer Network	42.01	Full	42	29	Replace the term anti-cancer drug with cytotoxic drug as many patients with non malignant conditions are treated with cytotoxic drugs which may cause neutropenia, but junior doctors may not treat appropriately if the drugs are not being used to treat cancer	Cytotoxic drugs cover more than just anti-cancer drugs. The scope of this guideline is restricted to cancer patients so we are unable to make this change.
East Midlands Cancer Network	42.14	Full	70	4	Re. Prevention There are other methods of protecting patients from neutropenic sepsis but everything in the draft guidance centres around prophylaxis. Should diet, for example, of been discussed?	We acknowledge that there are other potential methods of protecting patients from neutropenic sepsis however this was not identified as a priority for investigation in the guideline because the GDG agreed that there

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						was greater uncertainty and controversy surrounding the use of antibiotics and G-CSF prophylaxis. Therefore the evidence on these other methods has not been appraised and we are unable to make recommendations on it.
East Midlands Cancer Network	42.07	Full	84	1	The group have compatred quinolone prophylaxis to cotrimoxazole but have not considered the use of oral colistin which is widely used as prophylaxis and should be discussed and considered	After including co-trimoxazole in the PICO the guideline group decided that (due to changing anti-microbial resistance patterns) the cotrimoxazole trials were no longer a relevant comparator to quinolones or G-CSF. The justification is given in the linking evidence to recommendations section. Colistin was not included as a comparator because the GDG thought it was infrequently used in current practice and of low efficacty. Therefore the evidence on this has not been appraised and no recommendations can be made.
East Midlands Cancer Network	42.11	Full	113	10-16	Failure to recommend the use of G- CSF for groups of patients (especially elderly) receiving regimens giving a 20% risk of febrile neutropenia is outwith all Eureopean and US guidelines and would be indefensible. The statement that the studies were done outside the UK does not mean that they are not applicable here. Also there is the major issue of dose intensity	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance. In order to investigate this effect we would

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					and delivering the treatment on time which is another justification for giving growth factor support	need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this

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						guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices.
East Midlands Cancer Network	42.12	Full	113	10-16	Re. Recommendations on the use of GCSF The scope for this guidance in relation to the use of G(M)CSF was wrong from the beginning and the resulting draft guidance is clearly flawed as a result. The issues are: - The review of G(M)CSF only considers "survival during anti-cancer treatment" and does not consider any survival advantage for giving G(M)CSF for maintaining dose intensity which is the key reason for its use in many patients.	The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on

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						subsequent chemotherapy scheduling and dose.
					- The review considers giving G(M)CSF to all. All international guidelines we can find ii,iii,iv do not recommend using G(M)CSF in this way and recommend use on the basis of risk of febrile neutropenia. Therefore there is no assessment of the point at which G(M)CSF may becomes cost effective based on the risk of febrile neutropenia.	Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with recommendations in other non-NICE guidance.
					- GCSF is available to the NHS at contract price(s) that are significantly lower than the NHS list price.	As stated in the linking evidence to recommendations section, whilst the GDG acknowledged that clinicians in some settings are able to source G-CSF products at substantially reduced cost, it was noted that these arrangements are fluid and regional and therefore no national recommendations can be based on these discounted costs. One-way sensitivity analysis has shown that the model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg), and for patients with non-Hodgkins lymphoma who cannot take quinolones at less than £113.94 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount.

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					We realise the GDG was limited in its scope, and that it recognised that this period "may be too short to adequately assess the benefits of G(M)CSF use in encouraging clinicians to proceed in treatments with greater dose intensity.". They also recognised that "clinicians in some settings are able to source G(M)CSF products at substantially reduced prices which could potentially make its use cost-effective". The GDG clearly tried to make the best of a bad situation by making the following statement "Balancing these elements of uncertainty against the high ICER described by the economic model led to a strong decision not to recommend the use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis but also not to recommend that the use of these agents for other indications is discontinued." Our key concern is that despite this statement, in the current financial climate, commissioners may take the detailed review of the evidence and the extremely high ICER for G(M)-CSF in the prevention of neutropenic sepsis in the absence of any similarly detailed review of its potential benefits in maintaining dose intensity as a reason to decommission the use of G(M)CSF.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was

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						unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
					Therefore we firmly believe that the scope of this guidance should be increased to also cover the use of G(M)CSF in increasing dose intensity.	Unfortunately the scope is final and we are no longer able to change it.
					It should also be noted that in line with ASCO and other international guidelines support the targeted use of GCSF for primary and secondary prophylaxis (for example locally http://www.eastmidlandscancernetwork.nhs.uk/Library/EMCNDC005609GCSF.pdf) with this also reflected in the Manual of Cancer Standards peer review measures. In line with this, there is already widespread targeted use of GCSF prophylaxis which is already contributing to the current level of observed ferbile neutropenia post chemotherapy and at a wider level emergency readmissions and bed utilisation. As outlined above there is potential for decommissioning of current GCSF use with a detrimental effect on rates of febrile	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.

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					neutropenia, hospitalisation and in some cases maintenance in dose intensity all of which ultimately impact adversely upon clinical outcome and patient experience	
East Midlands Cancer Network	42.13	Full	113	10-16	Re. Recommendations on the use of GCSF - In our departmental audit, primary prophylaxis with GCSF in patients or regimes with FN risk>20% has reduced incidence by 64.5%. - Primary prophylaxis with GCSF allows us to offer chemotherapy to high risk vulnerable group of patients. - Primary prophylaxis with GCSF reduces bed occupancy. - Primary prophylaxis with GCSF improves quality of life by reducing FN in high risk group	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who

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						cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
East Midlands Cancer Network	42.09	Full	133	1	Re. The recommendation to just offer Tazocin as monotherapy and not to offer aminogycosides is controversial – there is no provision for penicillin allergic patients.	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.

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					Also again this may be OK for patients receiving outpatient based chemotherapy but is not suitable for those receiving inpatient chemotherapy and having a long hospital stay, as these patients are much more at risk of developing resistant organisms. Also the in patients are more likely to have long lines and have G+ve infections and tazocin has little staph aureus cover whereas gentamicin would generally offer some G+ve cover.	The recommendation states that there may be specific microbiological contraindications to monotherapy with piperacillin-tazobactam. However, the evidence appraised for this topic did not support addition of aminoglycosides to any group as initial empiric therapy.
East Midlands Cancer Network	42.10	Full	133	1	Re. Recommendation for piperacillin-tazobactam monotherapy as standard empiric therapy - The guidance lacks any recommendations for the treatment of those patients who have a type 1 beta-lactam hypersensitivity. This is a common occurance in practice and requires guidance. - This recommendation also ignores the huge rise in Extended Spectrum Beta-Lactamase (ESBL) producing coliforms	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a hypersensitivity as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. We agree that in some areas of the country, resistance to piperacillin-tazobactam will make monotherapy with this agent an

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					over the last few years. ESBL are resistant to the actions of penicillin/beta lactamase combinations such as Tazocin. In addition, and supporting point 2, prior quinolone use is also a risk factor for subsequent ESBL infection. - Whilst the recommendation also states "unless there are local microbiological contraindications" we again feel this recommendation requires discussion and agreement with the Healthcare Associated Infection and Antimicrobial Resistance Group at Department of Health, with the HPA and with the wider microbiology community.	inappropriate empiric antibiotic therapy. We have acknowledged this in the current wording of the recommendation and in the linking evidence to recommendations section of section 6.2. In such situations an appropriate empiric antibiotic therapy may be dual therapy including an aminoglycoside, or an alternative monotherapy, for example a carbapenim, but such decisions need to be based on local microbiological resistance patterns and can't be specified in the recommendation Comments have been received from the microbiology community, Department of Health and HPA as part of the consultation on the draft guideline.
East Midlands Cancer Network	42.16	Full	137	1, 17	Re . Recommendation for empiric glycopeptides for the initial empiric treatment of suspected neutropenic sepsis - We believe that the recommendation to "not offer empiric glycopeptides antibiotics to patients with neutropenic sepsis who have a central venous access devices" requires qualification. We would suggest this can be achieved by adding "routinely". There may be some situations, for example when treating a known MRSA carrier or someone with previous episodes of MRSA infection were initial empiric treatment may reasonably involve	We have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern.

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					vancomycin or teicoplanin.	
East Midlands Cancer Network	42.18	Full	228	6	It is of concern that the membership of the Guideline Development Group (GDG) did not include an anti-microbial pharmacist or a cancer pharmacist Cancer pharmacists in many cancer centres are heavily involved in, if not leading, the development of guidelines on both the prophylaxis and treatment of neutropenic sepsis and the use of GCSF. We believe that the GDG having this practical experience on the group would have allowed the guidance to be more realistic and practically useful. As for the value of an antimicrobial pharmacist to the GDG, this has already been recognised more broadly in previous Department of Health (DH) and Health Protection Agency (HPA) guidance which states that "all trusts should establish an Antimicrobial Management Team (AMT) or equivalent. This should consist of an antimicrobial pharmacist, a consultant microbiologist or infectious diseases specialist, and an information technology specialist. Antimicrobial pharmacists have a valuable role in AMTs and PCTs.....".	Thank you for your comment. At the time of scoping this guideline it became clear that the principal issue on antibiotic prescribing would be choosing drugs based on patterns of antibiotic resistance; this would be guided by the microbiologist on the GDG. Although the guideline recommends the classes of drugs that would be appropriate, it does not address the details of individual drugs and their administration, therefore the specific expertise of a pharmacist for these issues was not needed.
Health Protection Agency	23.18	Evidence Review	General	General	Consider the age and ongoing relevance of the data used from old sources in the current environment. For example, Figure 8.16 states that quinolone prophylaxis does not yet lead to colonisation with quinolone resistant bacteria dates from a time when it was thought that quinolone resistance was 'impossible' (Figure 8.16). Also there is considerable text on co-	The GDG acknowledged that the evidence about colonisation with quinolone resistant bacteria was sparse in the linking evidence to recommendations section for chapter 5. The GDG recognised that changing anti-microbial resistance patterns meant the cotrimoxazole trials may no longer be

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					trimoxazole as prophylasis based on papers published as long ago as the 1970s (Figure 8.11).	applicable, and did not make recommendations about cotrimoxazole.
Health Protection Agency	23.00	Full	General	General	Antibiotic resistance rates change (increase generally) over time. This would mean that some of the supportive material may no longer be valid. Consider whether any pre-2005 papers should guide the choice of the particular antibiotic. Earlier papers should instead be used to guide overarching principles such as the need for early initiation of therapy and for its duration.	Although there was no direct evidence, the GDG considered the effect of changing antibiotic resistance rates when making recommendations (see accompanying linking evidence to recommendations section).
Health Protection Agency	23.01	Full	General	General	Consider including information explaining why NICE is recommending using piperacillin-tazobactam as monotherapy. While there is no doubt that the drug has a good reputation in febrile neutropenia, resistance is increasing and EUCAST has lowered the breakpoint from 16+4 mg/L to 8+4 mg/L, further increasing the proportion categorised as resistant.	The GDGs reasons for recommending piperacillin-taxobactam are documented in the linking evidence to recommendations section for section 6.2
Health Protection Agency	23.02	Full	General	General	Consider including information on the shifting background and debate on the use of quinolone prophylaxis. In respect of quinolones there have been massive shifts. In 2000, *c*. 4% of *E. coli* from bloodstream infections in the UK were quinolone resistant; now the proportion is 17-20%. In addition, there is increasing gut carriage of quinolone resistant strains, many of them multiresistant, which may seed future infections. While using quinolone prophylasis accords with recent IDSA guidelines and benefits some patients, some authorities have questioned the wisdom of quinolone prophylaxis due to concern that this prophylaxis will enrich the resistant population and that any	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($<0.5 \times 10^9$/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a

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					subsequent infection will involve more difficult pathogens.	potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Health Protection Agency	23.03	Full	General	General	Consider whether it is prudent to advocate the use of the same antibiotic in all patients. Consider whether this would concentrate	Such decisions need to be based on local microbiological resistance patterns and can't be specified in the recommendation

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					selection pressure for resistance. It is said that alternatives might be used where indicated by the local microbiology but there is no guidance on the resistance rates at which this advice should be followed.	
Health Protection Agency	23.05	Full	9	16	Add comma after 'commissioned'.	We have made this amendment
Health Protection Agency	23.07	Full NICE	25 3	Figur e 1.1 5	The Short Guideline starts by stressing how good outcomes are in neutropenic sepsis saying 'intensive care is needed in fewer than 5% of cases etc'. This seems to be at variance with the Full Guideline, which shows rising mortality in neutropenic sepsis, almost doubling over the past decade.	Whilst the outcome of each individual episode of neutropenic sepsis has improved, the increased use of intensive chemotherapies to a broader population has also increased the rate of neutropenic sepsis – which explains this apparent contradiction.
Health Protection Agency	23.08	Full	34	15	Consider including a definition of 'door to needle' time. Many may not be familiar with the term. A definition would be useful for interpretation.	A definition of this term is included in the glossary.
Health Protection Agency	23.04	Full	35	20	There is very little advice on what the oral options are. The Full Document mentions co-amoxiclav, ciprofloxacin; also clindamycin for penicillin allergic patients. Clindamycin has a completely different spectrum of activity to the other agents (almost purely anti-gram-positive with a propensity to select *C. difficile*) while the other agents have anti-gram-negative activity. The advice appears too predicated on clinical response rather than the microbiological susceptibility of whatever bacteria have been isolated.	This text is from the needs assessment which describes current practice in the UK. It does not examine the evidence nor does it make recommendations for future practice. We have stated in the linking evidence to recommendations sections that local microbiological resistance patterns vary and consequently the GDG were unable to recommend a specific antibiotic strategy.
Health Protection Agency	23.06	Full	20, 21	Gene ral	Consider increasing the size of the font. Even when printed, text in table too small to read.	We have increased the size of the font as much as possible whilst keeping this algorithm on one page.
Health Protection	23.09	Full	41	19	Two full stops after 'antibiotics'.	Thank you for your comment. We have

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Agency						removed the extra full stop.
Health Protection Agency	23.10	Full	44	33 General for section 3.1	In the previous section the studies conducted found that examples of written information given to patients ranged from a 76 page patient held record book to a single sided sheet. It should be noted and specified in the guidelines that the written information provided to patients should not be too long. The information should highlight all important points yet be concise and in simple language for all to understand.	The information required will be different for individual patients. We have no evidence to specify the format or length of such information. Therefore it is not possible to specify this in the recommendation. We have recommended further research in this area.
Health Protection Agency	23.11	Full	49	General	Recommendation for future work: Consider development of prescribing competencies for all prescribers involved in anti-cancer therapy/neutropenic sepsis. These do not necessarily need to be done by NICE - can be done by a suitable body which NICE can cross reference through these guidelines in the future.	Thank you for this suggestion. It is not within the remit of this guideline to develop competencies for prescribing.
Health Protection Agency	23.12	Full	61	28	Recommendation states to carry out urinalysis in all children aged 5 years and younger. Why only this age group? No information in the evidence statements to back this up.	We have amended the text in the linking evidence to recommendation section for section 4.2.2 to clarify the reasons for making this recommendation.
Health Protection Agency	23.13	Full	81	Table 5.3	Consider including the dates the studies were performed to enable comparison.	The dates of individual studies are included in the evidence review, which accompanies the full guideline. Cross references to this document have been inserted.
Health Protection Agency	23.14	Full	126	1	Are the single agent ureidopenicillin trials underpinning the recommendation for piperacillin-tazobactam? If so, piperacillin is a piperazine penicillin, not a ureido-, and no true ureido-penicillin (azlocillin or mezlocillin) has been marketed for a decade or more. Consider whether the relevant table muddles trials with piperacillin and those with piperacillin-tazobactam (a broader spectrum combination).	Piperacillin has the chemical formula sodium 6-(d(–)-alpha-(4-ethyl-2, 3-dioxo-1-piperazinylcarbonylamino-alpha-phenylacetamido) penicillinate. There is a lack of consistency in how it is classified. Its molecule contains a side chain with an ureido group so that it may be termed a ureidopenicillin. However, because of chemical differences arising from its terminal

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						piperazine structure, it is sometimes not classified as a ureido-penicillin like mezlocillin and azlocillin but as a piperazine penicillin. Custom and practice among clinicians in the UK, supported by the BNF, classifies piperacillin as a ureidopenicillin, and hence this term is used to reduce confusion. It is also correct that neither azlocillin nor mezlocillin have been marketed for a decade or more. "The ureidopenicillin trials" are indeed with piperacillin-tazobactam or piperacillin alone.
Health Protection Agency	23.15	Full	127	Table 6.4	Ureidopenicllin has been misspelt as uridopenicllin.	This change has been made
Health Protection Agency	23.16	Full	166	1	Who can make this decision? Would it be a healthcare professional with recognised professional competence in managing anti-cancer treatment?	This decision would be made by someone competent to do so. We do not feel it is necessary to specify this in the recommendation as it is part of good clinical practice.
Health Protection Agency	23.17	Full	166	1	What are the indicators for 'neutropenic sepsis responding to treatment' (e.g. fever back in range etc)?	The GDG considered that "responded to treatment" meant a combination of symptoms receding, patient feeling better, and objective measures such as temperature and laboratory parameters. However due to the subjective nature of "a patient feeling better" and the potential for multiple objective measures, the GDG were not able to create a specific definition. They believe that the term "responded to treatment" would be understood by clinicians.
Impact of Neutropenia in Chemotherapy European Study	32.00	Full	General		This guideline is contrary to current European (EORTC), and International Guidance (NCCN, ASCO) as well a published and peer reviewed UK clinical practice (e.g. London Cancer New	Our recommendations in this guideline are based on a systematic search and appraisal of the clinical evidence and where relevant the results from a health economic model.

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Group (INC-EU)					Drugs Group)	Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
Impact of Neutropenia in Chemotherapy European Study Group (INC-EU)	32.07	Full	General		The type of cancer and whether the intention of treatment is curative or palliative needs also to be considered. Where there is evidence of a steep dose response curve (Hodgkin's, NHL and adjuvant breast cancer) and patients are being treated with curative intent, chemotherapy dose reduction and dose delay (relative dose intensity) has been shown to compromise both short term mortality and long term survival. The ability to deliver chemotherapy on time is important. The adverse effect on survival by following the guideline statement to stop treatment after two neutropenic events is in conflict with the Department of Health Guidance "Improving Outcomes: a strategy for cancer", 2011. Importantly there is no evidence that dose intensity can be maintained with prophylactic antibiotics.	The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose.
Impact of Neutropenia in Chemotherapy European Study Group (INC-EU)	32.03	Full	106	49	Leukaemia patients should also be covered by the modelling.	Due to limited time and resources, our economic analysis only focused on patients who are receiving outpatient chemotherapy (defined as patients with planned inpatient treatment less than 10-day post-chemotherapy). It is acknowledged that most leukaemia patients receive inpatient chemotherapy (defined as patients with planned inpatient treatment greater than 10-

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						day post-chemotherapy); so they are not covered in this economic analysis.
Impact of Neutropenia in Chemotherapy European Study Group (INC-EU)	32.06	Full	107	2, 3	The modelling ignores that the risk of neutropenic sepsis is strongly chemotherapy-dependent and patient-dependent and that very different cost-effectiveness ratios may result as a function of this risk.	We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant neutropenia ($\leq 0.5 \times 10^9$/litre) is an anticipated consequence of chemotherapy.
Impact of Neutropenia in Chemotherapy European Study Group (INC-EU)	32.02	Full	107	14, 15	The time horizon of the models is one course of chemotherapy; this implies different numbers of chemotherapy cycles depending on patient group evaluated. Because prior chemotherapy can be a risk factor of neutropenic sepsis and because neutropenic sepsis has a potential for long-term sequelae, inclusive of cancer recurrence due to reduced delivery of chemotherapy treatments with curative intent, the time horizon of the health economic model is not appropriate for the given decision problem. A life-long time horizon is required.	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality

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						qualitatively when making their recommendations. Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
Impact of Neutropenia in Chemotherapy European Study Group (INC-EU)	32.05	Full	107	29	In order to provide an overview and facilitate the understanding of the model calculations, we suggest including a table where all input parameters of the model are listed and where their values for health economic models A and B are provided.	The majority of input data are listed in table A17-A19. The input data are exactly the same for Model A and Model B.
Impact of Neutropenia in Chemotherapy European Study Group (INC-EU)	32.04	Full	108	49	The QALY does not seem to reflect the very large reduction in the price now paid for G-CSFs	All G-CSFs are biosimilars that in terms of regulation aren't treated as generics. Therefore, whilst each PCT probably has its own agreement, there is no nationally negotiated discount as normally found on the CMU website. Given this the GDG decided to use the BNF price since there is no other reliable NHS source. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible

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						to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A).
Impact of Neutropenia in Chemotherapy European Study Group (INC-EU)	32.01	Full	108	35, 36	The selection of strategies subjected to health economic analysis is based on the GDG's conclusion that "compared to quinolone alone, G(M)-CSF and G(M)-CSF + quinolone are more expensive and less effective in terms of preventing neutropenic sepsis". However, comparative clinical evidence on this topic is very sparse, as recognised by the GDG on p. 112. We doubt whether it provides a sufficient justification for excluding the 'primary prophylaxis with G-CSF' strategy. In our opinion, the clinical evidence base does not allow concluding that antibiotic prophylaxis is better than growth factor-based prophylaxis, with any acceptable degree of certainty particularly in patients receiving high risk febrile neutropenia regimens.	These recommendations are based on both clinical and cost-effectiveness evidence. We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant neutropenia ($\leq 0.5 \times 10^9$/litre) is an anticipated consequence of chemotherapy. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this

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						intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
					Also the very real concern of antibiotics resistance has not been tested with such a strategy and the length of follow-up is too short to detect emergence of resistant bacteria and resistance data were not routinely collected in the studies presented. It is surprising that the relative risk for developing infections caused by quinolone-resistant bacteria did not change over the years.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($<0.5 \times 10^9$/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was

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						considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.

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Impact of Neutropenia in Chemotherapy European Study Group (INC-EU)	32.08	Full	114	31, 32	We fully agree that more studies are needed to evaluate the cost-effectiveness of prophylactic strategies in neutropenia and neutropenic sepsis management.	Thank you for your comment.
Infection prevention society	43.00	Full	5	28 - 30	The membership have highlighted concern regarding the use of certain CDifficile infection associated antibiotics for prophylaxis management of neutropenic sepsis and would ask that the broad use of prophylaxis for the patient groups suggested be reconsidered.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff

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						rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Leeds Teaching Hospitals NHS Trust	33.00	Full	General		We welcome this enterprise to improve the prevention and management of neutropenic sepsis; and are very grateful for the work by the GDG *et al* to produce this guidance. We also appreciate the opportunity to comment at this stage. The full guideline is substantial so apologies if comments below do not appear to have taken into account every statement – however, they would certainly appear to apply to the draft summary NICE guideline. We have commented primarily on the clinical practice recommendations, as it is these which will be implemented by "us" (if not already in place) unless clear justification available as to why not. We are happy to provide further supporting references etc if desired.	Thank you for your comment.
Leeds Teaching Hospitals NHS	33.01	Full	General		There appears to be a lack of explicit recognition that individual patient circumstances	Recommendations in guidelines are designed to assist the practice of healthcare

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Trust					(e.g. clinical presentation / condition at time, history of previous drug allergy / intolerance, previous microbiological results etc) may suggest an alternative approach is preferable to that specified in the recommendations (specific examples below). The presence of the Disclaimer (18:45-51) is acknowledged. ? Refer to other guidelines for more detailed information / advice regarding other scenarios, if "allowed", e.g. "Prevention and Treatment of Cancer-related infections" issued / updated regularly by the (US) National Comprehensive Cancer Network (NCCN) [www.nccn.org] or those of the Infectious Diseases Society of America (IDSA).	professionals, however, they do not replace their clinical knowledge and skills. In cases where individual patient circumstances indicate an alternative approach, we would expect clinicians to use their clinical judgement to determine an appropriate alternative. It is not part of NICE methodology to cross-reference non-NICE guidance.
Leeds Teaching Hospitals NHS Trust	33.02	Full	General		Neutropenic sepsis is not synonymous with neutropenic fever (temp > 38oC). This appears to be recognised at times within these guidelines, but at other times, the two are conflated – including w.r.t evidence surveyed, and notably for the definitions. There is a danger that a) This will mean some patients who have sepsis (indeed severe sepsis as defined by other criteria) but are afebrile – or hypothermic, are "missed". b) It lessens the message (which is welcome) of the need to "stratify" febrile neutropenic patients & not to manage	The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. The evidence also showed that increased temperature was associated with an increase in infection. The lowest value for fever studied in the evidence was 38^{o}C and the GDG decided to adopt this value in their definition for neutropenic sepsis. The GDG did not find clear evidence to support the use of triage on admission to determine immediate management.

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					them all as a homogeneous entity (*cf* comment 2).	
Leeds Teaching Hospitals NHS Trust	33.03	Full	General		? Empirical rather than empiric	Thank you for your comment. We are unsure what area of the guideline this comment relates to.
Leeds Teaching Hospitals NHS Trust	33.04	Full	58	37	Confusing re "blood cultures" (*cf* 61:28) - ?make more clear the preference is for blood cultures collected approximately concurrently through each lumen of central venous access device (if *in situ*) and a peripheral set – ie "paired" blood cultures (cf IDSA guidance: Freifeld 2011).	The evidence comparing paired versus unpaired blood culture samples was not appraised and therefore we are unable to make recommendations on this issue. Blood cultures should be performed in accordance with national standard operating procedures.
Leeds Teaching Hospitals NHS Trust	33.05	Full	58	37	Other biomarkers of infection – such as procalcitonin - not mentioned (nor in the preceding evidence review) - ? is the view of the GDG that CRP is, currently, the "only" acceptable such marker in neutropenic patients.	The role of procalcitonin was not identified as a priority for investigation in the guideline as the GDG prioritised the appraisal of investigations in common clinical usage. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it. You may wish to consider referring procalcitonin as a topic to the medical diagnostic team at NICE.
Leeds Teaching Hospitals NHS Trust	33.06	Full	61	28	"Urinalysis in all children under 5" (and not for routine CXR) specifically mentioned – but no mention of any other site-specific tests if clinically indicated etc etc to identify "underlying cause of sepsis" – which is the stated aim of this recommendation – cf Comment 2.	Other clinically indicated tests were not identified as a priority for investigation in the guideline because management of specific infections is explicitly excluded from the scope. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it.
Leeds Teaching Hospitals NHS Trust	33.07	Full	112	1	Offering quinolone prophylaxis to "all adult patients"…"with acute leukaemias, stem cell transplants or solid tumours" during expected period of neutropenia is undoubtedly one of the more controversial aspects of these draft	We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant neutropenia ($\leq 0.5 \times 10^9$/litre) is an anticipated consequence of chemotherapy.

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					recommendations. This appears at odds with other recent major (internationally applied) guidelines (e.g. those of NCCN, V2.2011 – which suggests "low risk" patients – [where neutropenia is expected to last <7 days – applicable to standard chemotherapy regimens for most solid tumours] no "antibacterial" prophylaxis should be offered (although recognising that "data" does "support" (levofloxacin) prophylaxis in this group) & for "intermediate / high-risk" patients, consider fluoroquinolone prophylaxis). One is nervous of the risk of "collateral damage" with fluoroquinolones (FQ) – notably the potential increased risk of infections due to meticillin resistant *S aureus* (MRSA) and certain strains of *C difficile*. These draft recommendations from NICE, arguably, appear to be going "against" the perceived national aim of reducing infections with these specific organisms as currently promulgated by the Department of Health. More specifically: there is no recognition of previous results (e.g. a known "breakthrough" bacteraemia with a quinolone resistant, co-trimoxazole susceptible *E coli*) or if an FQ is contra-indicated in an individual patient (cf Comment 2). In the guidelines, the increase in bacterial resistance to co-trimoxazole (COT) since the evidence in "favour" of COT was collated is recognised – however there now also appears to be potentially increasing FQ resistance in Enterobacteriaceae *et al* isolated from blood cultures nationally - notably in the	The recommendations in this guideline are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with recommendations in other non-NICE guidance. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such

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					last decade. An issue for some patients is then which "oral" antibiotic regimen to switch them to if the patient was on preceding quinolone prophylaxis (*cf* comment 15)	prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Leeds Teaching Hospitals NHS Trust	33.08	Full	133	1	Offering "all" patients with suspected neutropenic sepsis piperacillin-tazobactam (PTA) unless "local microbiological contraindications" appears slightly odd. Documented penicillin allergy in a patient is not a "local microbiological contraindication" – but in a recent local survey, 100% of 50 relevant Adult Oncology specialists would not prescribe PTA to a patient with penicillin allergy (figure courtesy Dr M Afshar). (*cf* Comment 2)	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence

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						appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.
Leeds Teaching Hospitals NHS Trust	33.09	Full	133	1	? What is the definition of "local microbiological contra-indications" please – one accepts this could include an individual patient who had had previous infection with a PTA – resistant, carbapenem susceptible organism, but what is the desired interpretation on the basis of the treating unit's epidemiology? The meta-analysis of Paul 2010 (referred to in these guidelines to support the recommendation of PTA as first line) suggests 25% resistance rate in Gram negative bacteria as the cut-off (which is higher than been thought appropriate locally at 10%) – is that threshold, by implication, endorsed by the GDG?	Thank you for your comment, we have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern. The definition of local microbiological contra indications is included in the glossary of the guideline. The guideline did not investigate this cut-off and therefore is unable to make recommendations on this issue.
Leeds Teaching Hospitals NHS Trust	33.10	Full	137	1	This blanket recommendation of "not offering empiric glycopeptide antibiotics to patients with suspected neutropenic sepsis who have central venous access devices" (CVAD) also appears quite bullish. Whilst we very much support the recommendation of not using empirical glycopeptides in "all" patients with a CVAD - there are a number of reasons why an empirical glycopeptide might be clinically &/or microbiologically appropriate (*cf* NCCN	We have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern.

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					guidelines, V2.2011) (also *cf* comment 2).	
Leeds Teaching Hospitals NHS Trust	33.11	Full	139	34	? Need to define "initial empiric management" please – (*cf* comments 2,4 also). This doesn't appear to be defined in the subsequent section linking evidence to recommendations. If a patient presented in severe sepsis with strong clinical suspicion (+/- previous microbiological results) that the CVAD was the source, then at least "early" line removal should usually be (strongly) considered.	We have added text to the linking evidence to recommendations section to clarify what is meant by "initial empiric management". Management of specific infections is explicitly excluded from the scope of this guideline - the treatment is not, by definition, empiric.
Leeds Teaching Hospitals NHS Trust	33.13	Full	158	29-32	..follows on from comment 13, we are unclear why it would not be appropriate to switch such patients from iv therapy to oral at say 24 hours and then be "observed" for a further 24 hours (*cf* comment 15 also)	Whilst there was some evidence to support switching at 24 hours, the GDG did not consider that it was strong enough to support recommending this. Instead they recommended research into very early (first 24 hours) oral antibiotic therapy.
Leeds Teaching Hospitals NHS Trust	33.12	Full	158	1	The (effectively minimum) of 48 hours iv antibiotics in low risk patients doesn't appear to be specifically supported by the evidence referred to.	Whilst there was some evidence to support switching at 24 hours, the GDG did not consider that it was strong enough to support recommending this. Instead they recommended research into very early (first 24 hours) oral antibiotic therapy. However the GDG noted that in studies which undertook an early switch, patients were more likely to have treatment failure than those with a later time of switch. The clinical opinion of the GDG was that most adverse events would be clinically apparent within the first 48 hours of admission and so there would be less risk associated with switching after this time. This is documented in the linking evidence to recommendations section for section 7.2. Please also see the Evidence Review page 409-449.
Leeds Teaching	33.14	Full	159	1-2	No recommendation re specific oral antibiotic	We have stated in the linking evidence to

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Hospitals NHS Trust					strategy – we think it would be helpful if the GDG could address this please – notably in the light of the current recommendation re quinolone prophylaxis (*cf* comment 8). The oral regimes which would appear to have the best pedigree on published evidence to date usually contain a quinolone – but the NCCN guidelines (V2.2011) specifically recommend not to use these (e.g ciprofloxacin + co-amoxiclav, or ciprofloxacin + clindamycin) if patient been on quinolone prophylaxis (no alternative oral options are provided by them).	recommendations sections that local microbiological resistance patterns vary. We have added text to clarify that choice of antibiotic may be influenced by prior prophylaxis. Consequently the GDG were unable to recommend a specific antibiotic strategy.
Leeds Teaching Hospitals NHS Trust	33.15	Full	166	1	We welcome the recommendation that antibiotics can be stopped irrespective of neutrophil count (and recognise that this (also) appears different to some current "international" guidelines) – however we feel it would be helpful to have more clear guidance re "responded to treatment" – notably if "sepsis" remains synonymous with fever (*cf* comment 3). Otherwise there would appear to be a danger that empirical antibiotics will be stopped prematurely in certain patients in the absence of any positive blood cultures. It is recognised that in some cases, the "empirical" choice of PTA will remain appropriate as ongoing "targeted" treatment – and therefore a "minimum" course will be recommended to treat the specific organism / site of infection.	The GDG considered that "responded to treatment" meant a combination of symptoms receding, patient feeling better, and objective measures such as temperature and laboratory parameters. However due to the subjective nature of "a patient feeling better" and the potential for multiple objective measures, the GDG were not able to create a specific definition. They believe that the term "responded to treatment" would be understood by clinicians. Management of specific infections is explicitly excluded from the scope of this guideline - the treatment is not, by definition, empiric.
London Cancer	35.00	Full	General		We would like to confirm our unreserved agreement with the following recommendations:	Thank you for your comment.
London Cancer	35.06	Full	General		We feel that the following recommendation requires a minor change:	Thank you for your comment.

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London Cancer	35.10	Full	5-6	46(5) -2(6)	We agree with the following recommendations, but recognise that they will require major development:	Thank you for your comment.
London Cancer	35.11	Full	5-6	46(5) -2(6)	*Inpatient versus outpatient management strategies* Offer outpatient antibiotic therapy to patients with confirmed neutropenic sepsis and a low risk of developing septic complications, taking into account the patient's social and clinical circumstances and discussing with them the need to return to hospital promptly if a problem develops.	Thank you for your comment.
London Cancer	35.05	Full	5	37- 43	*Empiric intravenous antibiotic monotherapy or intravenous antibiotic dual therapy* Offer beta lactam monotherapy with piperacillin-tazobactam as initial empiric antibiotic therapy for suspected neutropenic sepsis unless there are local microbiological contraindications. Do not offer an aminoglycoside, either as monotherapy or in dual therapy, for the initial empiric treatment of suspected neutropenic sepsis unless there are local microbiological indications.	Thank you for your comment.
London Cancer	35.03	Full	5	16- 19	*Investigations appropriate for clinical management and risk stratification* Include in the initial clinical assessment of patients with suspected neutropenic sepsis: - history and examination - full blood count, kidney and liver function tests (including albumin), C-reactive protein, lactate and blood culture	Thank you for your comment.
London Cancer	35.07	Full	5	22- 25	*Assessing the patient's risk of septic complications* A member of the oncology team should assess	The GDG have reviewed this recommendation, and felt that to improve the patient experience and clinical management,

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					the patient's risk of septic complications as soon as possible and within 48 hours of presentation to secondary or tertiary care, basing the risk assessment on presentation features and using a validated scoring system. *We wish to insist on 24 hours – rather than 48 hours – for assessment. This is in line with the requirements of the Acute Oncology Measures.*	a patients risk of septic complications should be assessed within a maximum of 24 hours of presentation. They have also clarified that a healthcare professional with competence in managing complications of anti-cancer treatment should assess the patient's risk of septic complications.
London Cancer	35.08	Full	5	28-30	We disagree with the recommendation on *Preventing the septic complications of anti-cancer therapy*: Offer prophylaxis with a quinolone during the expected period of neutropenia to all adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours.	We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant neutropenia ($\leq 0.5 \times 10^9$/ litre) is an anticipated consequence of chemotherapy. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has also been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation.
London Cancer	35.09	Full	5	28-30	Our suggestion for an acceptable alternative is as follows: A risk stratification strategy should be adopted for the use of antibiotic primary prophylaxis We do not agree with a blanket introduction of antibiotic primary prophylaxis for all patients on	We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant neutropenia ($\leq 0.5 \times 10^9$/ litre) is an anticipated consequence of chemotherapy. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has also been added to the guideline.

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					myelosuppressive chemotherapy • High risk tumour types should be identified e.g. 1st cycle Lung cancer, Stem cell transplants, etc. o We have concerns about the widespread introduction of oral ciprofloxacin and prefer to have local flexibility e.g. Septrin for use in patients with Lung cancer and ofloxacin for haematological malignancies	The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The recommendation clarifies that relates to adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours.
London Cancer	35.01	Full	5	4-6	*Definition of neutropenia and fever* Diagnose neutropenic sepsis in patients with a temperature higher than 38^{o}C and a 5 neutrophil count lower than 0.5 x 10^{9}/litre.	Thank you for your comment.
London Cancer	35.04	Full	5	33-34	*Timing of initial antibiotic therapy* Treat suspected neutropenic sepsis as an acute medical emergency and offer empiric antibiotic therapy immediately.	Thank you for your comment.
London Cancer	35.02	Full	5	9-10	*Information and support for patients and carers* Provide patients having anti-cancer treatment and their carers with written and verbal information, both before starting and throughout their anti-cancer treatment…	Thank you for your comment.
London Cancer	35.12	Full	6	6-9	*Duration of inpatient care* Discharge patients having empiric antibiotic	Thank you for your comment.

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					therapy for neutropenic sepsis whose risk of developing septic complications has been re-assessed as low by a healthcare professional with recognised professional competence in managing complications of anti-cancer treatment using a validated risk scoring system.	
Lymphoma Association	39.00	Full	General		The Lymphoma Association is a national charity providing information and support to people affected by lymphoma. We publish a wide range of information for patients and their families and benefit greatly from the expertise of our medical advisory panel in ensuring that these are evidence-based and accurate. We have a comprehensive understanding of patients' views on a wide range of issues through feedback from our helpline service, our network of 42 local support groups and buddies scheme as well as our message boards and chatroom. In view of the short time-frame for responses to this consultation, we have not been able to seek patients' views. However, we have consulted out medical advisors who are consultant haematologists and oncologists. We welcome the opportunity to comment in detail on the draft guidelines but regret to say that we, and our medical advisors, have some serious concerns about them. One of the main problems is the umbrella approach to what are hugely variable and complex groups of conditions. This guidance fails to recognise the many different factors that are taken into account by experts in these fields when treating patients. Our concern is that such an approach may result in recommendations	Thank you for this information We appreciate the scope of this document is very broad. Where evidence of important variation existed, recommendations were phrased to reflect this. Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills.

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					being made that are inappropriate for certain groups and may take away the necessary flexibility for doctors to provide proper 'patient-centred' care. The main problem stems from the stated limitations of the scope "to survival during anti-cancer treatment" (p114; lines18–226). We believe this has led to conclusions that are likely to have an adverse impact on longer term survival, particularly for lymphoma patients who often present at a relatively young age and have a high chance of cure with appropriate therapy. This is particularly reflected in the sections on prophylaxis. The draft guidelines do not reflect current UK or international medical practice and represent a backwards step rather than an improvement. They are also at odds with accepted local and national guidance (LCNDG), European guidance (EORTC and international guidance (NCCN, ASCO).	The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose. As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the

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						results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
Lymphoma Association	40.33	Full	27	1-3	Fig 1.4 shows the high numbers of deaths from neutropenic sepsis in lymphoma patients (above most solid tumours).We therefore feel it is vital that recommendations that could potentially worsen rather than improve this situation are not made on the basis of sparse evidence or inappropriate modelling assumptions. From a patient's point of view, it is better to err on the side of caution rather than risk another avoidable death.	The limited data available meant we were not able to make a specific recommendation for patients with lymphoma. Whilst the recommendation to offer prophylaxis does not specifically include patients with lymphoma, we have not recommended that these patients don't have prophylaxis. We have amended our recommendation for further research to include these patients. Thank you for highlighting this omission.
Lymphoma Association	40.00	Full	28	25-29	We feel it would be helpful to include in the guidelines the requirement for an individual risk assessment of all patients prior to starting chemotherapy treatment to address the variability in risk. A number of possible models have been published. The following include patients with lymphoma: Lyman GH, et al. Cancer. 2011;117(9):1917–27 and Pettengell R, et al. Br J Haematol. 2009;144(5):677–85 It is vital that those most at risk are identified so that both the medical team (including GP) and the patient are aware of the increased likelihood of neutropenia. Furthermore, we feel that having identified those patients most at risk, clinicians should be able to use their judgement on prophylaxis rather than having to follow the blanket recommendation on	This text is from the needs assessment which describes current practice in the UK. It does not examine the evidence nor does it make recommendations for future practice. We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant

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					p112.	neutropenia ($\leq$0.5 x 10^9/litre) is an anticipated consequence of chemotherapy. Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills.
Lymphoma Association	40.01	Full	29	1	Table 1.2 quotes a 2% risk of NS for HL patients receiving ABVD. This is not consistent with the clinical experience of our experts, possibly because of the selected groups of patients in the studies quoted in this review (e.g. mainly young and with good performance status). Others articles indicate higher rates of neutropenic sepsis, which may be more typical of clinical practice. M Schwenkglenks, et al. (J Haematol Oncol. 2010; 3: 27) found a rate of 12%. Therefore it is likely that some high-risk patients receiving ABVD will in fact have a risk above 20%.	Many thanks for bringing this to our attention. The paper quoted noted a high incidence of neutropenic sepsis. We have added the evidence you have suggested to the table.
Lymphoma Association	40.02	Full	37	11	We agree with this recommendation but it should be made clear whose responsibility it will be to implement and fund this research.	It is not possible for NICE to determine who should implement or fund this research.
Lymphoma Association	40.03	Full	42	29	We agree with this recommendation and the conclusion that it is better to risk over-treatment than to under treat and put the patient at risk of developing life-threatening infection.	Thank you for your comment.
Lymphoma Association	40.04	Full	44	33	We believe that access to a 24-hour specialist oncology advice service is essential and will prove cost-effective in the long run. It is not clear however whether the intention is that this should be a *local* 24-hour advice service rather than a national one that might not be able to give the level of specific local advice	Thank you We agree but this will be a matter for local implementation, so it is not possible for the guideline to make recommendations on this issue.

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					needed.	
Lymphoma Association	40.05	Full	46	8 and 24-28	Resolving the uncertainty about the most helpful type of support and information to give patients and carers must be achieved urgently. There needs to be a national consensus to ensure consistency and clarity which is currently lacking.	Thank you, we agree.
Lymphoma Association	40.06	Full	49	1 and 13-22	The recommendation should state more clearly which health professionals should be included in this training. We feel that this should include primary care (GPs and nurses who might be visiting patients in their own homes, or nurses in residential homes) but this is not made explicit. We are aware of at least one unnecessary death as a result of a GP giving oral antibiotics instead of sending the patient for assessment in secondary or tertiary care. More specific advice, such as a national specification, on the minimum to be covered in this training would be useful in order to avoid an inadequate level of training being provided in some areas.	We believe that "healthcare professionals who come into contact with patients on anti-cancer treatment" is self explanatory. It is not within the remit of this guideline to develop minimum training standards. This recommendation has been highlighted to the Implementation team at NICE.
Lymphoma Association	40.07	Full	52	14	We agree with this recommendation.	Thank you for your comment.
Lymphoma Association	40.08	Full	53	23-32	We do not feel that urgent assessment in hospital for people who do not turn out to have neutropenic sepsis would cause unnecessary patient anxiety as patients are likely to be highly anxious about the risk of developing severe infections and would appreciate the reassurance.	Thank you for your comment. The GDG felt that patient anxiety could be a consequence of urgent assessment in hospital.
Lymphoma Association	40.09	Full	53	44	We agree that this would be valuable research.	Thank you for your comment.

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Lymphoma Association	40.11	Full	65	1	We agree with this recommendation though the motivation for this should not be to discharge patients early in order to discharge them and save money but to identify high risk patients. We would like to see 'haematology' added to 'oncology team' as leukaemia and lymphoma are associated with some of the highest risks of NS and are generally managed by haematologists not oncologists. This should be added throughout the guidelines wherever it occurs in order to avoid confusion and the risk of a lack of understanding among hospital staff of their own haematology team's role in NS.	Thank you. Our motivation for making this recommendation is not to get patients discharged early in order to save money. For clarity, the GDG have amended the recommendation to "a healthcare professional with competence in managing complications of anti-cancer treatment".
Lymphoma Association	40.12	Full	110	22 - 32	Primary and secondary prophylaxis for non-Hodgkin lymphoma patients – cost effectiveness We question the assumptions used in the modelling that reached the figure of £1.2 million/QALY. These assumptions undermine the credibility of the conclusions drawn. See our comments on the Appendix (pages 171, 172, 203 and 205). We agree that there are very few studies and that they are of poor quality, therefore we believe there must be considerable doubt over any conclusions drawn. NHL covers a huge spectrum of disorders, which are treated very differently, often with regimens more aggressive than CHOP21. In addition, factors such as underlying patient characteristics (particularly age) can make a	Thank you, we have responded to your concerns where you have made comments on appendix 1 later in your submission. For the purposes of economic modelling, lymphoma patients were split into NHL and hodgkins groups, but we appreciate that considerable variation exists within this coarse subdivision. We have modified the research recommendation to take into account the lack of evidence in lymphoma, which we agree is a considerably heterogeneous group of diseases.

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					huge difference. We do not believe it is safe for all lymphoma patients to be considered one group. If the guidelines do not recommend prophylaxis in NHL, this will take away the flexibility and options for specialists to treat some NHL patients appropriately. Our concern is that funders will use this omission to refuse doctors permission to use these agents in any patients with NHL, not understanding the complexity of the disorder and the variations that must apply when treating each patient as an individual.	Whilst the recommendation to offer prophylaxis does not specifically include patients with aggressive lymphoma, we have not recommended that these patients don't have prophylaxis.
Lymphoma Association	40.13	Full	111	14-18	The same concern applies about the validity of the assumptions made to achieve a >£11.6 million/QALY for adult/elderly patients with Hodgkin lymphoma.	For the purposes of economic modelling, lymphoma patients were split into NHL and hodgkins groups, but we appreciate that considerable variation exists within this coarse subdivision. We have modified the research recommendation to take into account the lack of evidence in lymphoma. Whilst the recommendation to offer prophylaxis does not specifically include patients with aggressive lymphoma, we have not recommended that these patients don't have prophylaxis.
Lymphoma Association	40.16	Full	112	23-42	The document states that the available evidence (which was of low quality) concerned only *short-term* data for mortality and	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low.

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						In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations. Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
					bacterial resistance. We feel that in both respects it is not acceptable simply to ignore possible longer term effects that are not apparent in these studies.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are

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						expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring

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						of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Lymphoma Association	40.15	Full	112	12-14	We are concerned at the recommendation that prophylaxis with quinolone should be given in *all* solid tumours and *not at all* in NHL. A statement is made that the analysis is focused on an outpatient group, yet it would appear that recommendations apply to all. Certain types of NHL require chemotherapy regimens that require inpatient care and are similar to therapy for leukaemia yet it appears that the recommendations apply to all cases of NHL rather than a restricted group. Again we feel it is vital to emphasise the complexity of lymphoma and the danger of producing guidelines that prevent specialists treating patients appropriately as individuals.	Whilst the recommendation to offer prophylaxis does not specifically include patients with aggressive lymphoma, we have not recommended that these patients don't have prophylaxis. No recommendation beyond a research recommendation has been made regarding NHL patients. This guideline has been produced to guide specialists in their management, and does not prevent the appropriate treatment of individuals.
Lymphoma Association	40.14	Full	112	1	While we welcome the fact that the recommendation of prophylaxis with quinolone includes all adult patients having stem cell transplants, we are disappointed that, on the basis of the above cost effectiveness data, there are no recommendations for prophylaxis with G-CSFs to be offered to high-risk lymphoma patients. Cost-effectiveness depends on the baseline risk of the patients yet this has not been considered in the analysis.	A range of different baseline risks were tested in one-way sensitivity analysis (5-100%) for each chemotherapy cycle. However, for all three patient sub-groups, the results show that even when 100% risk is tested, G-CSF is still not cost effective compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. A recommendation on the use of G-CSF for

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						the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible

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						to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
Lymphoma Association	40.17	Full	113	44-47	The document states that there is a lack of data so no recommendation can be made. We are concerned that in a document that is making many recommendations on sparse evidence, this will effectively be equivalent to a 'Do not use' recommendation.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices.

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						One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
Lymphoma Association	40.18	Full	113	49-52	We welcome this view and the inclusion of stem cell transplant patients in the recommendation. Again we wish to emphasise that some lymphoma treatment is equivalent to leukaemia treatment so we believe this should not be excluded.	Whilst the recommendation to offer prophylaxis does not specifically include patients with aggressive lymphoma, we have not recommended that these patients don't have prophylaxis. No recommendation beyond a research recommendation has been made regarding NHL patients.
Lymphoma Association	40.19	Full	114	13-26	While we welcome the CDG decision not to close the door on the use of G(M)-CSF, it is unacceptable that patients in some parts of the country are unable to access potentially beneficial treatments that are available to patients elsewhere. Access to G(M)-CSF should be on the basis of clinical judgement rather than	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity.

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					geographic location. In many places, this exclusion of a positive recommendation will be taken as a 'do not use' judgement.	Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of

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						G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
					We are disappointed at the limitations of the scope of the guideline. We believe the short-term assumptions used have distorted costs and therefore the recommendations. It is not acceptable to ignore long-term survival even though it adds complexity and uncertainty due to the lack of evidence.	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations. Reference: Sung L, Nathan PC, Alibhai SM,

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						Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
Lymphoma Association	40.20	Full	114	39	We believe this recommendation should include adults in the research to be conducted. There is an urgent need to address the lack of research in lymphoma.	We have amended our recommendation for further research to include these patients. Thank you for highlighting this omission.
Lymphoma Association	40.10	Full	58 and 61	37 and 28	We agree with these recommendations.	Thank you for your comment.
Lymphoma Association	40.21	Full	121	1	We agree with this recommendation.	Thank you for your comment.
Lymphoma Association	40.22	Full	139	34	We agree with this recommendation.	Thank you for your comment.
Lymphoma Association	40.23	Full	148	1	We agree, providing the patient's social and clinical circumstances are taken into full account. A patient living alone may not be as able to decide when and how to return to hospital 'if a problem develops'. It is also important that the hospital set-up is appropriate to facilitate the patient's early return. This outpatient therapy can only be effective if there is first a very robust assessment of the patient's risk by personnel who have been well trained. The patient's psychosocial attitudes to health (eg hesitancy to 'bother the doctor') become particularly important if they live alone or with an elderly partner, especially considering just how non-specific some septic symptoms can be	Thank you, we agree. Additional text has been added to the linking evidence to recommendations section to clarify a patients' "social and clinical circumstances".
Lymphoma	40.24	Full	154	1	We agree. Does the term 'a healthcare	We believe that this text provides an

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Association					professional with recognised professional competence in managing complications of anti-cancer treatment' need to be more precisely defined? We also suggest that it is emphasised that 'daily' includes the weekend.	overarching definition. We believe that "daily" would be commonly understood to include the weekend.
Lymphoma Association	40.25	Full	158	1	As above re defining the terminology more precisely.	We believe that this text provides an overarching definition.
Lymphoma Association	40.26	Full	159	4-9	This seems a sensible recommendation but we feel that patient inclusion and exclusion criteria would need to be carefully determined so that patients who remain septic at 24 hours are not put at risk of death. In addition, we wonder whether there would be recruitment and ethical issues for patients who might be putting themselves at risk by switching to oral antibiotics within 24 hours.	We agree these are important issues and believe that they should be taken into account when designing the trial.
Lymphoma Association	40.27	Full	163	1	We would support patients being in their own homes as soon as safely possible but it is important to emphasise that appropriate written/oral advice must be given, patients' home circumstances must be suitable and that the facilities are in place within the hospital for patients to re-access the service if needed. There should be a definition of exactly *which* healthcare professionals are professionally competent to assess these patients and make the decision.	Thank you, we agree. Additional text has been added to the linking evidence to recommendations section to clarify a patients' "social and clinical circumstances". We believe that "healthcare professionals who come into contact with patients on anti-cancer treatment" is self explanatory.
Lymphoma	40.28	Full	166	1	We agree with this recommendation.	Thank you for your comment.

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Lymphoma Association	40.29	Full	171 107	27-32 9-12	Model B: Dose-reduction chemotherapy The assumption used in the modelling that treatment would be dose reduced after a single episode of NS and would stop following two episodes of NS does not reflect clinical practice in lymphoma where large numbers of patients are young and being treated with curative intent. The results of an economic analysis that uses such an assumption have to be questioned.	It is acknowledged that not all Non-Hodgkin lymphoma (NHL) patients will necessarily receive dose-reduction chemo or discontinue chemotherapy after incidence of neutropenic sepsis. That's why structural sensitivity analysis (see section A4.1) has been conducted to test the robustness of results in model B. In structural sensitivity analysis, Model A has been adopted for NHL patients. However, the conclusion of Model A proved to be the same as Model B (see Section A7.1.2); which means our conclusion is robust to changes in model structure.
Lymphoma Association	40.30	Full	172	1 and 22-28	The limitation of the economic model to a very short time horizon does not reflect the real value of prophylaxis for lymphoma patients. Clearly using only a 3-month period will restrict the estimate of apparent benefit from a reduction in mortality. Using a lifetime horizon, particularly in young patients with lymphoma who may go on to live for 40 or more years, would give a very different cost/QALY.	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that

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						Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations. Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
Lymphoma Association	40.31	Full	203	1-25	We are concerned about the exclusion of the impact of different prophylactic strategies on subsequent courses of chemotherapy and RDI, particularly where there is curative intent. In DLBCL, HL and adjuvant breast cancer maintenance of dose-intensity is extremely important and the evidence shows that only G-CSFs (not antibiotics) improve RDI. Two papers not cited in the guidelines (Bosly A et al. Ann Haematol 2008; 87:277–283; Pettengell et al. Ann Haematol 2008; 87: 429–430) both demonstrate the importance of delivering full dose-intensity in NHL patients. In addition M Schwenkglenks, et al. J Haematol Oncol. 2010;3:27 describes the risk of death and how poor dose delivery is in HL patients who develop NS, particularly patients over 70 years.	In order to investigate this effect we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated

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					It is disappointing that there is no recommendation in the guidelines based on the statement that there is the possibility that secondary prophylaxis "will become the most cost-effective strategy, if the impact of prophylactic strategy on subsequent chemotherapy was modelled in cost-effectiveness analysis." If this is the case, there should be a recommendation in the guidelines that the research necessary to provide the data required to do the modelling should be carried out instead of leaving this buried in the Appendix.	19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline Although our systematic review of cost-effectiveness studies did identify several studies trying to model the impact of using G-CSF on patients long-term survival (by maintaining chemotherapy dose) (see cost effectiveness evidence section for chapter 5); none of these studies used any direct clinical data. Instead, these studies were trying to build an indirect relationship between use of G-CSF and long-term survival. They stated that G-CSF could prevent neutropenic sepsis; neutropenic sepsis is a risk factor of receiving dose-reduction chemotherapy and dose-reduction chemotherapy is a risk factor for patient long-term survival. Then based on this hypothesis, the authors claimed that G-CSF could improve patients long-term survival. Furthermore, a recent meta-analysis (Shitara et al., 2011) shows that neutropenia experienced during chemotherapy is actually associated with improved survival in patients with advanced cancer or haematological malignancies undergoing chemotherapy. This implies that experiencing side effects of chemotherapy might not be associated with impaired long term survival. Therefore the GDG were very unsure about the validity of

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						the indirect logic used in these published cost-effectiveness studies and the derived conclusion and did not consider it appropriate to use the methodology from the existing studies to model the impact of using G-CSF on patients long-term survival for this guideline.
Lymphoma Association	40.32	Full	205	7	The price of G-CSFs quoted here is not what is generally paid within the NHS and prices are coming down because of the availability of generics. Had more realistic costs been used in the economic modelling it is likely the analysis of cost-effectiveness would have been very different.	All G-CSFs are biosimilars that in terms of regulation and aren't treated as generics. Therefore, whilst each PCT probably has its own agreement, there is no nationally negotiated discount as normally found on the CMU website. Given this the GDG decided to use the BNF price since there is no other reliable NHS source. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A).
Medicines and Healthcare products Regulatory Agency	4.00	Full NICE guideline	112 7	1 13	The guideline states: 'Offer prophylaxis with a quinolone during the expected period of neutropenia to all adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours.'	Thank you for your comment. No recommendation has been made for a specific product.

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					Please note that only ciprofloxacin is approved .for 'prophylaxis of infections in neutropenic patients' and only in adults (not in children nor adolescents). Norfloxacin, ofloxacin, levofloxacin and moxifloxacin are not licensed for this purpose.	
Medicines and Healthcare products Regulatory Agency	4.01	Full NICE guideline	133 8 12	1 3 3	The guideline states that the 'recommendations are intended for use in patients of any age' (page 10, line 7). Section 1.4.3.1 states that (all patients) should be offered 'beta lactam monotherapy with piperacillin–tazobactam as initial empiric antibiotic' Tazocin (piperacillin–tazobactam) has approval for the indication "the management of neutropenic patients with fever suspected to be due to a bacterial infection" in the age range children 2–12 years, adolescents and adults.	The evidence appraised for this topic included patients of all ages. No excess adverse events were noted in children younger than 2. Therefore the GDG agreed it was appropriate to recommend the use of this drug for all ages. We have added a footnote to clarify the licensed indications.
Merseyside & Cheshire Cancer Network	15.09	Full NICE Version	general		The guidance needs to be explicit in terms of the use of GSCF for primary & secondary prophylaxis.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation.
Merseyside & Cheshire Cancer Network	15.03	Full NICE Version	42 12	28 17	The GDG recognise the limited evidence base for a strict definition of neutropenic sepsis. The strict adherence of a definition based upon fever 38 or more and ANC <0.5 may result in a large	We agree that patients with neutropenic sepsis may not present with fever but have other symptoms and signs consistent with significant infection. We have amended the

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					cohort of borderline cases not receiving appropriate antibiotics. MCCN current practice would advocate standard NS policies for all patients where ANC less than 1.	recommendations and algorithm to reflect this. The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of $\leq$0.5. The evidence also showed that increased temperature was associated with an increase in infection. The lowest value for fever studied in the evidence was 38^{o}C and the GDG decided to adopt this value in their definition for neutropenic sepsis.
Merseyside & Cheshire Cancer Network	15.04	Full NICE Version	65 13	1 4	Validated risk indices have been developed to determine the risk of mortality when assessed at presentation. There is no clear evidence base, that we are aware of, to support the use of MASCC etc in the decision to step down or promote early discharge. We believe that MASCC scoring should become routine for all cases but that this should be based upon presentation.	We acknowledge that evidence on the MASCC risk assessment tool is derived from status at presentation. However, there is good evidence from paediatric risk stratification tools that re-assessment is effective and they are able to assess fitness for discharge. Additional text has been added to the linking evidence to recommendations section to clarify this.

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Merseyside & Cheshire Cancer Network	15.00	Full NICE Version	112 10	1 24	We disagree with the recommendation that all solid tumour patients should receive primary prophylaxis with oral quinolones. The lack of evidence for evolving resistance and secondary infection is not considered a sufficient basis for this recommendation. We do not concur that the evidence suggests the benefits outweigh the risk but rather that more evidence is required.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only

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						be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Merseyside & Cheshire Cancer Network	15.01	Full NICE Version	121 11	1 10	The GDG recognise the lack of evidence for recommending 'immediate' antibiotics in cases of suspected NS. Local MCCN audit has shown that >50% of suspected NS is not shown to be proven and that a significant proportion of patients present with low risk NS. The recommendation of immediate treatment unnecessarily skews priorities within A&E depts. The guideline should emphasis the need for risk directed approaches whereby high risk patients based upon shock or MEWS are immediately resuscitated but that low risk groups may be managed adequately within existing 4hour targets and once full information on blood results are available.	We acknowledge that this is an important clinical issue and was debated at length by the GDG. However the evidence was not clear enough to recommend a specific time or specific clinical group where time to antibiotic delivery altered the patients outcome. Hence the recommendation does not define a specific time period or limit its indication to a specific clinical presentation.
Merseyside & Cheshire Cancer Network	15.02	Full NICE Version	133 12	1 3	The GDG fails to emphasise the evidence base for initial oral antibiotics for low risk cases. Oral antibiotics should be identified as an alternative from the outset where risk has been determined by a validated tool	We agree that the GDG has not specifically commented on the use of outpatient management at the outset of cases for low risk patients. Whilst there was some evidence to support immediate discharge, the GDG did not consider that it was strong enough to support recommending a specific timeframe. Instead they recommended research into very

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						early (first 24 hours) oral antibiotic therapy.
Merseyside & Cheshire Cancer Network	15.05	Full NICE Version	148 13	1 10	We are concerned that the GDG emphasises the serious medical complications of NS with rapid assessment and immediate antibiotics and then concludes that outpatient therapy is acceptable for those at low risk. The evidence base for OPD management is lacking and the practical aspects of determining risk at presentation are well described. We believe that the majority opinion supports 'early discharge' after an initial period of inpatient review and assessment rather than a high risk strategy of supportive outpatient care in the absence of a robust assessment pathway.	The GDG has not specifically commented on the use of outpatient management at the outset of cases for low risk patients. Whilst there was some evidence to support immediate discharge for low risk patients, the GDG did not consider that it was strong enough to support recommending a specific timeframe. Instead they recommended research into very early (first 24 hours) oral antibiotic therapy. We believe that other recommendations in the guideline are consistent with an admit/early discharge strategy.
Merseyside & Cheshire Cancer Network	15.06	Full NICE Version	154 13	1 16	The GDG recommendation that daily review should be based upon a validated risk assessment is not evidence based. The validated tools are based upon presentation	We have added text to the linking evidence to recommendation section to clarify why the GDG recommended daily review. We acknowledge that evidence on the MASCC risk assessment tool is derived from presenting status. However, there is good evidence from paediatric risk stratification tools that re-assessment is effective.
Merseyside & Cheshire Cancer Network	15.07	Full NICE Version	158 14	1	The GDG recommendation that a switch to oral antibiotics based upon a validated risk assessment is not evidence based. The validated tools are based upon presentation	We have added text to the linking evidence to recommendation section to clarify why the GDG recommended daily review. We acknowledge that evidence on the MASCC risk assessment tool is derived from presenting status. However, there is good evidence from paediatric risk stratification tools that re-assessment is effective. Additional text has been added to the linking evidence to recommendations section to clarify this.

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Merseyside & Cheshire Cancer Network	15.08	Full NICE	163 14	1 9	The validated risk assessment tools have not been developed to fitness for discharge.	We acknowledge that evidence on the MASCC risk assessment tool is derived from presenting status. However, there is good evidence from paediatric risk stratification tools that re-assessment is effective and they are able to assess fitness for discharge. Additional text has been added to the linking evidence to recommendations section to clarify this.
NCRI/RCP/RCR/ACP/JCCO	34.00	Full	General	general	The NCRI/RCP/RCR/ACP/JCCO are grateful for the opportunity to comment on the draft guideline. We would like to congratulate NICE on this document which we believe contains many sensible elements. However, our experts do have concern in some areas which are outlined below.	Thank you for your comment.
NCRI/RCP/RCR/ACP/JCCO	34.03	Full	General	general	Ciprofloxacin prophylaxis This is less contentious for out-patients but highly contentious for in-patients due to the risks of hospital acquired infections eg C diff and MRSA.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall

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						mortality (see linking evidence to recommendations section). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
NCRI/RCP/RCR/ACP/JCCO	34.04	Full	General	general	The role of G-CSF The lack of recommendation of G-CSF for any patients due to cost is considered highly contentious. Some experts feel that this is out of line with the EORTC updated guidelines 2010.	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their

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					The authors indicate that this does not matter as the EORTC guidelines are based on G-CSF vs no prophylaxis and that they were not based on UK studies. However, our experts feel that the lack of recommendation will be extremely concerning to the oncology community.	recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices.

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						One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
					The guidance also does not comment on the use of G-CSF to reduce in-patient stay in those who are admitted with neutropenic sepsis. In these circumstances usage may well be very cost-effective because of reduced LOS.	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered

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						by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Consequently, length of stay was not included in the model. Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
NCRI/RCP/RCR/ACP/JCCO	33.05	Full	General	general	Timing of therapy The recommendation to 'treat febrile neutropenia immediately' is not clear. It should be made more by giving a target eg 1 hour as per the NCEPOD guidance.	We acknowledge that this is an important clinical issue and it was debated at length by the GDG. However the evidence was not clear enough to recommend a specific time or specific clinical group where time to antibiotic delivery altered the patients outcome. Hence the recommendation does not define a specific time period or limit its indication to a specific clinical presentation.
NCRI/RCP/RCR/ACP/JCCO	34.01	Full	5 (and elsewhere)	6	Definition of Febrile Neutropenia The draft states that the neutrophil count should be < 0.5. The evidence given does not support this and from Figure 1.7 it is clear that the	The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad

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					majority of centres use a neutrophil count of < 1.0. Our experts would suggest that using <0.5 as a cut off point is potentially dangerous and may lead to additional deaths eg a neutrophil count of 0.6 on admission may be 0.1 within 24 hours after chemotherapy.	definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of $\leq$0.5.
NCRI/RCP/RCR/ACP/JCCO	34.02	Full	9	29	Audience In the Introduction part 'Who is the guideline intended for?' – it is stated that it is to prevent febrile neutropenia in cancer patients. However, with increasing numbers of rheumatology patients on MTX and Ulcerative colitis patients on 6-MP this really should be broadened to include all patients being treated with cytotoxic agents.	The remit for this guideline was to develop recommendations on the prevention and management of neutropenic sepsis in cancer patients. Consequently we have not looked at any other patient groups.
NCRI/RCP/RCR/ACP/JCCO	33.06	Full	70	17	Most centres do not use prophylactic quinolones as major concern about C difficile as a risk of this. At most use is restricted to very myelosuppressive regimens of chemotherapy	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia.

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						The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities

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						where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
Neonatal & Paediatric Pharmacists Group	20.00	Full	general		This response contains collated comments from members of the Neonatal and Paediatric Pharmacists Group. In addition we wish to support the comments made by the Royal Pharmaceutical Society in their response to the Consultation.	Thank you for your comment.
Neonatal & Paediatric Pharmacists Group	20.08	Full	General		The guidance needs to be very specific about whether all parts or only some apply to patients undergoing HSCT. For example it is clear that the guidance about quinolone prophylaxis includes patients undergoing HSCT. It is not apparent whether or not the monotherapy recommendation applies to HSCT patients.	The recommendations in the guideline are applicable to all patients unless otherwise stated. This is clarified in the foreword to the guideline.
Neonatal & Paediatric Pharmacists Group	20.04	Full NICE	42 8 and 12	28 11 17	In some units a temperature of >38 ºC on two occasions or >38.5º on one occasion is used in diagnosis.	We agree, this has been cited in chapter 1. However we do not think this would prevent the recommendation in the guideline from being followed.
Neonatal & Paediatric Pharmacists Group	20.06	Full NICE	114 17	39 19	We agree with this research recommendation. For children, in particular, the adverse events potentially associated with quinolone antibiotics should be evaluated. We also note that the GDG considered that the lack of evidence in this area meant they were unable to recommend either prophylactic antibiotics or GCSF in this patient group. This is a key issue for us as NPPG.	Thank you for your comment.
Neonatal & Paediatric Pharmacists Group	20.01	Full NICE	133 8 and 12	1 5	Piperacillin/tazobactam is not suitable for patients with penicillin allergy. This is common in clinical practice and should be mentioned in the Guidance. It would be useful if the Guidance proposed an alternative for such patients.	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst

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						we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.
Neonatal & Paediatric Pharmacists Group	20.02	Full NICE	133 8 and 12 and	1 6	Use of an aminoglycoside such as gentamicin is common practice in some Paediatric Oncology Units if the patient's condition is serious. For example we would have concerns about using monotherapy in a patient presenting with septic shock. In this clinical situation monotherapy is inappropriate and it may well be appropriate to combine piperacillin/tazobactam with an aminoglycoside. We would suggest that "CLINICAL" in addition to a microbiological indication should be considered for use of an aminoglycoside. It may also be appropriate to consider microbiological contraindications to monotherapy in networks of care rather than individual institutions ie reflecting actual patient pathways rather than flora of individual	The recommendations made were based on the evidence appraised for this topic which did not support addition of aminoglycosides to any group as initial empiric therapy. Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills. This is explicitly stated in the methodology section of this guideline. We have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern The term "local" in the recommendations is

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					institutions. We are aware that some institutions already use initial dual therapy due to "local microbiological considerations" such as resistance patterns and consider that this statement should be retained in addition to "Clinical" considerations.	not intended to specify individual institutions. The definition of this in the glossary clarifies that "local" refers to the community/healthcare setting. Thank you for your comment.
Neonatal & Paediatric Pharmacists Group	20.03	Full	137	1	The recommendation not to offer empiric glycopeptides to patients with central venous catheters needs further qualification. For example it would be reasonable to add vancomycin or teicoplanin to the therapy of patients who are known MRSA carriers or who have had previous episodes of MRSA infection. We would suggest that addition of the word "routinely" to this recommendation would provide clarification.	We have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern.
Neonatal & Paediatric Pharmacists Group	20.05	Full NICE	148 13	1 10	It would be useful if the guidance proposed options for outpatient antibiotic therapy. This may differ between adults and children.	We have stated in the linking evidence to recommendations section of section 6.5 that local microbiological resistance patterns vary. We have added text to clarify that choice of antibiotic may be influenced by prior prophylaxis. Consequently the GDG were unable to recommend a specific antibiotic strategy for adults or children.
Neonatal & Paediatric Pharmacists Group	20.07	Full NICE	159 18	8 11	We agree with this research recommendation which is important for the care of children.	Thank you for your comment.
Neonatal & Paediatric Pharmacists Group	20.09	Full and NICE	General		We wish to express our concern that there was no pharmacist input to the Guideline Development Group. It is widely recognised that	Thank you for your comment. At the time of scoping this guideline it became clear that the principal issue on antibiotic prescribing would

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					pharmacists have an important role to play in the management of cancer patients (both adults and children), often leading the development of guidelines for treatment. In addition antimicrobial pharmacists were previously recognised in Department of Health and Health Protection Agency Guidance with a recommendation that trusts should establish Antimicrobial Management Teams which should include an antimicrobial pharmacist. The lack of input from either of these groups of pharmacists needs to be considered carefully.	be choosing drugs based on patterns of antibiotic resistance; this would be guided by the microbiologist on the GDG. Although the guideline recommends the classes of drugs that would be appropriate, it does not address the details of individual drugs and their administration, therefore the specific expertise of a pharmacist for these issues was not needed.
NETSCC – Ref 1	8.08	Full	general		3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected? As far as the health economic side of the matter is concerned, recommendations are justified in the light of the lack of evidence (no relevant papers identified) and/or the unfeasibility of cost-effectiveness analysis (because the issue under investigation was considered of low/medium priority or of high priority but with no useful data for the economic evaluation of health care program to be performed). Due to the existing state of the art (weak evidence-based support), invoking the need for more research is hardly avoidable (although it might not be cost-effective for NHS). Eventually, the lack of evidence inspired the *de novo* economic model that gives a substantial added value to all this apparent research effort.	Thank you for your comment.
NETSCC – Ref 1	8.11	Full	general		3.2 Are any important limitations of the	Thank you for your comment.

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					evidence clearly described and discussed? All important limitations are clearly reported	
NETSCC – Ref 1	8.15	Full	general		4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence. Set aside the previous comments, the entire document is well conceived and written.	Thank you for your comment.
NETSCC – Ref 1	8.16	Full	general		Until page 68: As far as the health economic side of the matter is concerned, recommendations are justified in the light of the lack of evidence (no relevant papers identified) and/or the unfeasibility of cost-effectiveness analysis (because the issue under investigation was considered of low/medium priority or of high priority but with no useful data for the economic evaluation of health care program to be performed). In general, recommendations reflect the GDG's effort to offer guidance to clinicians and health care decision-makers, despite the general lack of empirical evidence.	Thank you for your comment.
NETSCC – Ref 1	8.19	Full	general		Some minor points:	Thank you for your comment.
NETSCC – Ref 1	8.01	Full	169-201		2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelines manual). The following comments refer to health economics issues: Appendix A (*de novo* economic model) perfectly complies with the	Thank you for your comments.

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					NICE's Guidelines Manual guidelines, Appendix H: Methodology checklist: economic evaluations. NICE, 2006.	
NETSCC – Ref 1	8.00	Full	223-226		1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached) No. The work fulfils perfectly the declared intentions of the NICE guideline detailed in the Appendix D of the document.	Thank you for your comment.
NETSCC – Ref 1	8.22	Full	7-8		4.2 Please comment on whether the research recommendations, if included, are clear and justified. Key research recommendations are clearly detailed and justified, due to the lack of epidemiological, clinical and cost-effectiveness data on neutropenic sepsis in UK. However, as commented in the previous sections of the referee's report, any remark about the cost-effectiveness for the NHS of the recommended, future research on this topic would be welcomed.	We agree that EVPI may have been an interesting avenue to explore. However a different topic was assessed as highest priority for economic investigation so it was not possible to undertake an EVPI analysis in addition.
NETSCC – Ref 1	8.02	Full	114	39	2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise. "If RCT should be undertaken to investigate the cost-effectiveness of primary prophylaxis…" there's probably a strong case for calculating (or mentioning in the document the need for, at least) in the subsequent *de novo* economic model the Expected Value of Perfect Information as a necessary (but not sufficient, though) condition to assess the cost-effectiveness for NHS of further research on this topic (Briggs, A., Claxton K, Sculpher M, Decision Modelling for Health Economic Evaluation. 2006, Oxford: Oxford University Press).	Undertaking an EVPI analysis for this question was not considered a priority for investigation.

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NETSCC – Ref 1	8.09	Full	148	37-38	"The GDG decided to recommend that patients at low risk of severe sepsis can be offered outpatient antibiotic therapy but did not specify a route of administration". As far as the outpatient setting is concerned, this recommendation was made by: 1) Bucaneve G, Menichetti F and Del Favero A. Cost analysis of 2 empiric antibacterial regimens containing glycopeptides for the treatment of febrile neutropenia in patients with acute leukaemia. PharmacoEconomics 1999;15:86-95; 2) Lamont E, Seaton AR, Macpherson M, Semple L, Bell E and Thomson AH. Development of teicoplanin dosage guidelines for patients treated within an outpatient parenteral antibiotic therapy (OPAT) programme. Journal of Antimicrobial Chemotherapy 2009; 64:181-187. However, the main issue is the availability of validated score systems to rank neutropenic patients at low, medium or high risk of developing sepsis and an effective and well organized OPAT(or outpatient, in more general terms) system.	Thank you for this information. Risk stratification regarding risk of septic complications was reviewed in section 4.4. The implementation of these recommendations will be a matter for local determination.
NETSCC – Ref 1	8.10	Full	154	31-32	The need for validated score systems is even more important for patient who develop neutropenic sepsis and are at risk of incurring (potentially high-cost) sepsis complications.	We have added this to the linking evidence to recommendations section.
NETSCC – Ref 1	8.20	Full	158	38	A full stop is missing after "…antibiotic"	Thank you for your comment. We have added

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						the full stop.
NETSCC – Ref 1	8.03	Full	159	8	The "Economics of more research is needed" (please see Phillips CV. Int J Epidemiol. 2001 Aug;30(4):771-6) is invoked (here and often throughout the document). In this instance, it refers to investigate when the right moment for the switch from iv to oral antibiotic occurs. Again, EVPI can be a useful tool to address this issue quantitatively within the subsequent *de novo* economic model. Besides, the EVPI for each single uncertain parameter (EVPPI) would be of remarkable interest to support funds and expertise allocation for further research (before planning and performing an expensive RCT). In the case of the switch to oral antibiotic, the EVPPI could focus on: number of days of fever; proportion of patients who fulfill the requirements to switch from iv to oral antibiotic; cost of failure of switch (premature switch); cost of delayed switch.	We agree this may have been an interesting avenue to explore. However a different topic was assessed as highest priority for economic investigation so it was not possible to undertake an EVPI analysis for this question.
NETSCC – Ref 1	8.04	Full	170	51	Authors assume that "The sensitivity and specificity of diagnosing neutropenic sepsis is 100%." These seem extremely optimistic research hypotheses. Moreover, I am not clear why these assumptions were not tested through sensitivity analyses (especially the probabilistic one).	The aim of this economic analysis was to evaluate the cost-effectiveness of different prophylactic strategies for preventing neutropenic sepsis. The GDG felt that the sensitivity and specificity of diagnosing neutropenic sepsis was unlikely to have an impact on the relative cost-effectiveness of different prophylactic strategies; therefore they agreed to make this assumption.
NETSCC – Ref 1	8.05	Full	176	1-36	Authors correctly focused on utility decrement due to incidence and treatment of neutropenic sepsis (base-case model) and death (explorative analysis only). However, it would be worth spending some lines to explain how the negative QALYs (which are perfectly legal) they	An explanation about why the QALY value is negative has been added to the full economics report.

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					report in the subsequent cost-utility tables were calculated.	
NETSCC – Ref 1	8.06	Full	178	20	Point estimate of the cost of an excess hospital bed day is £ £255, but the assumed range is £100-£1000. In all likelihood, the upper bound of this range refers to an excess day in Intensive Care Unit (ICU). Provided data availability, it would be interesting to detail in separate lines of the same table the cost of an excess hospital bed day in: oncological ward; oncohaematological ward (for both day-hospital and inpatient admission) and ICU (for inpatient admission only, I guess).	Thanks for your comment. However the NHS reference cost and PSSRU (Unit Costs of Health and Social Care 2010) didn't report any of the cost you mentioned except mean average cost for Local Psychiatric Intensive Care Units for 2009: £617 (range: £489-674). And the upper bound of this ICU cost was covered by the range that we used in the economic analysis. References: 1. NHS reference costs 2009-2010. Department of Health.13 January 2011. 2. Curtis L. unit costs of health and social care 2010. Canterbury: Personal social services research unit, University of Kent; 2010
NETSCC – Ref 1	8.17	Full	201	26-32	Results of the *de novo* economic model are very interesting, as they prioritize low-cost prophylactic strategy: - quinolone in primary prophylaxis is the most cost-effective prophylactic strategy in patients with a solid tumour who can take quinolone; - no prophylaxis is the most cost effective prophylaxis strategy for patient with a solid tumour who cannot take quinolone, as well as for patient with Hodgkin or non-Hodgkin lymphoma. As an aside, from a cost-effectiveness viewpoint these results can either support or discourage	Thank you for this information

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					the need for further empirical research on neutropenic sepsis in UK, in that they confirm that the cheapest prophylactic strategies are also cost-effective (although in the light of the existing evidence).	
NETSCC – Ref 1	8.13	Full	202	41-47	2) The comparison of each prophylactic strategy with nothing/placebo only and the possible resulting bias (of unknown direction, though), as well as the unfeasibility of a network meta-analysis. This is probably the most relevant limitation, in that it may reduce the external validity of the results. Provided the potential cost-effectiveness of the related research, it would be interesting to investigate on a sample of NHS facilities the proportion of would-be neutropenic patients undergoing chemotherapy who are not prophylaxed against sepsis (do nothing) but are only provided with empirical treatment after sepsis is clinically suspected or confirmed.	Thank you for your interesting observation. Such a strategy has been suggested in the research recommendation regarding the use of preventative GCSF and/or antibiotics in children and young people undergoing cancer treatment and at risk of NS.
NETSCC – Ref 1	8.12	Full	202	18-23	1) The possible impact of G(M)-CSF on short-term overall mortality (that may arise because of a statistical error due to the small sample size of the included studies).	The GDG acknowledged that the relative risk data of short-term overall mortality for each prophylactic strategy was very sparse. As a result, the GDG decided to not use the sparse data in the economic model, and assumed that none of the prophylactic strategies could improve patient's short-term mortality.
NETSCC – Ref 1	8.21	Full	202	8	Comma should be replaced by a full stop after "…probabilistic sensitivity analysis,"	The comma has been replaced by a full stop.
NETSCC – Ref 1	8.14	Full	203	6-14	3) The impact of different prophylactic strategies on subsequent courses of chemotherapy was not considered in the economic analysis for the	Thank you for your comment

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					following reasons: lack of data; uncertainty of the relationship between chemotherapy dose intensity and long-term survival; the impossibility to collect *ad hoc* data for investigating the relationship in terms of efficacy (if any) between each chemotherapy protocol and each prophylactic strategy on patient long-term survival.	
NETSCC – Ref 1	8.18	Full	204	53	Cost-effectiveness of quinolone in primary prophylaxis shall be wisely contrasted again "The impact of prophylactic quinolone on antibiotic resistance" (from an economic viewpoint, too).	We agree. Cost effectiveness could be taken into account in such future research.
NETSCC – Ref 1	8.07	Full	222	31-32	Interestingly, according to the most recent literature on modelling in health economics (Briggs, A., Claxton K, Sculpher M, Decision Modelling for Health Economic Evaluation. 2006, Oxford: Oxford University Press, 92) Authors reports that "Health states can be considered worse than death and thus have a negative value". This clarification – that allows shifting the lower bound of utility range from the (customarily) zero to minus infinity - helps the reader who comes across negative QALYs in the *de novo* economic model (as remarked in a previous comment).	In the economic analysis, we only considered the QALY loss due to incidence and treatment of neutropenic sepsis. This is why the derived QALYs are negative.
NETSCC – Ref 2	9.00	Full	General		1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached) Overall this is a comprehensive report that has covered the main issues: burden of disease, treatments (and their effectiveness), and cost-effectiveness.	Thank you for your comment.

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NETSCC – Ref 2	9.19	Full	General		4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.	Thank you for your comment.
NETSCC – Ref 2	9.01	Full	general		The authors identified well the areas where further research is needed, and explained the lack of data from which their recommendations arise.	Thank you for your comment.
NETSCC – Ref 2	9.02	Full	general		2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual). The methods seem reasonable generally. I did not find anything major to comment upon. Specific comments are given in Section 2.2	Thank you for your comment.
NETSCC – Ref 2	9.05	Full	general		In this guideline, several tables report sensitivity and specificity. The former is relevant, but specificity has less clinical importance than its converse (false-positive rate = 1-specificity). This is because if the specificity is say 90/100, nothing more is done to the 90 patients (they have 'negative' results); but further tests and sometimes treatments are given to the 10 (unnecessarily). Again, this is probably HTA/NICE style, but researchers in screening/diagnostic tests often calculate the false-positive rate to get a better idea of the performance of the test in people without disease.	Thank you for your comment. We believe that the false positive rate could easily be calculated from the figures provided and therefore have not made this change.
NETSCC – Ref 2	9.16	Full	general		3.1 How far are the recommendations based on	A recommendation on the use of G-CSF for

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					the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected? The recommendations were well supported by the findings. Perhaps more could be said on G-CSF, in line with other guidelines (i.e. a clearer statement that it is effective for reducing febrile neutropenia, but the costs do not make it financially viable as routine care).	the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible

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						to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation.
NETSCC – Ref 2	9.17	Full	general		3.2 Are any important limitations of the evidence clearly described and discussed? No major limitation found in the clinical aspects of the report.	Thank you for your comment.
NETSCC – Ref 2	9.20	Full	general		I found most of the report relatively easy to read, though struggled a bit with the health economic sections (as many often do), and the discussions contained there.	Thank you for your comment.
NETSCC – Ref 2	9.22	Full			I found most of the report relatively easy to read, though struggled a bit with the health economic sections (as many often do), and the discussions contained there.	Thank you for your comment.
NETSCC – Ref 2	9.23	Full	general		4.2 Please comment on whether the research recommendations, if included, are clear and justified. I agree with all of the research	Thank you for your comment.

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					recommendations	
NETSCC – Ref 2	9.25	Full	general		Please make any additional comments you want the NICE Guideline Development Group to see, feel free to use as much or as little space as you wish. It is probably the HTA/NICE style, but I wonder whether some of the tables that show summary results from combining several studies (eg Table 4.1, 5.1) could be supplemented by meta-analysis forest plots, which show the extent of variability or consistency between studies.	Forest plots for any meta-analysis are available in the evidence review which accompanies the full guideline.
NETSCC – Ref 2	9.26	Full	general		If available, would it be worth adding a simple table summarizing similar guidelines from other major organisations, for comparison?	It is not part of NICE methodology to cross-reference non-NICE guidance.
NETSCC – Ref 2	9.03	Full	72-85		Tables 5.1-5.4: These are important data, as they relate to the efficacy of prophylaxis treatments. The authors should expand the methods section for this, because it was not sufficiently clear where the combined estimates come from, for each clinical endpoint.	More detail on the studies included in the pooled estimates, including forest plots of meta-analyses are available in the evidence review which accompanies the full guideline.
NETSCC – Ref 2	9.04	Full	12-14		In the Methods it would be useful to comment on the hierarchy of studies. I think that published systematic reviews take precedence, but it is not clear whether the NICE guideline researchers update these systematic reviews if there are several individual studies published since; and if so how. If not, what happens if say 10 trials are published after a systematic review? This is worth mentioning in the Methods.	Systematic reviews were updated if additional studies were found. The hierarchy of studies is included in the NICE guidelines manual, which has been cross-referenced. We use GRADE to evaluate the body of evidence contained within a systematic review rather than the review itself
NETSCC – Ref 2	9.11	Full	51-52		Table 4.1: The data on signs/symptoms look quite unreliable from the table, with wide ranges in brackets. This would be good data to collect	Individual study details and results are available in the evidence review which accompanies the full guideline.

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					from the suggested national cohort study (page 7, line 4). Some indication of the rates in the larger (largest) studies in Table 4.1 could help interpretation of this aspect.	
NETSCC – Ref 2	9.18	Full	109-110		The cost analyses for various therapies seemed to be based on QALYs. However, G-CSF does not reduce mortality so it is not surprising that all ICERs were above the £20k threshold. It is worth discussing potential cost-effectiveness analyses based on reductions in the risk of febrile neutropenia and fewer hospital admissions (shorter stay), to give a more balanced assessment/discussion.	Thank you for your comment, a reduction in risk of neutropenic sepsis and treatment cost (including admission rate) due to prophylactic strategy were covered in the economic analysis: please see Section A3.2.1 and A3.3.3.
NETSCC – Ref 2	9.21	Full	55-56		I commend the NICE researchers in attempting to provide simple/easy estimates in these tables. However, some of the pooled estimates are based on so few studies (minimum of 3). The 'average' of say 3 studies might not reflect them well. When there are say ≤5 studies, could an appendix table be provided showing the individual results from each study? The interested reader can then see clearly how similar or different they are to each other, and importantly to the pooled estimate in the main tables. A minor point, but when there are only 2 studies, the word 'range' is used in the tables, when only the separate estimates are given.	Individual study details and results are available in the evidence review which accompanies the full guideline.
NETSCC – Ref 2	9.24	Full	7	4	A properly designed cohort study nationally to estimate incidence would be very useful, and could be incorporated into future health economic analyses for the NHS, using more reliable data.	Thank you
NETSCC – Ref 2	9.06	Full	23	18	2.2 Please comment on the health economics	Thank you for your comment. We have amended the text.

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					and/or statistical issues depending on your area of expertise. The table has only 9 studies/audits, with quite scant data. It was not clear whether the findings given in the text below the table comes from these 9 audit reports, because if it does, then I think 'demonstrated' might be too strong given the sparse data. I suggest show more clearly where the conclusions come from, or tone down the language.	
NETSCC – Ref 2	9.07	Full	25		The clear increase in sepsis deaths over time is significant, and the evidence looks strong (being based on national statistics). This further justifies the importance of getting reliable data on the incidence of suspected and confirmed neutropenic sepsis, many of which do not lead to death from the suggested national cohort study (in order to get a better idea of burden in the UK/NHS).	Thank you, we agree.
NETSCC – Ref 2	9.08	Full	27	11	Figure 1.4 seems to support the discussion (line 11) that much of the rising incidence could be due to younger adults not complying to treatment (given that the largest increase in incidence is in myeloid leukaemia). Would the authors wish to make bolder statements about compliance in young patients, and whether to draw more attention to this in clinical practice?	This text is from the needs assessment which describes current practice in the UK. It does not examine the evidence nor does it make recommendations for future practice. As such, the GDG are not able to make any bolder statements.
NETSCC – Ref 2	9.09	Full	29	41	Please add the number of questionnaires sent out, so that the reader can easily see the response rate (80 out of how many?). Also, some comment that these 80 generally represent all centres is useful.	This is a reasonable suggestion. However, we are unable to give these figures because of the way the questionnaire was distributed. No list of all acute trusts leads was available when the questionnaire was sent out, so it was distributed via the cancer networks. We have clarifed this point in the document.
NETSCC – Ref 2	9.10	Full	32		Figure 1.8: The recommendation on page 5,	The GDG acknowledged that having a very

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					lines 4-6, is that a diagnosis of neutropenic sepsis should be made with neutrophil count <0.5 x10^9/litre. Given that 55-70% of centres use <1.0 x10^9/litre, would the recommendation need further clarification/justification? This issue is also covered on pages 41-42. Does the cut-off of <0.5 primarily come from Apostolopoulou et al 2010 (page 42, line 6)? It might be worth providing some indication on the expected difference in the proportion of cases with counts <0.5 and <1.0. Could there be patients who warrant treatment if their values are above 0.5 but <1.0?	narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of $\leq$0.5.
NETSCC – Ref 2	9.12	Full	64		Table 4.4: These results are based on risk scoring methods, and they generally look better than factors considered on their own, but no method looks highly effective (pages 55-56). Again, there are few studies here, and it is difficult to see how consistent they are. I suggest adding the separate sensitivities and specificities to the table for each study; as well as the pooled estimates (which are already given). Examining and comparing different risk scoring methods, and developing better ones, could be part of the proposed national cohort study (page 7, line 4).	Individual study details and results are available in the evidence review which accompanies the full guideline.
NETSCC – Ref 2	9.13	Full	70	40-42	Preventing septic complications. The authors should clarify here what results were used from which of the 3 systematic reviews; and how. Some of the pooled results in Table 5.1 come	We updated the Sung meta-analysis where necessary with any additional studies from the Bohlius, *et al.,* 2008 and Cooper, *et al.,* 2011 reviews.

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					from Sung et al 2007. However, Cooper et al 2011 (which focused on febrile neutropenia) includes studies found after the Sung meta-analysis (i.e. after 2006/07), but the combined result in Table 5.1 is from Sung only. The estimates in Table 5.1 should be based on all available studies to date.	The "Source" column in Table A4.1 in the evidence review shows the source of the data (Sung, Bohlius, Cooper or Gafter-Gvili) used for the clinical effectiveness estimates to inform the cost effectiveness model.
NETSCC – Ref 2	9.14	Full	71	4-15	The two published systematic reviews (Sung et al 2007 and Cooper et al 2011), both concluded that G-CSF have significant benefits on febrile neutropenia. And these findings are repeated in Table 5.1. Also, the evidence was rated as 'moderate' in the tables, but the analyses are based on many trials, and they seem fairly consistent. I initially wondered why no firmer conclusion or recommendation was made about G-CSF, then later saw that this decision was based on cost-effectiveness (page 113, lines 38-47). Because many readers might not read the health economics sections in enough detail, I suggest saying more about why G-CSF was not recommended on page 71 (i.e. link the clinical outcomes to costs earlier on in the guidelines, even if only briefly). It is unfortunate that the costs of G-CSF remain relatively high, so that it does not become sufficiently cost-effective for more routine use in the NHS.	It is not NICE style to include explanations in recommendations. Also the text on the page you cite reports the clinical evidence that was appraised for this question. It is not supposed to contain the GDG's interpretation of this evidence which is included in the "linking evidence to recommendations" section.
NETSCC – Ref 2	9.15	Full	79		There is a clear effect on mortality using quinolone, and this treatment is appropriately	The GDG considered mortality a more important outcome than febrile neutropenia (see linking evidence to recommendations

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					recommended on page 5 (lines 27-30). However, the evidence is rated 'moderate', and while this therapy was recommended, G-CSF for neutropenia was not (also 'moderate' evidence). It appears inconsistent, so as mentioned above, it would be useful for the authors to expand on their justification/discussion of both quinolone and G-CSF early on in the report, and specifically refer to the health economic sections. See also the 2nd comment in section 3.2.	section for chapter 5). This is because, within the setting of the prevention and management of neutropenic sepsis, it is survival from these brief episodes (around 5 days) which is of major concern to patients.
Peninsula cancer research network	31.00	full	general		Concerns that although guideline does not state gcsf use is not 'do not use' recommendation, I have concerns that commissioners will now not fund use of growth factors. As you point out there are three international guidelines giving similar recommendations on use of prophylactic gcsf. Many areas, including our own have audited our neutropenic sepsis rates and have regional guidelines on gcsf use. The guidelines lump together all the evidence, and in certain areas, there is compelling evidence of effectiveness of primary prevention. The guidelines state that these guidelines are not UK based, but there is no reason to suspect that a cancer patient having high risk chemotherapy here, is different from another country. The guidelines state that the international guidelines compare gcsf vs nil, and not vs antibiotics. All evidence is based on a model, for which it states there is little/no evidence. The guidelines then use a model to construct a cost analysis.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this

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						intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis. We have amended the recommendation to clarify that quinolone prophylaxis is only recommended for patients where significant neutropenia ($\leq 0.5 \times 10^9$/litre) is an anticipated consequence of chemotherapy. We hope that the adjustments made to the recommendations will ensure that commissioners do not misinterpret the guideline.
					The guidelines also admit that they only look	The remit from the Department of Health was

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					into the short term effectiveness of prevention of neutropenic sepsis, and not at long term effects. UK practice does not generally use gcsf in metastatic disease, but in patients with high risk disease, having intensive chemotherapy with curative intent. In this situation, dose intensity is paramount to cure rates. If gcsf cannot be used, the only strategy to maintain dose intensity is dose delay or reduction, which will lead to increase recurrence, with huge financial and personal cost. A breast cancer patient who relapses will typically have multiple lines of palliative treatment, which may have been avoided. Although trials such as the significant trial, show less infective complications, they do not allow dose intensity to be maintained. The significant trial was conducted in an era of less intense chemotherapy (no TAC/FEC-T etc). The widespread use of prophylactic quinolones is totally out of keeping with UK practice, despite oncologists being thoroughly aware of these trials and the results. There was no long term collection of data in these trials with regards to future resistant strains and survival, so I'm not sure how the panel reached the conclusion that this was not an issue. We are also not sure where the three days of antibiotic use recommendation comes from, or where the odds ratio of 0.43 comes from(reduction in risk of sepsis with use of antibiotics), although the significant trial the	"to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose. The guideline has not recommended three days of antibiotics for every patient.

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					odds ratio was 0.71, and this trial accounts for over 90% of the patients. We accept that there is limited data on the use of secondary prophylaxis, however what data there is (Sprog trial), clearly shows that if you cannot use secondary gcsf, inevitably there will be loss of dose intensity with increased risk of recurrence. We accept that this was outside the scope of this document, but have serious concerns that these guidelines will be used in isolation. We would like to see the use of gcsf as recommended in patients, according to the ASCO/NCCN and EORTC guidelines. The cost effectiveness of PEG G is clear when compared to daily g, when used for more than 6 days, if discounted prices are used, which they commonly are, as stated in your guidance. Use of quinilones in all patients will not be taken up, and will make the guidelines irrelevant to UK practice.	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with recommendations in other non-NICE guidance
Royal College of General Practitioners	30.00	Full NICE	General		The importance of recognising neutropenic sepsis or suspecting it in the community cannot be underestimated in view of the potential dire consequences. The threshold for referral must be low. Factors that aid timely referral include communication to the GP/practice that a patient is undergoing chemotherapy which could suppress the bone marrow. when the expected nadir is , the effect of multiple rounds of chemotherapy and the cumulative effect on the immune system. The guidelines essentially say	Thank you for your comment. We agree that research in this area is a key priority.

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					refer when unwell, which is very wide but the research questions still need to be answered about what factors in the community predict for high risk of sepsis. Out of hours providers need to be alert. They would not have access to blood results unless the patients reports these and they must assume a patient undergoing treatment or having a condition that suppresses the immune system has neutropenia and make the appropriate referral.	
Royal College of Nursing	28.00	Full	General		The guideline states treat neutropenic sepsis as a medical emergency, there is no discussion here about surviving sepsis guidelines or goal directed sepsis therapy which improves outcome. There is no reference to obtaining where appropriate early critical care opinion.	It is not part of NICE methodology to cross-reference non-NICE guidance. The management of patients with severe sepsis by intensive/critical care units was specifically excluded from the scope of this guideline. Therefore we have not investigated this issue and cannot make recommendations on it.
Royal College of Nursing	28.03	Full	64	1	Is 48hrs not too long to state when managing confirmed sepsis - that, the oncology team should have assessed within 48hrs? Neutropenic sepsis patients can deteriorate quickly, we expect that patients/relatives would be concerned and will complain if there had been a delay of 48hrs for the oncologists to assess them?	Thank you for your comment. The GDG have reviewed this recommendation, and felt that to improve the patient experience and clinical management a patients risk of septic complications should be assessed within a maximum of 24 hours of presentation.
Royal College of Nursing	28.04	Full	140	7	If the patient is admitted to ICU/HDU and there is no primary source of where the infection is from, then lines would normally be removed.	The management of patients with severe sepsis by intensive/critical care units was specifically excluded from the scope of this

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						guideline. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it.
Royal College of Nursing	27.00	General	General		The Royal College of Nursing welcomes this guideline. It is timely, relevant and comprehensive.	Thank you for your comment.
Royal College of Nursing	28.01	General	General		The recognition of neutropenic sepsis could be cross referenced to NICE CG 50 guidelines on assessing and managing acutely ill patients in hospital.	NICE clinical guideline 50 is cross referenced on in the NICE version of the guideline
Royal College of Nursing	28.02	General			There appears to be no reference to the use of Track & trigger (Early warning scores) which could assess severity of illness.	The use of early warning scores was not identified as a priority for investigation in the guideline. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it.
Royal College of Paediatrics and Child Health	24.02	Full	General		The guideline appears to be particularly suitable for adult oncology practice. We acknowledge that there is less evidence to use specifically for children but people using the final document should keep this in mind.	Thank you for your comment.
Royal College of Paediatrics and Child Health	24.03	Full	General		We were concerned that the danger of fungal infection presenting as neutropenic fever was not addressed at all. No recommendations are made for starting anti-fungal therapy in febrile neutropenic patients who have not responded to empirical therapy.	Thank you for your comment, we acknowledge the danger of fungal infections. These are clinical issues which have been explicitly excluded from the scope of the guideline. Therefore the evidence on this has not been appraised and we are unable to make recommendations on fungal infections.
Royal College of Paediatrics and Child Health	24.04	Full	General		We found the constant referral to a validated risk assessment tool unhelpful as those available for children are, in our experience cumbersome. Additionally as they all allow for 'clinical judgement' if the score doesn't match the clinicians concern, they actually become	Examples of validated risk scoring systems include: • the Multinational Association for Supportive Care in Cancer (MASCC) risk index for adults (aged 18 years and over) (Klastersky J, Paesmans M, Rubenstein

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					ineffective.	EB et al. [2000] The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients (Journal of Clinical Oncology 18: 3038–51) • the modified Alexander rule for children (aged under 18) (Dommett R, Geary J, Freeman S et al. [2009] Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting (European Journal of Cancer 45: 2843–9). These have been included as footnotes within the guideline. The Dommett 2009 paper demonstrates the region-wide roll out of a risk stratification and step-down system of management for febrile neutropenia in children. This score, as an example, uses the clinical judgment element of "significantly unwell" to over-ride other factors which imply low-risk. It has been anecodataly noted that such criteria are liberally applied when a step-down system has been first introduced, but become more precisely and consistently used as confidence grows.
Royal College of Paediatrics and Child Health	24.00	Full NICE	General		No mention of lower age limit that this guideline applied?	Thank you for your comment. This guideline covers children, young people and adults with cancer.
Royal College of	24.05	Full	58	37	Our group felt that in children with febrile	As documented in the linking evidence to

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Paediatrics and Child Health					neutropenia but no haemodynamic compromise, a lactate measurement would not add significantly to the child's management and often may be difficult to obtain delaying more urgent management.	recommendations section of section 4.2.1, the evidence indicated that raised levels of lactate were suggestive of a patient being at increased risk of severe sepsis. We do not believe that obtaining a lactate measurement would be more difficult than any other blood test. Therefore we do not consider that it would cause a delay in urgent management.
Royal College of Paediatrics and Child Health	24.06	Full	61	28	Obtaining peripheral blood cultures in paediatric cancer patients, virtually all of whom have indwelling venous access is not of great practical value unless the patient's access device is not working and can be distressing for the patient and result in delay to starting treatment.	We agree that taking peripheral blood cultures in children can be challenging so have recommended that cultures be taken if clinically feasible. We disagree that there is no added value, the evidence review shows that 13% of bacteraemia's in children were only detected by peripheral culture.
Royal College of Paediatrics and Child Health	24.01	Full NICE	133 12	1 3	Appropriate choice of antibiotics.	Thank you for your comment.
Royal College of Paediatrics and Child Health	24.07	Full	154	1	We would be uncomfortable not switching empiric antibiotics with persistent fever and feel more emphasis could be put on searching for the cause of fever (viral?, fungal?, drug related?). We are concerned that no mention is made of covering the possibility of fungal infection in the neutropenic patient.	We acknowledge that persistent fever may be due to viral or fungal causes. However, these are clinical issues which have been explicitly excluded from the scope of the guideline. Consequently the evidence on this has not been appraised and we are unable to make recommendations on this issue.
Royal College of Paediatrics and Child Health	24.08	Full	157	1	We do not agree with the policy of switching from intravenous to oral antibiotic when no organism has been isolated, or cause for fever found. Firstly no recommendation of what to switch to is made and secondly no convincing reason for this recommendation is given.	The reasons for making this recommendation have been documented in the linking evidence to recommendations section for section 7.2. Within this we clearly acknowledge that a specific antibiotic strategy should be based on local microbiological resistance patterns. It should be noted that this has been successfully introduced in paediatrics in the South East of England

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						(Dommett R, 2009, Eur J Cancer 45:2843-9)
Royal Marsden NHS Foundation Trust	6.12	Full	General		The guidance needs to be very specific about whether all parts or only some apply to patients undergoing HSCT. For example it is clear that the guidance about quinolone prophylaxis includes patients undergoing HSCT. It is not easily apparent whether or not the monotherapy recommendation applies to HSCT patients.	The recommendations in the guideline are applicable to all patients unless otherwise stated. This is clarified in the foreword to the guideline.
Royal Marsden NHS Foundation Trust	6.01	Full	20	n/a	Currently the algorithm appears to recommend keeping a central venous access device in and not using a glycopeptide even if there are overt signs of infection. We would recommend altering the wording to include "in the absence line associated sepsis". (See below.)	Management of specific infections is explicitly excluded from the scope of this guideline - the treatment is not, by definition, empiric. Therefore this recommendation is not intended to cover the situation you have cited.
Royal Marsden NHS Foundation Trust	6.02	Full	20	n/a	It would help the reader if there was a definition of what a "patient at low risk of complications" is.	We have added a footnote to these boxes to identify where a definition of risk can be found
Royal Marsden NHS Foundation Trust	6.03	Full	21	n/a	Do you have a recommended antibiotic for switching patients empirically to oral therapy? Are you able to make a comment on the appropriate antimicrobial if a patient has been on ciprofloxacin prophylaxis?	We have stated in the linking evidence to recommendations sections that local microbiological resistance patterns vary. We have added text to clarify that choice of antibiotic may be influenced by prior prophylaxis. Consequently the GDG were unable to recommend a specific antibiotic strategy
Royal Marsden NHS Foundation Trust	6.00	Full	69		1. Prophylaxis is the main issue a. regular widespread use of antibiotics can cause problems with diarrhoea – no doubt there will be many comments about drug resistance b. however I think there is an	We have received comments on the issue of resistance. These have been responded to. The clinical effectiveness data was taken from

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					issue with compliance to antibiotics – patients – elderly and sick do not like to take them and will forget I am amazed there is no prominent mention of growth factors which is a much better solution - pegfilgrastim given day after chemo once, subcutaneous – no more intervention needed This also allows dose intensity – no dose delay and no dose reduction. 2. The data in fact shows that antibiotics and growth factors gives a better result in terms of prevention than either alone 3. If cost is the issue then the highest incidence of neutropenic sepsis in e.g. SCLC is in the first course – thereafter treatment can be tailored to patient.	pragmatic randomised controlled trials where such issues are incorporated into the study design. We are therefore satisfied that this issue has been taken into account. This clinical question investigated the use of both antibiotics and growth factors for primary prophylaxis. Pegfilgrastim was investigated as part of the clinical and economic analysis for this question. This issue is addressed in the clinical evidence for chapter 5. The evidence appraised demonstrates that there is uncertainty as to the additional benefit of combining these interventions. Sensitivity analysis was undertaken in the economic model to assess the impact of different incidence rates of neutropenic sepsis and differential incidence rates of neutropenic sepsis per cycle. The results were found to be robust to such changes.
Royal Marsden NHS Foundation Trust	6.04	Full	112	1	It is important to balance preventing sepsis and the development of ciprofloxacin resistance. Providing ciprofloxacin to all patients will inevitable accelerate the development of resistance. It is also highly associated with *C. difficile* infection and unjustified practice would be contrary to the DH Antimicrobial stewardship guidelines and DH/HPA Clostridium difficile guidelines. It would be sensible to analyse solid tumours separately or similarly to the Cochrane review, state "Prophylaxis may also be considered for patients with solid tumours or	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($<0.5 \times 10^9$/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was

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					lymphoma." Most of the trials relating to quinolone use for prophylaxis related to the most vulnerable immunocompromised patients due to their disease and not just their chemotherapy/radiation, i.e. leukaemias and stem cell transplants. Solid organ tumours and their treatment do not necessarily impair the immune system to the same extent or duration.	considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.

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					The number of solid tumour trials used in the analysis only make a small proportion of the review. Locally the different solid tumour units audit and review the need for prophylaxis.	We agree that there are a number of small trials in leukaemia and stem cell transplants but the largest single trial relates to patients with solid tumours.
Royal Marsden NHS Foundation Trust	6.05	Full	112	1	Are you able to comment on the role of GCSF in prophylaxis?	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-

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						CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
Royal Marsden NHS Foundation Trust	6.06	Full	133	1	There is no differentiation between high risk and low risk neutropenic sepsis patients. It may not be appropriate to initiate piperacillin-tazobactam in all patients with neutropenic sepsis, especially as this is only available intravenously.	We have amended the recommendation to clarify that it relates to patients who require intravenous therapy.
Royal Marsden NHS Foundation Trust	6.07	Full	133	1	We have concerns about using monotherapy in a patient presenting with septic shock. In this clinical situation monotherapy is inappropriate and it may well be appropriate to combine piperacillin-tazobactam with an aminoglycoside i.e. a CLINICAL rather than microbiological indication for using aminoglycoside. The guidance is perhaps too black and white.	The recommendations made were based on the evidence appraised for this topic which did not support addition of aminoglycosides to any group as initial empiric therapy. Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills. This is explicitly stated in the methodology section of this guideline.
Royal Marsden NHS Foundation Trust	6.08	Full	133	1	It may be appropriate to consider microbiological contraindications to monotherapy in networks of care rather than	We have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern.

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					individual institutions i.e. reflecting actual patient pathways rather than flora of individual institutions	The term "local" in the recommendations is not intended to specify individual institutions. The definition of this in the glossary clarifies that "local" refers to the community/healthcare setting.
Royal Marsden NHS Foundation Trust	6.09	Full	133	1	There is no mention of a recommended alternative to piperacillin-tazobactam in penicillin allergic patients, or how to stratify risks. Having clear consistent practice on this would be useful, especially since in our local experience, there is a higher proportion of penicillin allergy in the haematology patient group and they are most likely to endure neutropenic sepsis.	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.
Royal Marsden NHS Foundation Trust	6.10	Full	133	44	It would help to highlight "*unless there are local microbiological contraindications*" and give an example to clarify what is meant by this, e.g. there is a high incidence of *Ps. aeruginosa* infection or resistance to piperacillin-tazobactam.	Thank you for your comment, we have amended the recommendation to include "unless there are patient specific or local microbiological indications". We do not think it is necessary to add examples to the recommendation but they would include high levels of piperacillin-tazobactam resistance but aminoglycoside sensitivity in these organisms. We have stated this in the linking

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						evidence to recommendations section of section 6.2
Royal Marsden NHS Foundation Trust	6.11	Full	139	34	The evidence is "low" quality and it's appreciated that it is difficult to make firm recommendations. It would be logical that external signs of infection would guide the clinician to remove the line as it would be a likely source of the sepsis.	Management of specific infections is explicitly excluded from the scope of this guideline - the treatment is not, by definition, empiric. Therefore this recommendation is not intended to cover the situation you have cited.
Royal Pharmaceutical Society	47.00	Full	General		Our overarching comment is concern that the membership of the Guideline Development Group (GDG) did not include a cancer and/or anti-microbial pharmacist. • Cancer pharmacists in many cancer centres are heavily involved in, if not leading, the development of guidelines on both the prophylaxis and treatment of neutropenic sepsis and the use of GCSF. We believe that the GDG having this practical experience on the group would have allowed the guidance to be more realistic and practically useful. • As for the value of an antimicrobial pharmacist to the GDG, this has already been recognised more broadly in previous Department of Health (DH) and Health Protection Agency (HPA) guidance[i] which states that "all trusts should establish an Antimicrobial Management Team (AMT) or equivalent. This should consist of an antimicrobial pharmacist, a consultant	Thank you for your comment. At the time of scoping this guideline it became clear that the principal issue on antibiotic prescribing would be choosing drugs based on patterns of antibiotic resistance; this would be guided by the microbiologist on the GDG. Although the guideline recommends the classes of drugs that would be appropriate, it does not address the details of individual drugs and their administration, therefore the specific expertise of a pharmacist for these issues was not needed.

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					microbiologist or infectious diseases specialist, and an information technology specialist. Antimicrobial pharmacists have a valuable role in AMTs and PCTs……".	
Royal Pharmaceutical Society	47.01	Full	General		We believe that the scope for this guidance in relation to the use of G(M)CSF was wrong from the beginning and the resulting draft guidance is clearly flawed as a result. The issues are: - The review of G(M)CSF only considers "survival during anti-cancer treatment" and does not consider any survival advantage for giving G(M)CSF for maintaining dose intensity which is the key reason for its use in many patients. - The review considers giving G(M)CSF to all. All international guidelines we can find[ii,iii,iv] do not recommend using G(M)CSF in this way and recommend use on the basis of risk of febrile neutropenia. Therefore there is no assessment of the point at which G(M)CSF may becomes	The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, our recommendations may not be commensurate with recommendations in other non-NICE

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					cost effective based on the risk of febrile neutropenia.	guidance. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY.
					- GCSF is available to the NHS at contract price(s) that are significantly lower than the NHS list price.	As stated in the linking evidence to recommendations section, whilst the GDG acknowledged that clinicians in some settings are able to source G-CSF products at substantially reduced cost, it was noted that these arrangements are fluid and regional and therefore no national recommendations can be based on these discounted costs. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A).

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					We realise the GDG was limited in its scope, and that it recognised that this period "may be too short to adequately assess the benefits of G(M)CSF use in encouraging clinicians to proceed in treatments with greater dose intensity.". They also recognised that "clinicians in some settings are able to source G(M)CSF products at substantially reduced prices which could potentially make its use cost-effective". The GDG clearly tried to make the best of a bad situation by making the following statement "Balancing these elements of uncertainty against the high ICER described by the economic model led to a strong decision not to recommend the use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis but also not to recommend that the use of these agents for other indications is discontinued." Our key concern is that despite this statement, in the current financial climate, commissioners may take the detailed review of the evidence and the extremely high ICER for G(M)-CSF in the prevention of neutropenic sepsis in the absence of any similarly detailed review of its potential benefits in maintaining dose intensity as a reason to decommission the use of G(M)CSF. Therefore we firmly believe that the scope of this guidance should be increased to also cover the use of G(M)CSF in increasing dose intensity.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available

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						at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
Royal Pharmaceutical Society	47.03	Full	general		Alternative methods of neutropenic sepsis prevention There are other methods of protecting patients from neutropenic sepsis but everything in the draft guidance centres around prophylaxis. Should diet, for example, be discussed?	We acknowledge that there are other potential methods of protecting patients from neutropenic sepsis however this was not identified as a priority for investigation in the guideline because the GDG agreed that there was greater uncertainty and controversy surrounding the use of antibiotics and G-CSF prophylaxis. Therefore the evidence on these other methods has not been appraised and we are unable to make recommendations on it.
Royal Pharmaceutical Society	47.08	full	general		In addition to this response the RPS wishes to support the comments made by the Neonatal and Paediatric Pharmacists Group in their response to the consultation.	Thank you
Royal Pharmaceutical Society	47.02	Full	5		Recommendation on the use of quinolone prophylaxis. The evidence for the proposed benefits of quinolone prophylaxis is disputed by some microbiologists but more importantly we are now living in the era of C. Difficile 027 (CDI) which is a potentially life-threatening infection. Use of antibacterial prophylaxis may promote the	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of

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					development of bacterial resistance and the risk of superinfection with organisms including methicillin resistant S. aureus and CDI. There have been well documented outbreaks of CDI in North America and in the UK at Stoke Mandeville Hospital, Maidstone & Tunbridge Wells NHS Trust and others. There are several hospitals in our region which had excellent records vis-à-vis CDI and have witnessed 027-related deaths. The associated targets for reducing CDI in NHS Trusts could be thrown off track by increased use of quinolones. The DH and HPA produced guidance in 2008 that states: "Restrictive antibiotic guidelines should be developed by trusts, through the AMT, stressing the following recommendations: • Use narrow-spectrum agents for empirical treatment where appropriate. • Avoid use of clindamycin and second- and third-generation cephalosporins, especially in the elderly. • Minimise use of fluoroquinolones, carbapenems and prolonged courses of aminopenicillins." The DH and HPA's recommendations on fluoroquinolones was a grade B recommendation ie strongly recommended and supported by non-RCT studies and/or by clinical governance reports and/or the Code. As such we would suggest that the recommendation that "all adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours" are offered prophylaxis with a quinolone is	expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff

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					discussed and agreed with the Healthcare Associated Infection and Antimicrobial Resistance Group at DH, with the HPA and with the wider microbiology community.	rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis. Comments have been received from the microbiology community, Department of Health and HPA as part of the consultation on the draft guideline
Royal Pharmaceutical Society	47.07	full	58		7. Recommendation to include in the initial clinical assessment of patients with suspected neutropenic sepsis: lactate The recommendation with regards lactate surprised us. Practically we would question the value of this for all patients as we would suspect that we would treat someone with antibiotics if they had a high temperature and neutropenia even if they had a normal lactate.	This recommendation describes what tests to perform in the initial clinical assessment. This should not influence the clinical decision to treat somebody with suspected neutropenic sepsis as an acute medical emergency. As documented in the linking evidence to recommendations section of section 4.2.1, the evidence indicated that raised levels of lactate were suggestive of a patient being at increased risk of severe sepsis.
Royal Pharmaceutical Society	47.05	full	133		Recommendation for piperacillin-tazobactam monotherapy as standard empiric therapy The guidance lacks any recommendations for the treatment of those patients who have a type 1 beta-lactam hypersensitivity. This is a common occurance in practice and requires guidance.	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of hypersensitivity as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was

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						not possible to recommend piperacillin-tazobactam, then clinicians would be able to use their clinical judgement to determine an appropriate alternative.
					This recommendation also ignores the huge rise in Extended Spectrum Beta-Lactamase (ESBL) producing coliforms over the last few years. ESBL are resistant to the actions of penicillin/beta lactamase combinations such as Tazocin. In addition, and supporting point 2, prior quinolone use is also a risk factor for subsequent ESBL infection. Whilst the recommendation also states "unless there are local microbiological contraindications" we again feel this recommendation requires discussion and agreement with the Healthcare Associated Infection and Antimicrobial Resistance Group at Department of Health, with the HPA and with the wider microbiology community.	We agree that in some areas of the country, resistance to piperacillin-tazobactam will make monotherapy with this agent an inappropriate empiric antibiotic therapy. We have acknowledged this in the current wording of the recommendation and in the linking evidence to recommendations section of section 6.2. In such situations an appropriate empiric antibiotic therapy may be dual therapy including an aminoglycoside, or an alternative monotherapy, for example a carbapenim, but such decisions need to be based on local microbiological resistance patterns and can't be specified in the recommendation. Comments have been received from the microbiology community, Department of Health and HPA as part of the consultation on the draft guideline.
Royal Pharmaceutical Society	47.06	full	137		Recommendation for empiric glycopeptides for the initial empiric treatment of suspected neutropenic sepsis We believe that the recommendation to "not offer empiric glycopeptides antibiotics to patients with neutropenic sepsis who have a central venous access devices" requires qualification. We would suggest this can be achieved by adding "routinely". There may be	We have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern.

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					some situations, for example when treating a known MRSA carrier or someone with previous episodes of MRSA infection were initial empiric treatment may reasonably involve vancomycin or teicoplanin.	
Royal Pharmaceutical Society	47.04	Full	158		Recommendation to switch from IV to oral antibiotic therapy after 48 hours of treatment in patients whose risk of developing septic complications has been re-assessed as low by a healthcare professional with recognised professional competence in managing complications of anti-cancer treatment using a validated risk scoring system. The GDG do not recommend which oral treatment to use but it is our understanding that the quinolones would be most useful in this respect. There are two issues here: the issue of CDI covered in point 2; and the fact that if a patient develops a breakthrough bacteraemia while on quinolone prophylaxis, it's not beyond the bounds of probability that the isolate will be quinolone resistant. In this scenario guidance would be required. We also have concerns with the referenced validated scoring system. We feel that MASCC criteria are very complex particularly for those areas which have not used them previously.	We have stated in the linking evidence to recommendations section for section 7.2 that local microbiological resistance patterns vary. We have added text to clarify that choice of antibiotic may be influenced by prior prophylaxis. Consequently the GDG were unable to recommend a specific antibiotic strategy. Decisions on what to use in the event of quinolone resistance would need to be based on local microbiological resistance patterns and cannot be specified in a recommendation. We have specified in the recommendation that the validated risk scoring system should be used by a healthcare professional with recognised professional competence in managing complications of anti-cancer treatment. We have also recommended that training should be provided for these

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					We are also aware they were derived in order to assess suitability for, amongst other things, oral treatment in an era (published in 2000) when quinolone resistance was much lower than it is now and there was no 027 CDI.	individuals. We have no reason to believe that the risk scoring system has become less discriminatory over time (see Evidence Review, page 158, lines 2-3).
South Wales Cancer Network	14.02	Full	General		With regard to Tazocin Is there guidance for treatment if patients are penicillin allergic?	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of a penicillin allergy as this was not the focus of the question asked, and the evidence appraised does not support recommending a particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, as a result of penicillin allergy, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. Additional text has been added to the linking evidence to recommendations section to clarify this.
South Wales Cancer Network	14.00	Full	5	5	Definition of sepsis is based on a patient with a temp of> 38˚C. Patients with severe sepsis may be hypothermic.	We agree that patients with neutropenic sepsis may not present with fever but have other symptoms and signs consistent with significant infection. We have amended the recommendations and algorithm to reflect this.

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						The evidence also showed that increased temperature was associated with an increase in infection. The lowest value for fever studied in the evidence was 38^{o}C and the GDG decided to adopt this value in their definition for neutropenic sepsis.
South Wales Cancer Network	14.01	Full	5	28	With regard to prophylaxis with a quinolone: Concern that giving all solid tumour patients will lead to resistance: should only chemo regimens where the neutropenia is predicted to be profound or of a long duration have quinolones? Some regimens even though potentially neutropenic are low risk. There is no guidance as to an alternative antibiotic for those with an allergy to quinolone or who are epileptic, for example.	The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($\leq$0.5 x 10^{9}/litre) and only during the period of expected neutropenia. The GDG considered that if it was not possible to recommend a quinolone, for example as a result of an allergy, then the clinicians would be able to use their clinical judgement to determine an appropriate alternative
South Wales Cancer Network	14.04	Full	42		'Diagnose neutropenic sepsis in patients with a temperature higher than 38'C and a neutrophil count lower than 0.5 x 10 9/litre' Agree with this statement, but also need to acknowledge other groups e.g. those with neutrophil counts 0.5-1, who are febrile - even if only to say that it is then a matter of clinical judgement about treatment.	We have not made any recommendations on the management of this group of patients. However, for those patients not meeting these criteria, clinicians would be able to use their clinical judgement to determine an appropriate treatment.
South Wales Cancer Network	14.03	Full	42	29	*'Suspect neutropenic sepsis in patients on anti-cancer treatment who become unwell'.* What about those on hormones or RT which are also anti-cancer treatments? Suggest that the statement is better defined, most situations would require something a little more	Thank you for your comment. Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills. Therefore we do not think the wording of this

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					sophisticated, particularly in view of the later recommendation for immediate antibiotics in anyone with suspected neutropenic sepsis.	recommendation is likely to be misinterpreted.
South Wales Cancer Network	14.05	Full	121		'Treat suspected neutropenic sepsis as an acute emergency and offer empiric antibiotic therapy immediately' No definition of 'suspected neutropenic sepsis' other than the above. Could 'Immediately' be taken to suggest GP should be starting treatment?	We have described suspected neutropenic sepsis in section 4.1. We expect this to happen in secondary or tertiary care but in some remote rural areas it may need to happen in primary care/ambulance settings. Therefore we think that the current wording is appropriate.
Sussex Cancer Network	19.00	Full	General		These comments are from the Lead Cancer Clinician at an Acute Trust: 1. The guideline Incredibly long-winded and indigestible 2. using a neutrophil count of <0.5 - ignores the fact that the vast majority of people favour neutrophils of 1. It ignores the issue of underlying medical problems e.g. associated immunosuppression due to disease. Ignores the fact that the count could be above 0.5 but falling. The document admits the evidence is low quality so why go for the less safe option?	Thank you for your comments. Thank you for your comment. The NICE version is a shorter document containing only the recommendations from the full guideline. Also, NICE will develop an online pathway showing the content of this guideline and any related NICE guidance. The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a

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						neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of $\leq$0.5.
					3. Suggestion that prophylactic quinolones should be used: Will those patients receiving quinolones for this indication be removed from C.Difficile targets if they develop this complication?	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic ($<0.5 \times 10^9$/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection

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						is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis. Targets for C. diff are outside of NICE's role to consider. However NICE have been liaising with the Department of Health and the Health Protection Agency about the implementation of these recommendations.
					. They also advocate Outpatient antibiotics for low risk patients and an early switch from IV to oral, but this will be difficult since they have already received a quinolone and this would be the most obvious oral antibiotic to use. Therefore what would be the oral antibiotic that could be used for Outpatient treatment? The document says that most protocols they received excluded patients on oral prophylaxis	We have stated in the linking evidence to recommendations sections that local microbiological resistance patterns vary. Consequently the GDG were unable to recommend a specific antibiotic strategy. We have added text to clarify that choice of antibiotic may be influenced by prior prophylaxis.

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					from having oral Outpatient treatment empirically when they developed fever. 5. The use of Outpatient treatment advocates risk assessment by someone skilled in looking after such patients using a validated scoring system or early assessment again using a scoring system by an oncologist within 48 hours. Even when we have acute oncology in place, we won't manage 48 hours for patients admitted early on a weekend. Many pts present Out of hours so there won't be a skilled person to undertake a score when they present so Outpatient treatment won't be an option. They also couldn't make any recommendations on what scoring system to use 6. There are considerable gaps e.g. use of antifungals in patients with non-responsive fever. They say they can't make recommendations one way or the other about G-CSF. There is a danger that commissioners will regard this as shouldn't be done Sorry a bit of a ramble, but personally we don't find these very helpful. When we are being urged by NPSA to ratchet up treatment for neutropenic sepsis these guidelines seem to take a somewhat opposite approach. I suspect	The GDG have reviewed this recommendation, and felt that to improve the patient experience and clinical management, a patients risk of septic complications should be assessed within a maximum of 24 hours of presentation. They have also clarified that a healthcare professional with competence in managing complications of anti-cancer treatment should assess the patient's risk of septic complications. Thank you for your comment. We acknowledge the danger of fungal infections. These are clinical issues which have been explicitly excluded from the scope of the guideline. Therefore the evidence on this has not been appraised and we are unable to make recommendations on fungal infections. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use

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					we will continue to use our own guidelines based on our own local experience and sensitivities.	of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.

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Sussex Cancer Network	19.01	Full	General		These comments are from a group of oncologists, nurses and pharmacists at the Cancer centre: Using the neutrophil count of 0.5 x10 9/L would mean a change in clinical practice and many clinicians would feel uncomfortable with this lower level, especially for those patients whose count is still dropping after chemo. Does measuring lactate routinely add anything to the treatment options based on its result? this isn't routinely monitored currently and would add extra costs. Who constitutes the 'oncology team' - this is vague and needs clarifying. For example, would a haematologist be involved as part of the 'oncology team' in such scenarios where a review is required within 48 hours at a weekend?	Thank you for your comments. The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of $\leq$0.5. As documented in the linking evidence to recommendations section of section 4.2.1, the evidence indicated that raised levels of lactate were suggestive of a patient being at increased risk of severe sepsis. For clarity, the GDG have amended the recommendation to "a healthcare professional with competence in managing complications of anti-cancer treatment". The GDG also felt that to improve the patient experience and clinical management a patients risk of septic

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					Using a quinolone conflicts with the local & National C. Diff reduction initiatives	complications should be assessed within a maximum of 24 hours of presentation. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme

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						alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
					The cost effectiveness of GCSF may need to be reviewed given the reduction in price since the introduction of the biosimilar GCSF's.	All G-CSFs are biosimilars that in terms of regulation aren't treated as generics. Therefore, whilst each PCT probably has its own agreement, there is no nationally negotiated discount as normally found on the CMU website. Given this the GDG decided to use the BNF price since there is no other reliable NHS source. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available

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					Clinicians are uncomfortable with not using GCSF in higher risk patients. A suggestion would be a risk stratification on how it may be used rather than suggesting no use.	at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-

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						CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
Teenagers and Young Adults with Cancer (TYAC)	5.00	Full	general		TYAC support this document and the drive towards consistent practice across the country. The group is concerned with teenagers and young adults and we welcome the fact that this group have been considered in the production of these guidelines. This age group are often having intensive treatments that lead to neutropenic sepsis episodes, these episodes often occur away from the principal treatment centre and therefore a strengthening of guidelines especially in peripheral hospitals is very much welcomed.	Thank you for your comment.
The Christie Hospital NHS foundation trust	18.00	FULL	General		The draft guidelines for the management of neutropenic sepsis are an important attempt to deal with a significant and potentially life threatening complication of anti-cancer chemotherapy. A number of concerns have been raised however by the different disease groups within the Chistie Hospital NHS	Thank you

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					Foundation Trust which should be addressed in the final document. As Chairman of the Drugs and Therapeutics Committee I have collated the concerns of these groups. The main areas of concern are summarised under 3 headings 1. Serious concerns are expressed about the routine use of quinolones. The evidence is weak and not enough attention has been paid to the serious risk of c.diff infections and acquired resistance to these drugs.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group.

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						The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
					2. The guidelines use mortality rates rather than admission rates to assess the impact of gCSF usage. Given the high quality of acute care available, mortality rates are low and do not accurately reflect the impact of neutropenic sepsis.	Reduction in neutropenic sepsis is the primary outcome measure used in the economic analysis. It was assumed that all patients with neutropenic sepsis will be admitted to hospital; which means reduction in neutropenic sepsis is equal to reduction in admission rates. Please see Section A3.1.1 for more details. Admission rates were used as the main index to evaluate the effectiveness of all prophylactic strategies, including G-CSF.
					3. The use of early assessment to triage	The GDG felt that there was no clear

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					patients is handicapped by the lack of a validated scoring system. The guidelines also assume a fully functioning acute oncology service is in place in all acute hospitals. This is not the case in Greater Manchester and has significant resource implications. On behalf of the Christie Hospital I hope that these concerns can be addressed in the final document.	evidence to support the use of a non-clinical triage system, but felt there was strong evidence for validated scoring systems (e.g. MASCC score) for risk stratification on admission. Implementing the recommendations in the guideline will be a matter for local determination
The Christie Hospital NHS foundation trust	18.01	Full	General		Lung Cancer Disease Group Comments on Draft Guidance on Neutropenic Sepsis: • In general terms, the scope of the document is appropriate as are most of the key priorities for implementation. However there are a number of areas of concern: • There are differences between the proposed NICE Guidance and the Christie policy in the definition of Neutropenic Sepsis (Temp >38.0 and ANC<0.5)	Thank you for your comments. We have responded to them individually below. The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. Whilst we realise that 2/3 of centres use a neutrophil cut-off of <1, the strongest

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						evidence is that significant infection occurs with lower neutrophil counts. Consequently the GDG recommended a neutrophil cut-off of $\leq$0.5. The evidence also showed that increased temperature was associated with an increase in infection. The lowest value for fever studied in the evidence was 38^{o}C and the GDG decided to adopt this value in their definition for neutropenic sepsis.
					• The guideline suggests significant changes in patient management compared to current management e.g. discharge of patients after 48hrs of iv antibiotics regardless of neutrophil count, providing the patient is assessed as low risk on a validated risk scoring system. This recommendation is based, in the authors' own words, on "low quality" data with "no evidence available for any of the outcomes required". Whilst we agree that the amount of time patients spend as an inpatient should be reduced this needs to be balanced with appropriate evidence in the area to which the guidance is being applied. In the only randomised study in this setting, readmission rates were 5% (and up to 13% in non-randomised studies). Whilst we need to ensure that patients do not remain in hospital for	The GDG recognised that early discharge may be associated with readmission, but felt that the majority of patients would more highly value time at home (see the linking evidence to recommendations section of section 6.5). As with all clinical decisions, the balance of risks and benefits should be shared with patients enabling them to make an informed and supported choice.

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					any longer than necessary, we have some concerns that this guidance may result in patients being discharged precipitously which may lead to readmission and loss of patient confidence. • The recommendation to offer quinolone prophylaxis to all patients (not just 1st chemotherapy cycle) may have consequences in terms of increased rates of C diff infections and microbial resistance.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see the linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All

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						antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
					• Growth factor support, as either primary or secondary prevention, is neither recommended nor discouraged. However in the two studies reviewed for the guidance in which patients with lung cancer were treated, G-CSF was shown to improve outcomes (Neutropenic sepsis and mortality) compared to antibiotic prophylaxis alone. The cost effectiveness of G-CSF support is called into question for all solid tumours	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians

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						in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
					• • The NCEPOD report has resulted in increased scrutiny of the treatment of	Recommendations in guidelines are designed to assist the practice of healthcare professionals, however, they do not replace their clinical knowledge and skills.

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					patients receiving chemotherapy particularly those dying within 30 days of treatment. As Lung Cancer Oncologists treating patients with small cell lung cancer (who often have significant co-morbidities) we increasingly find ourselves acting as witnesses at Coroners Inquests, having to justify treatment decisions. We are concerned that commissioners will inevitably use some aspects of these guidelines and consequently influence clinical decision making to the detriment patient care.	
The Christie Hospital NHS foundation trust	18.03	Full	General		1. The economic analysis does not take into consideration the cost of admission for febrile neutropenia or its impact on the quality of life of the patient. Febrile neutropenia is a major cause of acute oncology admissions. A GMCCN audit of non-elective admissions indicated that at least 20% of acute oncology admissions in patients receiving systemic anti-cancer therapy are due to FN. The number of acute oncology admissions throughout the network for 2010/11 was ~ 40,000. Approximately 8,000 of these will have been due to FN. 2. The primary outcome measures should have been a reduction in admission rates for febrile neutropenia rates rather than mortality. The mortality rates are low, due to the strict, protocol-driven management of febrile neutropenia, and thus it was always statistically	The impact of neutropenic sepsis on both treatment cost and patients quality of life have been considered in the model: • Impact of neutropenic sepsis on resource use: Section A3.3 • Impact of neutropenic sepsis on patients quality of life: Section A3.2 Reduction in neutropenic sepsis is the primary outcome measure used in the economic analysis. It was assumed that all patients with neutropenic sepsis will be admitted to hospital; which means reduction in neutropenic sepsis is equal to reduction in

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					unlikely that a significant reduction in mortality was going to be detected from this analysis. A reduction in admissions for febrile neutropenia is more clinically and economically meaningful. A recently completed audit conducted by the Christie breast group in 150 patients with early breast cancer, and involving > 1000 episodes of chemotherapy has shown that FEC_{100} and FEC-T regimens are associated with febrile neutropenia rates of 19.4% and 28.9% respectively in patients who don't receive primary GCSF prophylaxis, compared to febrile neutropenia rates of 11.1% and 13.3 % respectively in patients who did receive primary GSCF prophylaxis, confirming that primary prophylaxis halves FN rates. Our findings that primary prophylaxis halves FN rates are mirrored by a large meta-analysis of RCTs involving all solid tumours and lymphomas by Kurderer et al, who also showed a significant reduction in early mortality. This meta-analysis does not appear to have been included in the evidence summary. 3. Most febile neutropenic events occur during the first cycle of chemotherapy. This was shown by Crawford et al and also confirmed in our own SACT data and reinforces the need for primary rather than secondary prophylaxis. 4. The document does not take into consideration the importance of maintaining dose intensity when delivering adjuvant	admission rates. Please see Section A3.1.1 for more details. Admission rates were used as the main index to evaluate the effectiveness of all prophylactic strategies, including G-CSF. The Sung et al (2007) review included the trials in the Kurderer et al meta-analysis. The relative risk of neutropenic sepsis has been modelled in our economic analysis: see Section A3.1.1. In order to investigate this effect we would need to conduct a systematic review to identify which specific patient group(s) were

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					chemotherapy. When dose intensity falls ≤ 85% there is a significant detrimental impact on outcome (Bonadonna 1995). The use of primary prophylaxis allows dose intensity to be maintained in more patients.	likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline Although our systematic review of cost-effectiveness studies did identify several studies trying to model the impact of using G-CSF on patients long-term survival (by maintaining chemotherapy dose) (see cost effective section in chapter 5); none of these studies used any direct clinical data. Instead, these studies were trying to build an indirect relationship between use of G-CSF and long-term survival. They stated that G-CSF could

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						prevent neutropenic sepsis; neutropenic sepsis is a risk factor of receiving dose-reduction chemotherapy and dose-reduction chemotherapy is a risk factor for patient long-term survival. Then based on this hypothesis, the authors claimed that G-CSF could improve patients long-term survival. Furthermore, a recent meta-analysis (Shitara et al., 2011) shows that neutropenia experienced during chemotherapy is actually associated with improved survival in patients with advanced cancer or haematological malignancies undergoing chemotherapy. This implies that experiencing side effects of chemotherapy might not be associated with impaired long term survival. Therefore the GDG were very unsure about the validity of the indirect logic used in these published cost-effectiveness studies and the derived conclusion and did not consider it appropriate to use the methodology from the existing studies to model the impact of using G-CSF on patients long-term survival for this guideline.
					5. The recommendation to routinely use quinolones for primary prophylaxis is concerning. It does not take into consideration the increased risk of C. difficile and the evidence supporting its efficacy in the role of primary prophylaxis is minimal, and far less robust than the evidence supporting the use of G-CSF, particularly pegfilgastrim.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia.

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						The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities

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						where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
The Christie Hospital NHS foundation trust	18.04	Full	General		As usual, a very thorough document from the NICE GDG, but with some serious concerns: 1. The use of primary GCSF: We have shown in 2 audits within the breast group that for certain regimes, there is a reduction in febrile neutropaenia rates and this is also the conclusion of a review recently published (Younis et al 2012,). The draft NICE guidance, by it's own admission does not look at admission rates or dose intensity for curative treatments and only looks at mortality to assess (cost-) effectiveness. Given the high quality medical care available in most hospitals and their CCUs, many patient with sepsis do not die and hence mortality is not the best indicator of benefit when looking at prophylaxis with GCSF. The results of our audit support of our use of primary GCSF and I think clinically it will be very difficult to advise not using primary prophylaxis based on this evidence. 2. We are also concerned about the recommendation that quinolones should be used routinely: the evidence for this (within these draft guidelines) is very weak and the conclusion they have reached is somewhat surprising based on the evidence they have presented. Our local microbiologists actively	Reduction in neutropenic sepsis is the primary outcome measure used in the economic analysis. It was assumed that all patients with neutropenic sepsis will be admitted to hospital; which means reduction in neutropenic sepsis is equal to reduction in admission rates. Please see Section A3.1.1 for more details. Admission rates were used as the main index to evaluate the effectiveness of all prophylactic strategies, including G-CSF. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic

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					discourage the use of quinolones due to the risk of c.diff. It would appear that this has not been considered by the NICE GDG.	(<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in

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						infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
					The recommendation not to use aminoglycosides is also contrary to our local protocol and we will need advise from our microbiologists about this. 3.The lack of a single credible scoring system to predict whether a patient with febrile neutropaenia will or won't develop septic complications makes it difficult to triage patients who may be safe to be treated at home and a lot of work will have to be put in to implementing this.	The recommendations made were based on the evidence appraised for this topic which did not support addition of aminoglycosides to any group as initial empiric therapy. The GDG noted that a series of valid scoring systems had been produced and have indicated two systems, one primarily for use in adults and one for use in children, to assist practitioners in undertaking this.
The Christie Hospital NHS foundation trust	18.13	Full			Hence summary of points made so far: 1. The draft CG does not reflect current clinical practice; 2. The draft CG "lumps" all patients and disease groups together;	The recommendations in this guideline are based on a systematic search and appraisal of the clinical evidence and where relevant, the results from a health economic model. Consequently, they may not be commensurate with current clinical practice. The guideline covers all cancer patients, from paediatric to adult, who experience neutropenic sepsis. Consequently the evidence has sometimes had to be drawn from heterogeneous populations. Where possible we have conducted sub-group analysis and sensitivity analysis to reduce the effect of this heterogeneity.

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					3. The draft CG dismisses international guidelines; 4. The draft CG ignores chemotherapy RDI as it was formally outside of the scope;	The recommendations in this guideline are based on a systematic search and appraisal of the clinical evidence and where relevant, the results from a health economic model. Consequently, they may not be commensurate with recommendations in other non-NICE guidance. The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health. The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity.

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						Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation.
					5. The draft CG does not consider secondary prophylaxis;	As stated in the guideline, by making a recommendation for primary prophylactic treatment a recommendation for secondary prophylactic treatment was no longer relevant.
					6. The draft CG ignores antibiotic resistance;	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast

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						cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
					7. The evidence for antibiotics is of low quality, sparse, and not in comparable patient groups;	The quality of the underlying evidence for all recommendations, and any associated limitations, have been documented in the clinical evidence sections and taken into account when making decisions as a GDG (as documented in the linking evidence to recommendations section).
					8. The draft CG will not standardise treatment across UK;	We believe the clear statements in this guideline will harmonise treatments to a

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						greater degree than is currently undertaken.
					9. The cost utility analysis has not been conducted according to NICE methods [use of Mortality and QUALY not appropriate in a preventative setting].	The GDG felt that the QALY is the most appropriate generic measure of health benefit that reflects both mortality and HRQL effects in a preventative setting. This is consistent with NICE methods.
The Christie Hospital NHS foundation trust	18.05	Full	4	3	The draft guidance deals more with management of febrile neutropaenia and does not adequately look at prevention. Key outcome measures of prevention including hospitalisation rates, maintenance of Relative Dose intensity [RDI] of chemotherapy	Reduction in neutropenic sepsis is the primary outcome measure used in the economic analysis. It was assumed that all patients with neutropenic sepsis will be admitted to hospital; which means reduction in neutropenic sepsis is equal to reduction in admission rates. Please see Section A3.1.1 for more details. Admission rates were used as the main index to evaluate the effectiveness of all prophylactic strategies, including G-CSF. The remit from the Department of Health was "to produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". When the content of the scope was developed, it was agreed by NICE that whilst the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose was a very important issue it was not possible to investigate such a vast and complicated area as a single topic within the scope. Neither was this issue covered by the remit which had been set by the Department of Health.

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						The scope of the guideline therefore explicitly excludes the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose.
					and impact on survival from cancer are ignored. Hence the guidance cannot claim to be for prevention, but rather on the management of febrile neutropaenia	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations.

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						Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
The Christie Hospital NHS foundation trust	18.06	Full	5	27	All solid cancers have been grouped together with no distinction between different chemotherapy regimes and patient risk factors. This is frankly a very bizarre guidance as the risk of febrile neutropaenia changes with different chemotherapy regimes and different patient factors [age, co-morbidities]	We agree that the evidence for this recommendation has been drawn from heterogeneous populations. We have attempted to reduce the population heterogeneity by excluding paediatric patients, patients receiving inpatient chemotherapy and patients whose regimen includes G-CSF from the model. In addition we have performed sub-group analysis for patients with solid tumours, non-Hodgkin lymphoma and Hodgkin lymphoma. The potential effect of this heterogeneity on the health economic model results has been assessed by sensitivity analysis on the relevant model inputs. A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY.
The Christie Hospital NHS	18.02	Full	54	29	From a biochemistry point of view:	

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foundation trust					Firstly we agree with the recommendation that lactate would be useful in the initial assessement of patients with suspected neutropenic sepsis (Section 4.2.1 p58 line 37 & page 59 lines 17-19). However I think the guidelines are a little confusing regarding their recommendation for blood gases. Section 4.2.2 (page 61 lines 8-9) report the evidence for blood gases was reviewed in the previous section – but table 4.2 (p55-57) only covers the evidence for lactate not blood gases per se. Although in many places the lactate can be measured on a point of care blood gas analyser, strictly speaking it is not a blood gas. The papers quoted which provide evidence on the value of lactate, used lactate measured in serum on a main chemistry analyser (not whole blood POCT). Further clarity is needed, particularly for centres which measure lactate in the main lab and not on the blood gas machine, as to whether blood gases are also required and if so does this need to be an arterial sample or if a (less painful) venous sample would suffice if there are no respiratory symptoms. Secondly, it would have been really useful if the paper had included procalcitonin in its evaluation of which tests predict outcome and response to treatment (section 4.2.1). Procalcitonin is a marker of sepsis which has been around for many years, with a quick pubmed search of procalcitonin and sepsis revealing 814 articles. There are 20 articles on procalcitonin specifically in neutropenic sepsis, most of which appear indicate procalcitonin to be of value. The biggest problem is that it costs	We have removed "blood gases". Thank you for pointing out this error. The role of procalcitonin was not identified as a priority for investigation in the guideline as the GDG prioritised the appraisal of investigations in common clinical usage. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it. You may wish to consider referring procalcitonin as a topic to the medical diagnostic team at NICE.

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					much more than CRP (exact costs will vary according to local contracts – but for us it is 100-200X more), however this cost is probably minimal in terms of the cost of ICU bed stays.	
The Christie Hospital NHS foundation trust	18.07	Full	112	44	Use of Quinolones as 'prophylaxis': Quinolones do not reduce the risk of neutropaenia only GCSF can do so. The risk of antibiotic resistance is underplayed and not given enough thought. What about the risk of spreading resistant bacteria within the community? What about the cost of the spread of resistant bacteria within the community? These issues have been ignored by the GDG. The guidance contradicts the government strategy of reducing the use of unnecessary antibiotics and reducing antibiotic resistance.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All

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						antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
					The methodology of assessing the effectiveness of quinolones is flawed: by ignoring the rate of admissions due to FN the GDG has missed the entire concept of 'prevention'. Looking at only the mortality from FN is a myopic strategy and out with current clinical concerns and understanding	Reduction in neutropenic sepsis is the primary outcome measure used in the economic analysis. It was assumed that all patients with neutropenic sepsis will be admitted to hospital; which means reduction in neutropenic sepsis is equal to reduction in admission rates. Please see Section A3.1.1 for more details. Admission rates were used as the main index to evaluate the effectiveness of all prophylactic strategies, including G-CSF.
The Christie Hospital NHS foundation trust	18.08	Full	113	10	The GDG have ignored peer-reviewed international guidance on the prevention of FN and maintaining RDI from ESMO/ASCO. These international guidelines reflect current best practice. Ignoring them makes the NICE	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and

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					guidance highly irrelevant to current UK practice. It is bizarre to suggest that these well researched and evidence based international guidelines are irrelevant as they were not developed in the UK. Does the GDG seriously consider that patients in the UK who are given the same drugs as in the rest of world have a lower level of FN or react differently?	did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
The Christie Hospital NHS foundation trust	18.09	Full	114	4	There is no evidence to suggest that the use of quinolones reduces hospital admission rates or reduces length of stay in hospital. There is no evidence that this improves the quality of life. This statement should be removed.	We have information from the evidence review to demonstrate that quinolones reduce hospital admission rates (see clinical evidence for chapter 5). We have not commented on length of stay. While the GDG had no direct evidence on quality of life (see clinical evidence for chapter 5) it was the opinion of the group including three patient representatives that fewer deaths and reduced hospital rates would potentially improve quality of life.
The Christie Hospital NHS foundation trust	18.10	Full	114	13	The GDG completely ignores the impact of reduction in FN rates and admissions to hospitals with prophylactic GCSF for high risk patients and high risk regimes. In our hospital we conducted 2 audits over 3 years looking at the impact of primary prophylaxis with GCSF on FN rates amongst patients receiving FEC-100 and FEC-D chemotherapy in a curative setting for breast cancer. The overall FN rate reduced from 18.9% to 7.2% with the biggest impact on FEC-D where the rate reduced from 28.9% to 8.7%. How can such results be ignored? Similar figures are available from Liverpool [Full report	Audit reports are not routinely looked at in NICE guidance. We have acknowledged that prophylaxis with G-CSF reduced the rate of febrile neutropenia in the clinical evidence for chapter 5. A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens,

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					available on request]. This reflects findings of a wide ranging review recently published [Primary G-CSF prophylaxis for adjuvant TC or FEC-D chemotherapy outside of clinical trial settings: a systematic review and meta-analysis Tallal Younis & Daniel Rayson & Kara Thompson, SCC January 2012] Hence if the GDG is not amended to take into account the full clinical impact of using prophylactic GCSF, at best it will be ignored by clinicians and at worst it will lead to a reduction in the use of GCSF and a resultant increase in FN, hospital admissions and probably deaths.	or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs.,The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the

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						GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
The Christie Hospital NHS foundation trust	18.11	Full	178	13	Cost of treating Neutropaenic Sepsis: this is based on assumptions with no real data to back up the costs, duration of stay and length of antibiotic treatment. The costing assumes that low-risk patients will stay in hospital for a shorter period of time, but does not consider cost savings if the admission was prevented by GCSF [see point 6 above] Most hospitals are not set up for early discharge, IV antibiotics in the community and telephone follow up: the costs of implementing this service are not taken in to account. The cost of treating each episode of FN is seriously underestimated by the GDG: the NHS reference cost per episode is £5,959. the guidance assumes that 90% of admissions will be low risk and stay in hospital for only 2 days. This highly flawed assumption with no data to underpin it, gives a cost of only £766 per episode of FN! This is completely wrong.	Reduction in neutropenic sepsis is the primary outcome measure used in the economic analysis. It was assumed that all patients with neutropenic sepsis will be admitted to hospital; which means reduction in neutropenic sepsis is equal to reduction in admission rates. Please see Section A3.1.1 for more details. Admission rates were used as the main index to evaluate the effectiveness of all prophylactic strategies, including G-CSF. Unfortunately, it is not standard practice for implementation costs to be considered in the economic model. The GDG agreed it would be more appropriate to use costs based on the clinical pathway represented by the guideline recommendations, rather than the HRG cost you cite. This was because the economic analysis only considered adult patients (solid tumour, NHL and HL) who are receiving outpatient chemotherapy. In contrast to those patients who are receiving inpatient chemotherapy, our target population rarely use ICU (ITU) or antifungal drugs (both of which are very expensive). This means the treatment cost for our target population (outpatient) will be much lower than it is for

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						the inpatient group. Consequently the GDG agreed it would be inappropriate to use the HRG cost (which is also likely to cover all cancer patients).
The Christie Hospital NHS foundation trust	18.12	Full	186	11	QUALY as a measure of cost-effectiveness: It is confusing to have a QUALY associated with preventative treatment and I question the validity of the methodology and assumptions made by the GDG. The GDG has ignored the true measures of effectiveness: namely hospital admissions and Relative Dose Intensity [RDI]. There is ample evidence that for curative treatments a fall in RDI reduces survival. This has been ignored in the guidance. Also, it is advised by the guidance to consider reducing the dose of treatment after 1 episode of FN and stopping after 2 episodes. This is bizarre when we have an intervention [namely GCSF] that would allow safe continuation of treatment which is essential to improve survival. Ignoring the effect of RDI on long term survival, ignoring the effect of primary and secondary prophylaxis on maintaining RDI and the overall effect that chemotherapy has on survival is a fatal flaw in this draft guidance and there will be very poor acceptance of this unless the guidance is completely reviewed and amended.	The GDG felt that the QALY is the most appropriate generic measure of health benefit that reflects both mortality and HRQL effects in a preventative setting. This is consistent with NICE methods.
The Royal College of Radiologists (Faculty of Clinical Oncology)	44.00	FULL	General		This version is well researched, comprehensive but very long (242 pages) and we feel few will be able to read it in full. However it acts as a good source of reference. We do not believe that there are any major omissions of points or areas that are not covered. However there are points in the recommendations for the key priorities for implementation that will raise	Thank you for your comment. The NICE version is a shorter document containing only the recommendations from the full guideline. Also, NICE will develop an online pathway showing the content of this guideline and any related NICE guidance.

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					further discussion. These are highlighted in our comments below.	
The Royal College of Radiologists (Faculty of Clinical Oncology)	44.02	Full	44-46		We feel the information and support for patients and carers is entirely appropriate.	Thank you for your comment.
The Royal College of Radiologists (Faculty of Clinical Oncology)	44.01	Full	42 5, 43 and 52		Definition of neutropenic sepsis – Diagnose Neutropenic sepsis with a temperature over 38 and neutrophil count lower than 0.5 We feel this definition is too narrow and does not take account of the unwell neutropenic patient who may be apyrexial but in septic shock. Although this is mentioned on p43 and highlighted on p52, it does not appear in the definition box in the Algorithm (p20). Repeatedly the guidance limits it to the patients who have a temperature of 38.	We agree that patients with neutropenic sepsis may not present with fever but have other symptoms and signs consistent with significant infection. We have amended the recommendations and algorithm to reflect this. The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection. Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections. By recommending the current definition of neutropenic sepsis, the GDG were trying to strike an appropriate balance between under and over treatment. The evidence also showed that increased temperature was associated with an increase in infection. The lowest value for fever studied in the evidence was 38^{o}C and the GDG decided to adopt this value in their definition for neutropenic sepsis.
The Royal College of Radiologists (Faculty of Clinical Oncology)	44.03	Full	57	37	With regard to investigations, the inclusion of Lactate is not routine in many centres. However the evidence as a predictor of worse outcome is compelling.	Thank you for your comment
The Royal College	44.04	Full	65	1	Assessing the patient's risk by an Oncology	The GDG have reviewed this

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of Radiologists (Faculty of Clinical Oncology)					member within 48 hrs is sensible and forms part of the development of Acute oncology services.	recommendation, and felt that to improve the patient experience and clinical management a patients risk of septic complications should be assessed within a maximum of 24 hours of presentation.
The Royal College of Radiologists (Faculty of Clinical Oncology)	44.09	Full	111	1	GCSF recommendation We anticipate some concerns about the strength of the negative recommendation on the use of GCSF. There is a risk that many commissioners may take this as evidence to decommission the use of GCSF as not cost effective for the prevention of infectious complication and death from neutropenic sepsis, without taking into account the benefits in maintaining dose intensity and its benefit on long term survival.	In order to investigate the effect of G-CSF on maintaining dose intensity we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline A recommendation on the use of G-CSF for

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						the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible

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						to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
The Royal College of Radiologists (Faculty of Clinical Oncology)	44.05	Full	112		Recommendation to offer prophylaxis with a quinolone to all adult patients with acute leukemias stem cell transplants or solid tumours – we feel there may be significant opposition to this recommendation for all solid tumours in view of the risk of c difficile. Although this was the practice a few years ago, many centres have moved on to using it only in those at highest risk of neutropenia. We understand that the Department of Health and Health Protection Agency (HPA) produced guidance in 2008 to minimise use of fluoroquinolones. We would suggest that a unifying recommendation should be developed which would be risk stratified.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5). The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group.

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						The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
The Royal College of Radiologists (Faculty of Clinical Oncology)	44.06	Full	131	1	Empiric antibiotic monotherapy with piperacillin-tazobactam – do not offer aminoglycoside. We feel this policy might be disputed by local microbiologists who formulate the local guidelines, which are in turn developed from analysis of local infection rates. Many centres will be concerned about recommending this as best practice for all because of local susceptibility patterns and the difference in the degree of immunosuppression. This recommendation seems to ignore the rise in extended spectrum Beta-Lactamase (ESBL) producing coliforms which are resistant and	We agree that local resistance patterns may affect whether this recommendation can be implemented. This is why we have stated this in the recommendation. We agree that in some areas of the country, resistance to piperacillin-tazobactam will make monotherapy with this agent an

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					prior quinolone use is a risk factor for subsequent ESBL infections.	inappropriate empiric antibiotic therapy. We have acknowledged this in the current wording of the recommendation and in the linking evidence to recommendations section for section 6.2. In such situations an appropriate empiric antibiotic therapy may be dual therapy including an aminoglycoside, or an alternative monotherapy, for example a carbapenim, but such decisions need to be based on local microbiological resistance patterns and can't be specified in the recommendation
					Although the evidence is well reviewed and appears convincing, we suggest that a wider input from the microbiology community is warranted.	A microbiologist was appointed to the GDG who was able to advise on prophylaxis and treatment of neutropenic sepsis. Comments have been received from the microbiology community as part of the consultation on the draft guideline. These have all been responded to as part of the consultation process.
					The single agent monotherapy may apply for solid tumour practice in the 'well' patient.	We agree.
					There is no guidance for the patients who have beta-lactam hypersensitivity. This is a common occurrence and requires guidance.	The clinical question which generated the recommendation to offer beta lactam monotherapy focussed on the effectiveness of empiric intravenous monotherapy compared with empiric intravenous dual therapy. Whilst we acknowledge the issue that you have raised, we are unable to recommend what alternative beta lactam should be used in the event of hypersensitivity as this was not the focus of the question asked, and the evidence appraised does not support recommending a

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						particular drug. However the GDG considered that if it was not possible to recommend piperacillin-tazobactam, then clinicians would be able to use their clinical judgement to determine an appropriate alternative. We have added "unless there are patient specific or local microbiological indications" to this recommendation to address this concern.
					The recommendation to 'not offer empiric glycopeptides to patients with neutropenic sepsis who have a central venous access device' should have the word 'routinely' added. We suggest that known MRSA carriers or having suffered previous episodes of MRSA infection may benefit from initial empiric treatment with Vancomycin or teicoplanin.	
The Royal College of Radiologists (Faculty of Clinical Oncology)	44.07	Full	140 (Section 6.5)		Inpatient versus outpatient management strategies We note there is no guidance given as to which oral antibiotics to use. Quinolone traditionally have been the most useful but if a patient develops bacteremia whilst on a quinolone prophylaxis it is likely that the organisms may be resistant. Again the risk of C Difficile has been highlighted.	We have stated in the linking evidence to recommendations section of section 6.5 that local microbiological resistance patterns vary. We have added text to clarify that choice of antibiotic may be influenced by prior prophylaxis. Consequently the GDG were unable to recommend a specific antibiotic strategy.
The Royal College of Radiologists (Faculty of Clinical Oncology)	44.08	Full	159 (Section 7.3)		Duration of inpatient care The use of the MASCC index has been gaining popularity in many units and seems sensible, but we feel that early discharge and outpatient management has to be backed up by the ability	We agree. We have amended the recommendation to cover this issue.

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					to rapidly readmit or review.	
The Royal College of Radiologists (Faculty of Clinical Oncology)	44.10	NICE version	General		We did not find this version very user-friendly or concise for practising clinicians. We feel that the key information and recommendations are better represented and found in the Full version (p5-7 and the 2 algorithms on pages 20-21). As most people will only look at the shorter version, we would suggest that they use the format as stated above.	We have passed this feedback on to NICE, as they hold editorial control of the short version
Thermo Fisher Scientific	16.05	Full	General		Thank you for the comments. I had registered and was about to comment myself. Your comment no 1 mentions 'ivd'. Please could you expand as this may be misread. If possible - mention that the test is available on most 'major diagnostic test mainframe analysers' and access to the test is available in almost every hospital. Also if possible, please could you mention that the test - Procalcitonin would be able to help not only in diagnosis but also in the monitoring ie management as well. See if you can mention diagnosis & management instead of diagnosis.	We believe that this comment is querying the comment submitted by another individual from your organisation. As such we are not able to respond to it. The role of procalcitonin was not identified as a priority for investigation in the guideline as the GDG prioritised the appraisal of investigations in common clinical usage. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it. You may wish to consider referring procalcitonin as a topic to the medical diagnostic team at NICE.
Thermo Fisher Scientific	16.00	Full	General		The role of Procalcitonin in diagnosis of neutropenic sepsis is complety neglected despite a substantial bibilography. The test is widely available in the UK on the laboratory systems of major ivd providers (Biomerieux,	The role of procalcitonin was not identified as a priority for investigation in the guideline as the GDG prioritised the appraisal of investigations in common clinical usage. Therefore the evidence on this has not been

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					Diasorin, Siemens Healthcare Diagnostics, Thermo Fisher Scientific, Roche) used in all UK hospitals.	appraised and we are unable to make recommendations on it. You may wish to consider referring procalcitonin as a topic to the medical diagnostic team at NICE.
Thermo Fisher Scientific	16.04	Full	General		In this draft version many studies are missed: that establish the role of Procalcitonin for diagnosis.of sepsis in neutropenic patients: • Giamarellos-Bourboulis E J et al., Clin Infect Dis 2001, 32: (12); 1718-25 • Giamarellou, H et al., Clin Microbiol Infect 2004; 10: (7); 628-33 • Sauer, M et al., Bone Marrow Transplant 2003; 31: (12); 1137-1142 • G. R. Stryjewski GR et al., Pediatr Crit Care Med 2005; 6: (2); 129-135 • Semararo M et al., Pediatr Blood Cancer 2010;54:284–290 • Juutilainen A et al., Leuk Lymphoma 2011; 53(12):2349-55 • Kim DY et al., Can Res Treat 2011; 43(3):176-180 • Gac AC et al., Leuk Res 2011; 35: 1294-1296 • Koivula I et al., Scand J Infect Dis 2011; 43:471-478 • Cornillon J et al., J Infect 2011; 63: (1); 93-5 • Sarmati L et al., Am J Hematol 2010; 85(5):380-3. • Lodahl D et al., Dan Med Bul 2011, 58:A4233	The role of procalcitonin was not identified as a priority for investigation in the guideline as the GDG prioritised the appraisal of investigations in common clinical usage. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it. You may wish to consider referring procalcitonin as a topic to the medical diagnostic team at NICE.
Thermo Fisher Scientific	16.01	Full	55	15	Erten et al. is only referenced for diagnosis of severe sepsis by CRP but the conclusion states	The role of procalcitonin was not identified as a priority for investigation in the guideline as

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					"PCT and CRP are comparable with each other in prediction of the clinical severity of febrile neutropenic attacks."	the GDG prioritised the appraisal of investigations in common clinical usage. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it. You may wish to consider referring procalcitonin as a topic to the medical diagnostic team at NICE.
Thermo Fisher Scientific	16.02	Full	56	8	Hatzistilianou et al. is referenced to document the diagnostic accuracy of CRP in patients with documented infections although this is not the conclusion from the study: The authors conclusion states "Procalcitonin is a specific and sensitive marker of microbial infection in patients with neutropenic fever. The markers, C-Reactive Protein, Interleukin-6 and NO2/NO3 may NOT help to identify infections and distinguish the etiology of infection in neutropenic febrile children with acute lymphoblastic leukaemia."	The role of procalcitonin was not identified as a priority for investigation in the guideline as the GDG prioritised the appraisal of investigations in common clinical usage. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it. You may wish to consider referring procalcitonin as a topic to the medical diagnostic team at NICE.
Thermo Fisher Scientific	16.03	Full	58	26	Some of the referenced studies not only investigated CRP but also PCT which showed comparable or even advantageous diagnostic accuracy (Hitoglou-Hatzi et al., 2005, Martinez-Albarran *et al.,* 2009, Massaro *et al.,* 2007, Secmeer et al., 2007)	The role of procalcitonin was not identified as a priority for investigation in the guideline as the GDG prioritised the appraisal of investigations in common clinical usage. Therefore the evidence on this has not been appraised and we are unable to make recommendations on it. You may wish to consider referring procalcitonin as a topic to the medical diagnostic team at NICE.
UK Clinical Pharmacy Association	25.00	Full	General		We have no comments to make on this document.	Thank you for your comment.

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University Hospital Birmingham NHS Foundation Trust	12.00	Full			NICE appears to have ignores guidance from ASCO and the EORTC showing that the incidence of febrile neutropenia was significantly reduced by using prophylactic growth factors when there was > 20% risk. Also it has ignored that increasing use of quinolone antibiotics will cause drug resistance and increased potential rates of c diff infection	We have acknowledged that prophylaxis with G-CSF (as recommended by ASCO and EORTC) reduced the rate of febrile neutropenia in the clinical evidence of section 5.1. As noted in the linking evidence to recommendation section for chapter 5, the ASCO and EORTC recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5).

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						The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
University Hospitals Southampton (Formerly Southampton University Hospitals Trust)	21.00	Full	49	1	We would like to have seen this recommendation strengthened with some specific guidance on the form of training that should be undertaken.	It is not within the remit of this guideline to develop minimum training standards. This recommendation has been highlighted to the Implementation team at NICE.

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University Hospitals Southampton (Formerly Southampton University Hospitals Trust)	21.01	Full	58	37	The data to support an assessment of the lactate level in the evaluation of uncomplicated neutropenic sepsis is very limited. It is infrequently used in NHS practice.	As documented in the linking evidence to recommendations section of section 4.2.1, the evidence indicated that raised levels of lactate were suggestive of a patient being at increased risk of severe sepsis.
University Hospitals Southampton (Formerly Southampton University Hospitals Trust)	21.08	Full	65	1	Assessment by Oncology within 48 hours does not match Acute Oncology standard of 24 hours	The GDG have reviewed this recommendation, and felt that to improve the patient experience and clinical management a patients risk of septic complications should be assessed within a maximum of 24 hours of presentation.
University Hospitals Southampton (Formerly Southampton University Hospitals Trust)	21.02	Full	112	1	As an organisation we have grave concerns about a recommendation to offer prophylactic quinolones to all patients. These agents are associated with increased risk of clostridium difficile infection. Our Microbiology team strongly discourage their widespread use. The guidance makes no comment on this risk.	The issues of infection and resistance patterns, and Clostridium difficile (C. diff) rates, were considered extensively by the GDG. The recommendation for quinolone use has been revised to emphasise the provision of prophylaxis only to patients who are expected to become significantly neutropenic (<0.5 x 10^9/litre) and only during the period of expected neutropenia. The potential increase in antibiotic resistance and its impact on cancer patients was considered by the GDG. This was supported by studies in the evidence appraised for this topic. These indicated that while there is a potential increase in rates of resistance with the use of quinolone prophylaxis, there is a continued and substantial decrease in overall mortality (see linking evidence to recommendations section for chapter 5).

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						The GDG are aware that the use of such prophylaxis has become increasingly common in particular patients e.g. patients with breast cancer on TAC chemotherapy, without an increase in problems, and it has become a standard of care for this group. The GDG acknowledged that C. diff infection is a significant challenge in hospitals. All antibiotics may contribute to increasing C. diff rates. Anti-microbial stewardship is a key element to the C. diff reduction programme alongside multi-faceted interventions addressing environmental cleaning and hand hygiene. We agree that antibiotics should only be used where there is clear evidence that their benefit outweighs the risks and consider that quinolone prophylaxis would meet this standard. The GDG would support continued monitoring of microbiological data to detect changes in infection and resistance patterns and C. diff rates, and have recommended that this is done in patients within treatment facilities where patients are receiving quinolone prophylaxis to prevent neutropenic sepsis.
University Hospitals Southampton (Formerly Southampton University Hospitals Trust)	21.03	Full	112	1	The GDG makes no recommendations about the use of growth factors for primary or secondary prophylaxis. This is a dangerous stance as we are at risk of these agents not being commissioned as a result when there is good evidence that they reduce episodes of febrile neutropenia, shorten hospital stays and in some series have been shown to have an impact on overall survival.	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not

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						been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. The GDGadditionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic

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						sepsis.
					Both ASCO and ESMO have presented clear evidence based guidelines for their use which the GDG appear to have paid little attention to. We are at risk of taking a very large retrograde step in the management of FN.	As noted in the linking evidence to recommendation section for chapter 5, the ASCO and ESMO recommendations were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics and did not assess the cost effectiveness of their recommendations. Our recommendations for this topic are based on a systematic search and appraisal of the clinical evidence and the results from a health economic model. Consequently, they may not be commensurate with current clinical practice or recommendations in other non-NICE guidance.
					The cost model presented is over simplified and does not take into account the very reasonable procurement costs that individual Trusts have negotiated over the years for these agents and the market pressures that continue to drive the prices down with the competition for biosimilars.	All G-CSFs are biosimilars that in terms of regulation aren't treated as generics. Therefore, whilst each PCT probably has its own agreement, there is no nationally negotiated discount as normally found on the CMU website. Given this the GDG decided to use the BNF price since there is no other reliable NHS source. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg).

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						However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A).
					This analysis should be reperfromed looking at individual chemotherapy regimens and the primary data on their FN risk working an individual cost model for each based upon current procurement prices.	A range of different baseline risks were tested in one-way sensitivity analysis (5-100%) for each chemotherapy cycle. However, for all three patient sub-groups, the results show that even when 100% risk is tested, G-CSF is still not cost effective compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY.
					There also needs to be a clear statement to guide commissioners about the use of growth factors in regimens that have them included to enhance dose density/delivery so that if this shameful recidivist step is allowed to pass, the use of these agents in these circumstances will not be stopped. Additionally no specific mention of use of growth factors in those patients with FN at high risk or with septic complications (see ESMO guidance).We are very concerned about this	A recommendation on the use of G-CSF for the prevention of neutropenic sepsis has been added to the guideline. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation. The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid

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						and regional, and therefore no national recommendations can be based on these costs. The GDG additionally noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices. One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G-CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take quinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis.
University Hospitals Southampton (Formerly Southampton University Hospitals Trust)	21.04	Full	121	1	There is no mention of the 1 hour door to needle time standard	We acknowledge that this is an important clinical issue and was debated at length by the GDG. However the evidence was not clear enough to recommend a specific time or specific clinical group where time to antibiotic delivery altered the patients outcome. Hence the recommendation does not define a specific time period or limit its indication to a specific clinical presentation.

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University Hospitals Southampton (Formerly Southampton University Hospitals Trust)	21.05	Full	133	1	There is a role for the immediate addition of an aminoglycoside in patients presenting with septic complications (eg hypotension). This is not considered in the evidence presentation.	The recommendations made were based on the evidence appraised for this topic which did not support addition of aminoglycosides to any group as initial empiric therapy.
University Hospitals Southampton (Formerly Southampton University Hospitals Trust)	21.06	Full	148	1	No clear guidance is given on the need for a period of inpatient observation for septic complications in those low risk patients offered community antibiotics	The GDG has not specifically commented on the use of outpatient management at the outset of cases for low risk patients. Whilst there was some evidence to support immediate discharge for low risk patients, the GDG did not consider that it was strong enough to support recommending a specific timeframe. Instead they recommended research into very early (first 24 hours) oral antibiotic therapy.
University Hospitals Southampton (Formerly Southampton University Hospitals Trust)	21.07	Full	166	1	It was hoped that the GDG would make a stronger recommendation on the duration of empirical antibiotics	The evidence appraised did not support recommending a specific duration of empirical antibiotics.
University of Sheffield	10.00	Appendices	general		The commentators are some of the authors of the paper "Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in breast cancer: modelling different prophylaxis strategies. Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. *Value in Health* 2011;14(4):465-474." referred to in the draft guidelines. These comments mostly relate to Appendix A, the cost utility analysis. GENERAL COMMENTS:	We have responded to your individual comments below.

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					We find that there are serious issues with the modelling assumptions, the modelling approach and the results derived. Several key assumptions made are considered incorrect. The modelling approach has a serious flaw and also does not correctly reflect the decision problem. Lastly, the results derived are highly suspect as they depend heavily on these assumptions.	
University of Sheffield	10.06	Appendices	general		A contents page for this appendix A would be a useful addition for the reader.	Thank you for your comment. We have inserted a contents page for appendix A
University of Sheffield	10.05	Full	General		MINOR COMMENTS:	Thank you for your comments.
University of Sheffield	10.04	Full	105	28	*The draft suggests that there are serious limitations with the Whyte et al 2011 paper but the reasons provided are incorrect.* *Table 5.10 "This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF. Part of the effectiveness data (survival rates for breast cancer patients) was obtained from Cancer Research UK. However it is noted that the survival data of Cancer Research UK related to breast cancer patients who are receiving all kinds of treatment (chemotherapy, surgery, radiotherapy etc), not only patients who are receiving chemotherapy alone. Therefore this study is likely to significantly over-estimate the effectiveness of chemotherapy and G-CSF."*	We have removed the sentence about using data of Cancer Research UK from the guideline. We have amended footnote 28 of table 5.10 to clarify the limitations of the Whyte 2011 analysis.

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					Table 5.10 suggests that the use of the Cancer Research UK survival data is a "serious limitation". We believe that this survival data was the best source available. However, irrespective of that view, as this survival data is used in all arms of the model (as all arms receive chemotherapy regardless of prophylaxis strategy) there will not be a significant bias when incremental benefits are considered. The comment in Table 5.10 suggests that the model population consists of patients receiving chemotherapy alone. However, the population of interest must surely be all those who are eligible for NS prophylaxis which includes both persons receiving chemotherapy alone, and persons who receive chemotherapy together with another kind of treatment. The comment also suggests that the survival data used will overestimate survival. Whether the survival data used is an over or under estimate is not clear. For example, the Cancer Research UK data will include some persons who receive no treatment and these patients may have worse survival than those receiving chemotherapy.	
University of Sheffield	10.07	Full Appendices	169	36	*Section A1.1 "pegylated G-CSF are available but expensive."* This seems to be a misleading statement as pegylated G-CSF is only slightly more expensive than G-CSF and is in fact cheaper than the upper range for G-CSF cost according to Table A11.	Thank you for your comment, we have amended this sentence to read 'pegylated G-CSF are available; but the cost-effectiveness is unknown.

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					Total cost per cyc PEG-G-CSF £ 703.18 G(M)-CSF £ 668.32 (Range:	
University of Sheffield	10.08	Full Appendices	169	47	*Section A1.2 Eligibility criteria for prophylaxis" Compared to primary prophylaxis, secondary prophylaxis prevents less episodes of neutropenic sepsis, and thus is associated with a higher cost."* An eligibility criterion which could depend on the NS risk associated with the type of chemotherapy administered is not mentioned as a possibility. The comments on the cost of primary versus secondary prophylaxis seem out of place here. Are these comments based on the results of the model?	Thank you for your comment, we have amended this sentence to '*Compared to primary prophylaxis, secondary prophylaxis prevents less episodes of neutropenic sepsis, and thus is associated with a higher cost of treating neutropenic sepsis*.'
University of Sheffield	10.09	Full Appendices	170	31	*Section A2.1 "This economic analysis does not cover: Cancer patients whose chemotherapy regimen includes G-CSF for dose intensity reasons (for example, patients with breast cancer)"* This statement seems quite unclear and the reader is left unsure whether all breast cancer patients are excluded?	Thanks for your comment, we have amended the sentence to make it clearer what is excluded.
University of Sheffield	10.10	Full Appendices	171	28	*Section A2.3 "This model assumes that if patients develop one episode of neutropenic sepsis, they will then receive dose-reduction chemotherapy. If they develop two episodes of neutropenic sepsis chemotherapy will be discontinued."* The assumption seems quite simplistic and	It is acknowledged that not all patients will necessarily receive dose-reduction chemo or discontinue chemotherapy after incidence of neutropenic sepsis. Structural sensitivity analysis (see section A4.1) has been conducted to test the robustness of results in model B. This has shown that our conclusions

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					potentially quite important. Perhaps it would it be more realistic to assume that a proportion will be discontinued? If current standard care is that a proportion of persons receiving secondary prophylaxis with G-CSFs this should be included.	are robust to changes in model structure.
University of Sheffield	10.02	Full Appendices	172	22	*The short time horizon used in modelling is incorrect. Thus, the results in the draft guidelines do not come close to reflecting the actual benefits associated within NS prevention. (Section A2.4 "The time horizon of both models (A and B) was one course of chemotherapy, as the GDG were only interested in short-term outcomes.")* This assumption has two effects. Firstly, it does not allow enough time for differences in survival over time that would be expected as a consequence of different dose intensities to manifest themselves; secondly, it restricts any estimate of benefits from reduced mortality to those achieved in the first three months. The exploratory analysis in the draft guidelines incorporates mortality due to NS. Any model which affects mortality requires a lifetime time frame to correctly capture benefits. NICE methods guide 2.2.8 states that "A lifetime horizon should normally be adopted if a treatment affects survival at a differential rate	Data on the effect of quinolones or GCSF on short-term mortality for the different sub-populations included in the model is very sparse. Of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. In addition there are feasibility problems with extending the time horizon to model the long term impact of GCSF on short-term mortality. To do this, data would be needed on patients life expectancy and future treatment costs. Given the heterogeneous population covered by the guideline it is unlikely that all the data needed to populate a model would actually exist and therefore any model would have to rely heavily on assumptions. Given the above difficulties and the fact that Sung et al. (2007) concluded that although G-CSF is effective in reducing incidence of febrile neutropenia, it has little or no impact on short-term mortality, the GDG agreed not to extend the time horizon of the existing model. Instead they assessed short-term mortality qualitatively when making their recommendations.

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					when compared with the relevant comparator." A lifetime model would have been the correct choice here and would have more accurately estimated the QALY gains associated with preventing a death. This mistake will have a dramatic impact on results since with a 3 month time frame and a utility value of 0.68 the benefits associated with preventing one death from NS are at most 0.17 QALYs. However, the likely QALY loss evaluated over a lifetime time horizon will actually be considerable particularly for those who are young and have early stage cancer.	Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
University of Sheffield	10.03	Full Appendices	173	18	*The modelling approach considers a fixed rate for the risk of NS which does not correctly reflect the decision problem. (Section A3.1 Table A2 states that a value of 34% was used for solid tumour baseline risk of NS.)* Applying a fixed rate for the risk of NS seems to be a poor approach to take within the modelling. A patient's risk of NS will depend on factors such as the neutropenic toxicity of the chemotherapy regimen and their performance status. These factors will be considered by physicians when deciding whether to administer GCSFs. The fact that there are many different regimes is cited in the draft guideline as a reason for not considering their importance, but this misses the fact that what drives cost effectiveness in part is the risk of NS and this	A range of different baseline risks were tested in one-way sensitivity analysis (5 - 100%) for each chemotherapy cycle. However for all three patient sub-groups, the results show that even when 100% risk is tested (which means all patients will develop neutropenic sepsis in each chemotherapy cycle), G-CSF is still not cost-effective when compared to quinolones or no prophylaxis, at a NICE willingness to pay threshold of £20,000/QALY. The results of all one-way sensitivity analyses have been added to the guideline.

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					risk is itself a function of the regime chosen. Therefore the fact that there are many regimes is the reason why their risk neutropenic risk should be considered. The study by Whyte et al 2011 demonstrated that cost-effectiveness is indeed a function of these baseline risks.	
University of Sheffield	10.11	Full Appendices	173	28	*Table A3: Relative risk of neutropenic sepsis & Table A6: Relative risk of overall mortality for patients with neutropenic sepsis* It would be useful if the author presented 95% Confidence Intervals or some measure of uncertainty for these parameter estimates. This is important to illustrate to the reader whether the effects are significant.	The aim of Section A3 is to report all input data that was used in the economic model. When building the economic model only mean and standard deviation were used. Since 95% CI was not an input to the model we have not reported these in this section to avoid potential confusion.
University of Sheffield	10.01	Full Appendices	174	15	*The base-case assumption that the use of GCSFs does not affect mortality is considered incorrect. (Section A3.1.2 "The volume of evidence to inform overall mortality and relative risk of overall mortality was very sparse for the three patient subgroups of interest. Therefore, in the base-case analysis, it was assumed that the relative risk of overall mortality was one for all prophylactic strategies.")* Mortality associated with NS should be included within the model base case.	Mortality from neutropenic sepsis was considered in the model base case. Sung et al. (2007) concluded that G-CSF had little or no impact on short-term mortality. Our evidence review showed prophylactic quinolones reduced short-term mortality compared to no prophylaxis. However this

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						data was limited and of moderate quality. Consequently it was assumed that none of the prophylaxis strategies included in the model could improve patient's short-term mortality Reference: Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.Meta-analysis: effect of prophylactic hematopoietic colony stimulating factors on mortality and outcomes of infection. Annals of Internal Medicine 2007;147(6):400–11.
					Being able to maintain a higher dose is associated with better mortality outcomes and represents one of the prime reasons that GCSFs would be given.	In order to investigate this effect we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complex to model, requiring a vast amount of data and time. The neutropenic sepsis guideline investigated 19 topics. Given the scale of the work involved to attempt to model the effect of

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						neutropenic sepsis on subsequent chemotherapy scheduling and dose, the GDG agreed it was not practical to investigate this issue as only part of one such topic. Consequently this issue was explicitly excluded from the scope of the guideline
					Section A3.1.2 refers to Appendix 4 of the full evidence review. Although Appendix 4 tabulates the evidence it does not include any details of why the evidence is considered sparse. Appendix 4 describes the meta-analysis performed but no details of the results are included e.g. which relative risks were found to be significant.	Appendix 4 contains the study data and methods used to obtain the results presented in tables A5 and A6
University of Sheffield	10.12	Full Appendices	176	38	*Section* A3.3 *Resource use and cost. This section includes a detailed description of all costs included within the model.* It would be illustrative and useful to the reader if the author could present the average total treatment cost per NS episode.	Thanks for your comment, the average total treatment cost per NS case has been added to the guideline

These organisations were approached but did not respond:

Alder Hey Children's NHS Foundation Trust
Association of Anaesthetists of Great Britain and Ireland
Association of Cancer Physicians
Association of Chartered Physiotherapists in Oncology and Palliative Care
Astrazeneca UK Ltd
Barnsley Hospital NHS Foundation Trust
Bowel Cancer UK
Bradford District Care Trust
Breakthrough Breast Cancer
Breast Cancer Care
British Medical Association
British Medical Journal
British National Formulary
British Paediatric Allergy, Immunology & Infection Group
British Psychological Society
British Society for Immunology
British Thoracic Society
Cambridge University Hospitals NHS Foundation Trust
Camden Link
Cancer Network Pharmacists Forum
Cancer Research UK
Cancer Services Co ordinating Group
Care Quality Commission (CQC)
Children and Young People's Cancer Nurses Community
Chronic Lymphocytic Leukaemia Support Association
Chugai Pharma Europe Ltd
Commission for Social Care Inspection
Cumberland Infirmary
Department for Communities and Local Government
Department of Health, Social Services and Public Safety Northern Ireland
Dorset Cancer Network
Dorset Primary Care Trust
East Lancashire Hospitals NHS Trust
Equalities National Council
Faculty of Intensive Care Medicine
Gateshead Health NHS Foundation Trust
George Eliot Hospital NHS Trust
Gilead Sciences Ltd
Gloucestershire Hospitals NHS Foundation Trust
Gloucestershire LINk

Great Western Hospitals NHS Foundation Trust
Greater Manchester and Cheshire Cancer Network
Greater Midlands Cancer Network
Guy's and St Thomas' NHS Foundation Trust
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Hindu Council UK
Hospira UK Limited
Independent Healthcare Advisory Services
Institute of Biomedical Science
Intensive Care Society
Jo's Trust
Kidney Research UK
Lancashire Care NHS Foundation Trust
Lancashire Teaching Hospitals NHS Trust
Letterkenny General Hospital
Leukaemia & Lymphoma Research
Leukaemia CARE
Leukemia Research Fund
Liverpool Community Health
Liverpool Primary Care Trust
Luton and Dunstable Hospital NHS Trust
Macmillan Cancer Support
Maidstone and Tunbridge Wells NHS Trust
Medway NHS Foundation Trust
Ministry of Defence
Mount Vernon Cancer Centre
Myeloma UK
National Alliance of Childhood Cancer Patient Organisations
National Clinical Guideline Centre
National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health
National Institute for Health Research Health Technology Assessment Programme
National Lung Cancer Forum for Nurses
National Patient Safety Agency
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
NHS Bournemouth and Poole
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS Direct
NHS Plus
NHS Sheffield

NHS Worcestershire
North East London Cancer Network
North Essex Mental Health Partnership Trust
North of England Cancer Network
North Tees and Hartlepool NHS Foundation Trust
North West London Cancer Network
Northamptonshire Primary Care Trust
Northern Ireland Cancer Network
Nottingham City Hospital
Oxfordshire Primary Care Trust
Paediatric Intensive Care Society
PERIGON Healthcare Ltd
Pfizer
Pharmametrics GmbH
Pilgrims Hospices in East Kent
Public Health Wales NHS Trust
Rochdale and District Disability Action Group
Roche Diagnostics
Royal Berkshire NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners in Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition
Royal College of Physicians
Royal College of Psychiatrists
Royal College of Surgeons of England
Royal Society of Medicine
Royal United Hospital Bath NHS Trust
Sacyl
Scarborough and North Yorkshire Healthcare NHS Trust
School of Health and Related Research
Scottish Intercollegiate Guidelines Network
Sheffield Teaching Hospitals NHS Foundation Trust
SNDRi
Social Care Institute for Excellence
Social Exclusion Task Force
Society for Acute Medicine
Society for General Microbiology
South Asian Health Foundation
South East Coast Ambulance Service
South Staffordshire Primary Care Trust
South Tees Hospitals NHS Trust
South West Midlands Newborn Network

Takeda UK Ltd
Teenage Cancer Trust
The Association for Clinical Biochemistry
The British In Vitro Diagnostics Association
The Lymphoma Association
The Rotherham NHS Foundation Trust
UCL Partners
United Kingdom Chemotherapy Redesign Group
United Kingdom Oncology Nursing Society
University College London Hospital NHS Foundation Trust
University Hospitals of Leicester NHS Trust
Welsh Government
Welsh Scientific Advisory Committee
West Midlands Ambulance Service NHS Trust
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
Whipps Cross University Hospital NHS Trust
Wirral University Teaching Hospital NHS Foundation Trust
York Hospitals NHS Foundation Trust

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[i] The Health Act 2006: Code of practice for the prevention and control of healthcare associated infections (Department of Health, 2008a)

[ii] Aapro et al. 2010 Update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 47 (2001): 8 – 32

[iii] Smith et al. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol July 1 2006; 24 (19): 3187 – 3205

[iv] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (2011). Myeloid Growth Factors. V.I.2011