
Monograph:
Whyte, S, Cooper, KL, Stevenson, MD et al. (2 more authors) (Completed: 2011) Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in breast cancer in the United Kingdom. Discussion Paper. HEDS Discussion Paper (11-01). (Unpublished)

HEDS Discussion Paper 11-01

ScHARR

School of Health and Related Research

Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in breast cancer in the United Kingdom

Whyte S[1], Cooper KL[1], Stevenson MD[1], Madan J[1], Akehurst R[1]

1. School of Health and Related Research, University of Sheffield, Sheffield S1 4DA, UK

* Correspondence to: Sophie Whyte, Health Economics and Decision Science, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK
Telephone: +44 (0)114 222 0859
Fax: +44 (0)114 272 4095
E-mail: sophie.whyte@sheffield.ac.uk

Abstract

Introduction: We report a cost-effectiveness evaluation of granulocyte colony–stimulating factors (G-CSFs) for the prevention of febrile neutropenia (FN) after chemotherapy in the United Kingdom (UK).

Methods: A mathematical model was constructed simulating the experience of women with breast cancer undergoing chemotherapy. Three strategies were modelled: primary prophylaxis (G-CSFs administered in all cycles), secondary prophylaxis (G-CSFs administered in all cycles after an FN event), and no G-CSF prophylaxis. Three G-CSFs were considered: filgrastim, lenograstim, and pegfilgrastim. Costs were taken from UK databases and utility values from published sources. A systematic review provided data on G-CSF efficacy. Probabilistic sensitivity analyses examined the effects of uncertainty in model parameters.

Results: In the UK, base-case analysis with a willingness-to-pay (WTP) threshold of £20,000 per quality-adjusted life-year gained and using list prices, the most cost-effective strategy was primary prophylaxis with pegfilgrastim for a patient with baseline FN risk greater than 38%, secondary prophylaxis with pegfilgrastim for baseline FN risk 11% to 37%, and no G-CSFs for baseline FN risk less than 11%. Using a WTP threshold of £30,000 and list prices, primary prophylaxis with pegfilgrastim was cost-effective for baseline FN risks greater than 29%. In all analyses, pegfilgrastim dominated filgrastim and lenograstim. Sensitivity analyses demonstrated that higher WTP threshold, younger age, earlier stage at diagnosis, or reduced G-CSF prices result in G-CSF prophylaxis being cost-effective at lower baseline FN risk levels.

Conclusion: Pegfilgrastim was the most cost-effective G-CSF. The most cost-effective strategy (primary or secondary prophylaxis) was dependent on the FN risk level for an individual patient, patient age and stage at diagnosis, and G-CSF price.

Key words: Cost-effectiveness; economic model; febrile neutropenia; granulocyte colony–stimulating factors; prophylaxis.

* * * * *

Acknowledgements: The research underlying this study was funded by Amgen Ltd., and a research grant from Amgen (EUROPE) GmbH was provided to support the production of the article. Amgen staff reviewed and suggested edits, but the final content, authorship, and right to publication remained with the research team.

INTRODUCTION

Neutropenia is the major dose-limiting toxicity of many chemotherapy regimens. Febrile neutropenia (FN) and its consequences are associated with substantial morbidity, mortality, and costs.(1) Chemotherapy-induced neutropenia and FN are also associated with dose reductions and delays to chemotherapy that can compromise patient survival.(2)

In the UK the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) performed a review of the care of patients who died within 30 days of receiving systemic anti-cancer therapy (SACT).(3) They report that the most commonly reported grade 3-4 toxicities associated with patients dying within 30 days of chemotherapy were neutropenia, neutropenic sepsis and infection.

Recombinant human granulocyte colony-stimulating factors (G-CSFs) stimulate production of mature, functional neutrophils (4) which reduce the duration and severity of neutropenia and the incidence of FN when used as prophylaxis alongside chemotherapy.(5;6) G-CSF prophylaxis may be beneficial during treatment for many different cancers, depending on the risk of FN which is a factor of combined chemotherapy regimen and patient risk factors.(7) This analysis focuses on breast cancer as the evidence base for G-CSF prophylaxis is well developed in this setting. Three G-CSFs were in use at the time of this analysis: filgrastim, pegfilgrastim, and lenograstim. Pegfilgrastim is given as a single injection per chemotherapy cycle. Filgrastim and lenograstim prophylaxis both involve administration of a number of daily injections per cycle. It is recommended that filgrastim and lenograstim are given daily until the neutrophil count returns to the normal range (for up to 14 days per cycle for filgrastim, or up to 28 days for lenograstim).(8;9)

G-CSFs can be administered as primary prophylaxis (in all cycles) or as secondary prophylaxis (in all remaining cycles following an episode of FN). A 2003 UK audit of 422 breast cancer patients found that only 3.6% of patients received prophylactic G-CSFs and all use was as secondary prophylaxis.(10) The introduction of newer breast cancer chemotherapy regimens such as TAC (docetaxel, doxorubicin, and cyclophosphamide) and FEC-T (fluorouracil, epirubicin, and cyclophosphamide, docetaxel) associated with higher FN risks may further increase the need for primary prophylaxis.(11)

Clinical guidelines on the use of G-CSFs have been produced by the European Organisation for Research and Treatment of Cancer (EORTC)(7) and also in the US by the American Society of Clinical Oncology (ASCO)(12) and the National Comprehensive Cancer Network (NCCN) (13). All sets of guidelines recommend that prophylactic G-CSFs should be used where the risk of FN associated with the chemotherapy regimen is greater than or equal to 20%, and may be considered where the risk is 10-20%, particularly where additional patient risk factors are present.

The objective of this study is to model the cost-effectiveness of G-CSF prophylaxis of FN in patients with breast cancer compared with no G-CSF provision. In the analyses seven prophylaxis strategies are evaluated: primary prophylaxis and secondary prophylaxis for each of three G-CSFs (pegfilgrastim, filgrastim and lenograstim) and no G-CSF prophylaxis.

METHODS

Model structure

A mathematical model was constructed using TreeAge Software (TreeAge Software Inc, USA) to estimate the costs and quality adjusted life years (QALYs) accrued by different strategies of G-CSF use. The model provided the basis for a submission to the All Wales Medicines Strategy Group, and this body subsequently recommended pegfilgrastim for use both as primary and secondary prophylaxis in the NHS in Wales.(14) A lifetime horizon was used as an FN episode may impact on patient survival.

The modelling approach conforms to the National Institute for Health and Clinical Excellence (NICE) methods guidance. (15) The model takes the perspective of the UK National Health Service (NHS) and was populated with UK data where possible. A meta-analysis was performed to obtain efficacy data, EQ-5D utility values were used, and future costs and benefits were discounted at a rate of 3.5% per annum.

The base case for the analysis consisted of a cohort of 52 year old female patients diagnosed with stage 2 breast cancer in line with data on presenting characteristics.(16) (17) In line with the NICE reference case, willingness-to-pay (WTP) thresholds of £20,000 and £30,000 were used (15) to calculate net monetary benefit (NMB).

The majority of clinical trials of filgrastim and lenograstim alongside chemotherapy cycles of 3-week duration used approximately 11 injections per cycle, by which point the neutrophil count had generally recovered.(5;18;19) Therefore we have assumed that 11 days' treatment with either lenograstim or filgrastim is consistent with the efficacy evidence reported within the RCTs.

Several FN risk factors and breast cancer survival risk factors are included in the modelling and these relations are shown in Figure 1, and discussed below.

The model structure is shown in Figure 2. A regimen consisting of 6 chemotherapy cycles of 21 days each is modelled, and in each chemotherapy cycle a patient may or may not experience an FN event. A regimen of 6 cycles was modelled because this is the number of cycles commonly given for breast cancer in the UK. An FN event may cause chemotherapy dose delays/reductions (i.e. sub-optimal relative dose intensity, RDI) which may affect patient survival. Post-chemotherapy, the model uses a state transition model with a cycle length of 1 year. Life expectancy is estimated using

breast cancer survival data (which is dependent on stage at diagnosis). Patients may die of FN during chemotherapy and from breast cancer or other causes after chemotherapy. During chemotherapy only deaths due to FN are considered but post chemotherapy deaths from breast cancer and other causes are considered.

One and two way sensitivity analyses were undertaken. Probabilistic sensitivity analyses (PSA) were run using 10,000 sets of parameters sampled independently from the distributions described in Table 3. Distributions used were taken from published sources where available and otherwise they were chosen to fit to published 95% confidence intervals. Further details on choice of distributions are given in the data population section. The appropriateness of 1,000 configurations was tested using jack-knife techniques,(20) which on an example dataset showed that the confidence interval around a mean cost per QALY was small (less than £500 in all cases).

Data Population

Calculating FN risk for patients receiving no prophylaxis

Baseline risk, defined as the likelihood of having at least one FN episode over all cycles of chemotherapy without G-CSF provision, can vary widely amongst patients. The EORTC guidelines show that baseline risk can vary from 1% to 71%, depending on chemotherapy regimen, patient age, performance status, and other risk factors.(7) It has also been established that the risk of an initial FN episode is greatest in chemotherapy cycle 1.(6;21;22) The relative risk of an initial FN event in cycles 2 onwards compared with cycle 1 was calculated as 0.2 (95% CI: 0.154 – 0.293) using data from a study which distinguished between initial and subsequent FN events.(21) In addition, occurrence of an FN event indicates that a patient is at a higher risk of further FN events in subsequent cycles. The relative risk of further FN episodes in a patient with prior episodes was calculated as 9.09 (95% CI 6.19-13.35), using data from a study which reported first occurrence of FN events by cycle.(21) Lognormal distributions fitted to these confidence intervals were used for these FN related relative risks.

To inform decision-making for a broad population of patients, we modelled the cost-effectiveness of G-CSF for a range of baseline risk values. Our model required the FN risk per cycle, which we calculated from the baseline risk using the information given above, and assuming 6 cycles of chemotherapy. For example, to model a baseline FN risk of 20%, this was split into a cycle 1 risk of 10% and a risk of 2% for each of cycles 2-6. If a patient had an FN episode in cycle 1, this increased the FN risk in each subsequent cycle to 18%. Further details on these calculations are given in Appendix 1.

G-CSF efficacy

A full systematic review of literature relating to G-CSF efficacy was undertaken. The comparative efficacy of the three G-CSFs in reducing FN risk is evaluated using meta-analyses of trials of each G-CSF compared with no primary G-CSF prophylaxis (see Table 1). This work updated an existing meta-analysis by Kuderer et al. (23) and will

be published separately. Details of the trials of the pegfilgrastim versus no GCSF are included in Appendix 2. In line with NICE methods guidance the results of the meta-analysis were used in the base-case analysis. Lognormal distributions fitted to the confidence intervals from the meta-analysis were used to represent uncertainty in G-CSF efficacy relative risk values.

In general the studies included in the meta-analysis by Kuderer et al(23) described administration of filgrastim/lenograstim for approximately 11 days where the chemotherapy cycle length was three weeks. The use of filgrastim and lenograstim for 6 days was also considered as a 2003 UK audit of breast cancer patients found that such a regimen is sometimes used, although the number of patients in this audit was small (n=15).(10) A US observational study of 205 breast cancer patients also found that patients received on average 6 days of filgrastim per cycle.(24) Clinically it is expected that 6-day filgrastim is less efficacious than 11-day filgrastim since trial evidence indicates that neutrophil count does not fully recover until around 11 days of filgrastim treatment.(5;18;19) Trial evidence relating to using filgrastim or lenograstim for six days is limited and inconclusive. (25) (21) We have therefore conservatively assumed the efficacy for 6-day use to be the same as that for 11-day use; this assumption is favourable to the 6-day strategy.

Mortality rates used within the model

A study by Kuderer et al analysed 3,077 breast cancer patients hospitalised for FN in the US between 1995 and 2000.(1) The mortality rate from FN for breast cancer patients was 3.6% (95% CI 2.9% to 4.3%) and a normal distribution was used to model uncertainty.

Breast cancer survival data are dependent on stage of diagnosis and years since diagnosis. Data from Cancer Research UK 2007 for patients diagnosed in 1985 gives survival rates by cancer stage at diagnosis and years since diagnosis; with survival rates at 10 years of 78%, 55%, 28% and 5% for stages 1-4 respectively.(26) More recent survival data from 2001-2003 reports breast cancer survival at 1, 5, 10, 15 and 20 years as 94%, 80%, 72%, 68% and 65% respectively for all stages combined.(27) The relative proportion of patients in each stage at diagnosis is 39%, 48%, 8% and 5% for stages 1 to 4 respectively (28) and it was assumed that improvements in survival since 1985 affect all stages equally. After adjustment, breast cancer survival rates at 10 years were calculated as 86%, 70%, 46% and 16% for stages 1-4 respectively.

A limitation of the above data is that it relates to all breast cancer patients, not just those who undergo chemotherapy. It is not clear in which direction this will bias results as the fact that a patient is receiving chemotherapy may indicate a good performance status but it may also indicate advanced disease and hence an increased risk of mortality.

Mortality due to other causes is taken from Office for National Statistics data.(16)

Reduced relative dose intensity (RDI) of chemotherapy

Reduced RDI is commonly defined as receipt of <85% of the planned chemotherapy dose intensity (either as a result of a reduced dose or a delay between doses).(2;29) Being aged 65 years or older and having a history of an FN event are both predictors of receiving a reduced RDI.(2;30) As age is also a predictor of FN,(30) age and FN are not independent as predictors of RDI. The correlation between these variables was explicitly modelled by Shayne et al using a multivariate logistic regression analysis.(2) The reported odds ratios were used to calculate the risk of having a reduced RDI for the following four groups: age < 65 years without a prior FN event, age<65 years with a prior FN event, age ≥65 years without a prior FN event, and age ≥65 with a prior FN event; see Table 2. Log-normal distributions were used to model uncertainty in these odds ratios.

Impact of RDI on survival

The relationship between chemotherapy dose intensity and survival is uncertain. However, it is generally considered that a reduction in RDI below the optimum is likely to be detrimental to long-term survival from cancer.(29) In particular, in situations where dose-dense or dose-intense chemotherapy strategies are used reduction in RDI may be detrimental to survival. (7)

Estimations can be made either from prospective trials that try to determine optimal dose or from retrospective studies but both have limitations. In prospective studies there is likely to be a ceiling above which further dose increases will not increase survival. Long-term retrospective studies may be confounded by the fact that patients who have their dose intensity reduced may be those who are more likely to die due to other factors such as older age and poorer performance status. A retrospective study by Chirivella et al. reports a hazard ratio of 1.73 for survival associated with RDI >=85% versus RDI<85%.(31) In this study 88% of patients received RDI >=85% and 12% received RDI<85%.

The reciprocal of the reported HR was used to estimate mortality rates for low and high RDI from the mean age dependent mortality rate as follows:

Mean mortality = (probability RDI <85%)*(mortality if RDI <85%)
+ (probability of RDI >=85%)*(mortality if RDI >=85%).

Hence rearranging we get:
Mortality if RDI <85% = mean mortality/(12%+88%*HR), and
Mortality if RDI >=85% = mean mortality*HR/(12%+88%*HR).

The model applies this hazard ratio to survival of patients with low RDI for the remainder of their lifetime. As mentioned above the retrospective nature of the Chirivella study may result in confounding. For this reason a sensitivity analysis in which low RDI has no effect on survival has been included.

Utility values

Utility values which are dependent on both health state and patient age were used. The average population utilities, categorised by age, have been taken from Kind et

al.(32) Each adverse health state (FN, receiving chemotherapy for breast cancer, local or regional recurrence, distant metastases and disease free) is assumed to be associated with a decreased utility for the duration of the event. Each chemotherapy cycle is assumed to last for 3 weeks and the mean length of hospitalisation following an FN event is estimated to be 8 days. (1)

Utility values for the health states "FN" and "receiving chemotherapy for breast cancer" were reported as 0.33 and 0.70.(33) (34;35) These were converted into utility multipliers of 0.398 and 0.843 (by dividing by 0.83 the age factor for age 55,(32) assuming published utility is for patients aged 55). Utility multipliers for disease-free state, local or regional recurrence and distant metastases were taken from Hind et al 2007; see Table 3.(36) For cancer survivors in years 1-5 it is assumed that 77% are disease free, 7% have local or regional recurrence and 16% have distant metastases.(36) These proportions were combined with the relevant multipliers to produce an average utility multiplier of 0.855. For cancer survivors in years 6-20 it is estimated from ONS survival data that 81% are disease free, 9.5% have local or regional recurrence and 9.5% have distant metastases hence an average utility multiplier of 0.879 was used. For 20+ years post-diagnosis, it was assumed that patients were disease-free and a utility multiplier of 0.94 was used. Beta distributions were used to model uncertainty in utility values.

Valuation of Costs

All cost parameters were taken from UK sources. For other parameter values where UK data sources were not available the best quality non-UK data sources identified were used. Only costs incurred during the time on chemotherapy are included in the model. It was assumed that costs incurred after chemotherapy was completed were independent of G-CSF prophylaxis strategy.

The unit costs used within the model are given in Table 3. It is assumed that G-CSF injections are administered by a district nurse at the patient's home. It is assumed that FN treatment is administered on an inpatient basis. Filgrastim and lenograstim were assumed to be administered as weight based doses at 5mcg/kg/day. Patient weights were reported in three of the studies and a weighted mean was calculated to be 72.3kg (SD 14.7kg). (5;37;38) Using this patient weight distribution, the following vial size requirements were calculated: 20% of patients weigh <60kg and require a single 300mcg vial; 74% of patients weigh 61kg-96kg and require a single 480mcg vial; and 5% of patients weigh at least 97kg and require two 300mcg vials. Similarly for lenograstim, 10% of patients weigh <53kg and require a single 263mcg vial; 45% of patients weigh 54-74kg and require a 263mcg vial plus a 105mcg vial; and 45% of patients weigh at least 75kg and require two 263mcg vials. Since the G-CSF market in the UK is driven by competitive tenders it is common for discounts to be provided on list prices. Therefore various discounted prices were considered in a sensitivity analysis.

The costs of chemotherapy are dependent on the number of chemotherapy cycles received. If a patient dies from an FN event during chemotherapy, no further cycles are given and no further costs incurred. Chemotherapy costs vary depending on the

regimen. For simplicity the cost of TAC is used at £1,234 per cycle.(39) Costs of chemotherapy have been assumed independent of RDI rate.

RESULTS

Results are presented for a baseline FN risk of 24%, the mean risk for a patient receiving TAC chemotherapy.(7) We calculate the incremental costs and QALYs compared with a strategy of no G-CSF prophylaxis. These are presented alongside the net monetary benefits and incremental cost effectiveness ratio (ICER) in Table 4. At this risk level, the ICER for primary prophylaxis with pegfilgrastim is £38,482. The cost effectiveness acceptability curve (CEAC) (40) is shown in Figure 3. All strategies are presented in the CEAC but only primary and secondary pegfilgrastim and no G-CSFs have a probability of being cost effective of over 0.05 so the other strategies are very close to the x-axis. With a WTP threshold of between £20,000 and £30,000 per QALY secondary prophylaxis with pegfilgrastim is the most cost effective strategy over 90% of the time. We also calculated results for the regimen epirubicin-docetaxel (ET75) which is reported to have an FN risk of 31% (Table 4). (41;42) At this risk level, the ICER for primary prophylaxis with pegfilgrastim is £26,824.

Results are highly sensitive to baseline FN risk. The base case analysis with a WTP threshold of £20,000 per QALY demonstrated that for a patient with an FN risk level of 11-37% secondary prophylaxis with pegfilgrastim is most cost effective and for patients with higher FN risk levels primary prophylaxis with pegfilgrastim becomes the most cost effective. Using a WTP threshold of £30,000, primary prophylaxis with pegfilgrastim was cost-effective for baseline FN risks greater than 29%.

Deterministic one-way sensitivity analysis on baseline FN risk level was performed for a selection of scenarios and results are presented in Figure 4. For a particular chemotherapy regimen, the baseline FN risk, and therefore the cost-effectiveness of G-CSF prophylaxis, will vary for individual patients depending on patient risk factors such as performance status, age, etc. A clinician would be assumed to estimate the risk of FN for an individual patient according to factors such as performance status as well as the chemotherapy regimen they were receiving. As age increases, there will be a decrease in remaining expected QALYs but an increase in expected baseline FN risk which impact the cost-effectiveness in opposing directions

The scenario analyses performed demonstrate that age at diagnosis, stage at diagnosis, WTP threshold and G-CSF price all significantly affect the level of baseline FN risk at which G-CSF prophylaxis becomes cost effective. The scale of the effect these variables can have on the ICER is shown in a tornado diagram, Figure 5.

We observe that all the strategies involving the once-daily G-CSFs filgrastim and lenograstim are never optimal. Our analysis indicated that pegfilgrastim would dominate filgrastim and lenograstim given for 11 days (as pegfilgrastim has lower cost and higher efficacy), and had small ICERs compared with 6 day treatment courses. As previously mentioned trial evidence relating to using filgrastim or

lenograstim for six days is limited and inconclusive. We note that if 6 day filgrastim was assumed to be less effective than 11 day filgrastim this would result in lower expected QALYs and slightly higher expected costs for 6 day filgrastim compared with 11 day filgrastim. As discussed earlier evidence comparing the efficacy of 6 and 11 day filgrastim/lenograstim is inconclusive but, as an example, if the relative risk of FN for 6 day filgrastim versus no G-CSF was 0.8 then primary prophylaxis with 6-day filgrastim is associated with an expected 10.102 QALYs and £12,330.

DISCUSSION

The most cost-effective strategy is dependent on the estimated baseline risk of FN for an individual patient, the cost per QALY threshold, patient age and stage at diagnosis and G-CSF price. It is noted that in all scenarios the most cost-effective strategy was one of primary pegfilgrastim, secondary pegfilgrastim or no G-CSFs. Strategies involving 11-day filgrastim or lenograstim were dominated and in no scenario was the use of 6-day treatment with filgrastim or lenograstim the most cost-effective strategy.

This study had several limitations. Several assumptions had to be made due to limitations in the data available. For example UK-specific data was not available for all parameter values so data from other countries was used. A statistical analysis relating patient age, performance status and chemotherapy to FN risk was not available but the modelling would be improved if the relationship between these factors was included. The availability of further data reporting FN events with details of chemotherapy cycle number and initial FN events would make the modelling more robust.

If an FN event leads to reduced RDI then this could lead to higher breast cancer recurrence rates. Hence breast cancer treatment costs may be higher for strategies which result in more FN events. There is very limited data to estimate the change in treatment costs due to low RDI and there is considerable uncertainty surrounding the relationship between FN and RDI and RDI and survival. Hence, the modelling of costs was simplified by assuming all post-chemotherapy costs were the same independent of prophylaxis strategy. This assumption that the post chemotherapy costs are the same for all strategies may bias against G-CSF use.

Sensitivity analyses for stage at diagnosis and age at diagnosis demonstrate that for some subgroups primary prophylaxis with pegfilgrastim will be the most cost effective strategy at lower levels of FN risk. Since the G-CSF market in the UK is driven by competitive tenders it is common for discounts to be provided on list prices. Including the possible discounting of G-CSFs within the modelling also greatly reduces the FN risk threshold at which primary prophylaxis with pegfilgrastim is cost effective. The overall decision on whether to use G-CSFs will depend on the clinician's assessment of risk factors for a particular patient.

Currently there are two filgrastim biosimilars available in the UK with list prices approximately 10% less than the originator filgrastim (Neupogen). (43) A sensitivity analysis on cost of filgrastim was performed using a WTP threshold of £20,000. Regardless of FN risk level, if the cost of filgrastim is reduced to 50% of list price the most cost effective strategies still do not involve filgrastim. As an example, for the base case FN risk level of 24%, primary prophylaxis with filgrastim for 6 days becomes the most cost effective strategy if the cost of filgrastim discounted to 18% of the list price. However, if pegfilgrastim is discounted to 50% of the list price then prophylaxis with filgrastim is never the most costs effective even if filgrastim is free.

Published cost-effectiveness analyses (44) (45) for different healthcare systems have reached different conclusions regarding the cost-effectiveness of G-CSF prophylaxis for febrile neutropenia and have more closely supported international clinical guideline recommendations on the use of G-CSFs (7;12). Differences in the conclusions of these analyses are due to: the use of different pegfilgrastim efficacy values, different costs and care pathways for different countries, and differences between the structures of the models used.

REFERENCES

(1) Kuderer N, Dale D, Crawford J, et al. Mortality, Morbidity, and Cost Associated with Febrile Neutropenia in Adult Cancer Patients. CANCER 2006;106(10):2258-66.

(2) Shayne M, Crawford J, Dale D, et al. Predictors of reduced dose intensity in patients with early-stage breast cancer receiving adjuvant chemotherapy. Breast Cancer Res Treat 2006;100:255-62.

(3) The national confidential enquiry into patient outcome and death (NCEPOD). A review of the care of patients who died within 30 days of receiving systemic anti-cancer therapy. 2008.

(4) Welte K, Gabrilove J, Bronchud MH, et al. Filgrastim (r-metHuG-CSF): the first 10 years. Blood 1996 Sep 15;88(6):1907-29.

(5) Green M, Koelbl H, Baselga J, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Annals of Oncology 2003;14:29-35.

(6) Vogel C, Wojtukiewicz M, Carroll R, et al. First and Subsequent Cycle Use of Pegfilgrastim Prevents Febrile Neutropenia in Patients With Breast Cancer: A Multicenter, Double-Blind, Placebo-Controlled Phase III Study. J Clin Oncol 2005;23(6):1178-84.

(7) Aapro M, Cameron D, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of

chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. European Journal of Cancer 2006;42:2433-53.

(8) Summary of Product Characteristics(SPC) for Neupogen (filgrastim). 2008. http://emc.medicines.org.uk/medicine/7907.

(9) Summary of Product Characteristics(SPC) for Granocyte (lenograstim). 2008. http://emc.medicines.org.uk/medicine/8133.

(10) Leonard RC, Miles D, Thomas R, Nussey F. Impact of neutropenia on delivering planned adjuvant chemotherapy: UK audit of primary breast cancer patients. Br J Cancer 2003 Dec 1;89(11):2062-8.

(11) Verrill M. Chemotherapy for early-stage breast cancer: a brief history. Br J Cancer 2009 Sep;101 Suppl 1:S2-S5.

(12) American Society of Clinical Oncology (ASCO). White Blood Cell Growth Factors: 2006 Update. Journal of Oncolocy Practice 2006;2(4):196, http://jop.ascopubs.org/cgi/content/full/2-4/196.

(13) National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Myeloid Growth Factors. 2010. http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf.

(14) All Wales Medicines Strategy Group (AWMSG). Final Appraisal Report: Pegfilgrastim (Neulasta) for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy. 2008. http://www.wales.nhs.uk/sites3/docmetadata.cfm?orgid=371&id=104699.

(15) National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf; 2008.

(16) Office for National Statistics UK. Mortality Statistics. Review of the Register General on deaths by cause, sex and age, in England and Wales, 2004. Series DH2 no. 31. 2004. http://www.statistics.gov.uk/downloads/theme_health/Dh2_31/DH2No31.pdf.

(17) Northern and Yorkshire Cancer Registry and Information Service (NYCRIS). Cancer in the 21st Century: NYCRIS Statistical Report 2000-2004. 2007. http://www.nycris.nhs.uk/uploads/doc55_1_nycris_stats_report_06.pdf.

(18) Holmes F, O'Shaughnessy J, Vukelja S, et al. Blinded, Randomized, Multicenter Study to Evaluate Single Administration Pegfilgrastim Once per Cycle Versus Daily Filgrastim as an Adjunct to Chemotherapy in Patients With

High-Risk Stage II or Stage III/IV Breast Cancer. JOURNAL OF CLINICAL ONCOLOGY 2002;20(3):727-31.

(19) Holmes F, Jones S, O'Shaughnessy J, et al. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. Annals of Oncology 2002;13:903-9.

(20) Inglehart DL. Simulating stable stochastic systems, V: Comparison of ratio estimators. Naval Res Logist Quart 1975;22:553-65.

(21) von Minckwitz G, Kummel S, du Bois A, et al. Pegfilgrastim +/- ciprofloxacin for primary prophylaxis with TAC (docetaxel/doxorubicin/cyclophosphamide) chemotherapy for breast cancer. Results from the GEPARTRIO study. Annals of Oncology 2008;19:292-8 (Epub Sept 2007).

(22) Timmer-Bonte J, de Boo T, Smit H, et al. Prevention of Chemotherapy-Induced Febrile Neutropenia by Prophylactic Antibiotics Plus or Minus Granulocyte Colony-Stimulating Factor in Small-Cell Lung Cancer: A Dutch Randomized Phase III Study. J Clin Oncol 2005;23(31):7974-84.

(23) Kuderer N, Dale D, Crawford J, Lyman G. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. JOURNAL OF CLINICAL ONCOLOGY 2007;25(21):3158-6731.

(24) Weycker D, Hackett J, Edelsberg JS, et al. Are shorter courses of filgrastim prophylaxis associated with increased risk of hospitalization? Ann Pharmacother 2006 Mar;40(3):402-7.

(25) Martin M, Lluch A, Segui MA, et al. Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC): impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen. Ann Oncol 2006 Aug;17(8):1205-12.

(26) Cancer Research UK. CancerStats Factsheet, Breast Cancer. http://publications.cancerresearchuk.org/WebRoot/crukstoredb/CRUK_PDFs/CSFSBREAST.pdf; 2007.

(27) Office for National Statistics UK. Long-term Breast Cancer Survival, England and Wales, up to 2003. http://www.statistics.gov.uk/statbase/ssdataset.asp?vlnk=9132&More=Y; 2005.

(28) Northern and Yorkshire Cancer Registry and Information Service (NYCRIS). Northern and Yorkshire cancer networks: a report on incidence and

management for the main sites of cancer, 1999. http://www.nycris.org.uk/reports/netwks99/netwks99.pdf; 2002.

(29) Bonadonna G, Moliterni A, Zambetti M, et al. 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study. BMJ 2005;330(7485):217-22.

(30) 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 Oncol , abstr 1571. 2001.

(31) Chirivella I, Bermejo B, Insa A, et al. Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. Breast Cancer Res Treat 2009 Apr;114(3):479-84.

(32) Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. British Medical Journal 1998;316:736-41.

(33) Hillner BE, Smith TJ, Desch CE. Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. Estimates using decision analysis while awaiting clinical trial results. JAMA 1992 Apr 15;267(15):2055-61.

(34) Brown RE, Hutton J. Cost-utility model comparing docetaxel and paclitaxel in advanced breast cancer patients. Anticancer Drugs 1998 Nov;9(10):899-907.

(35) Brown R, Hutton J, Burrell A. Cost Effectiveness of Treatment Options in Advanced Breast Cancer in the UK. Pharmacoeconomics 2001;19(11):1091-102.

(36) Hind D, Ward S, De Nigris E, et al. Hormonal therapies for early breast cancer: systematic review and economic evaluation. Health Technology Assessment 2007;11(26):1-154.

(37) Romieu G, Clemens M, Mahlberg R. Pegfilgrastim supports delivery of FEC-100 chemotherapy in elderly patients with high risk breast cancer: A randomized phase 2 trial. Critical Reviews in Oncology/Hematology 2007;64:64-72.

(38) Grigg A, Solal-Celigny P, Hoskin P, et al. Open-label, randomized study of pegfilgrastim vs. daily filgrastim as an adjunct to chemotherapy in elderly patients with non-Hodgkin's lymphoma. Leuk Lymphoma 2003 Sep;44(9):1503-8.

(39) Ward S, Simpson E, Davis S, et al. Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation. Health Technology Assessment 2007;11(40).

(40) Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001 Dec;10(8):779-87.

(41) Zielinski CC, Awada A, Cameron DA, et al. The impact of new European Organisation for Research and Treatment of Cancer guidelines on the use of granulocyte colony-stimulating factor on the management of breast cancer patients. Eur J Cancer 2008 Feb;44(3):353-65.

(42) M.Spielmann, H.Roché, T.Delozier, et al. Safety analysis from PACS 04--A phase III trial comparing 6 cycles of FEC100 with 6 cycles of ET75 for node-positive early breast cancer patients, followed by sequential trastuzumab in HER2+patients: Preliminary results. American Society of Clinical Oncology Annual Meeting Abstract 632. 2006.

(43) British National Formulary: BNF 59 www.bnf.org. 2010.

(44) Danova M, Chiroli S, Rosti G, Doan QV. Cost-effectiveness of pegfilgrastim versus six days of filgrastim for preventing febrile neutropenia in breast cancer patients. Tumori 2009 Mar;95(2):219-26.

(45) Lyman GH, Lalla A, Barron RL, Dubois RW. Cost-effectiveness of pegfilgrastim versus filgrastim primary prophylaxis in women with early-stage breast cancer receiving chemotherapy in the United States. Clin Ther 2009 May;31(5):1092-104.

(46) Balducci L, Al-Halawani H, Charu V, et al. Elderly cancer patients receiving chemotherapy benefit from first-cycle pegfilgrastim. Oncologist 2007 Dec;12(12):1416-24.

(47) Hecht JR, Pillai M, Gollard R, et al. Pegfilgrastim in colorectal cancer (CRC) patients (pts) receiving every-two-week (Q2W) chemotherapy (CT): Long-term results from a phase II, randomized, controlled study. JOURNAL OF CLINICAL ONCOLOGY 2009;27(15 Suppl):Abstract 4072.

(48) del Giglio A, Eniu A, Ganea-Motan D, et al. XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer 2008;8:332.

(49) Curtis L. Unit Costs of Health and Social Care 2007. Canterbury: Personal Social Services Research Unit, University of Kent; 2007.

(50) Sweetenham J, Hieke K, Kerrigan M, et al. Cost-minimization analysis of CHOP, fludarabine and rituximab for the treatment of relapsed indolent B-cell non-Hodgkin's lymphoma in the U.K. Br J Haematol 1999 Jul;106(1):47-54.

Figure 1: Factors affecting FN risk and survival

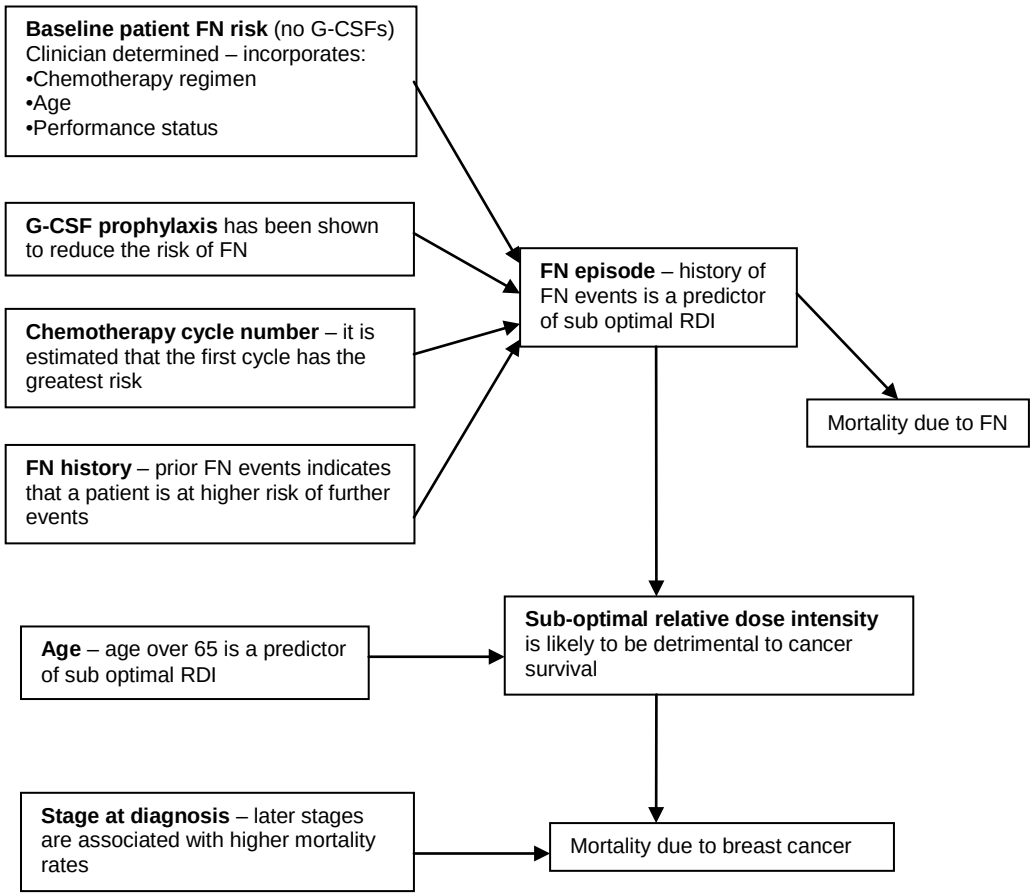


Figure 2: Schematic of the decision analytic model

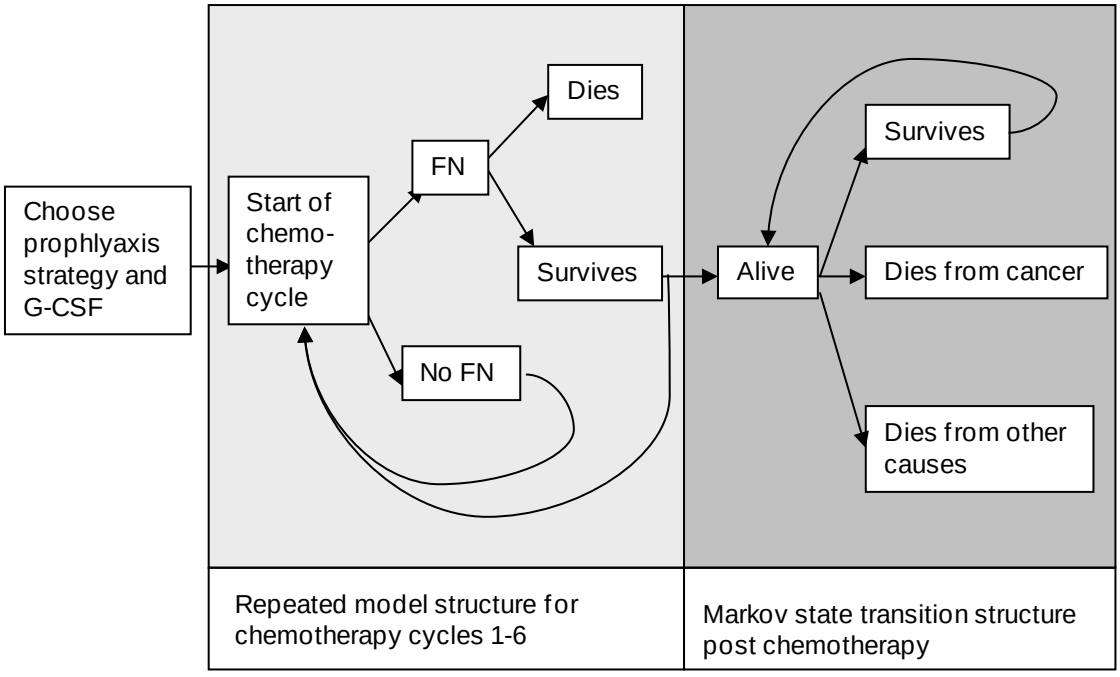


Figure 3: Cost Effectiveness Acceptability Curves for base case analysis
(Base Case: TAC chemotherapy, FN risk level 24%, age 52, stage at diagnosis 2, list price GCSFs)

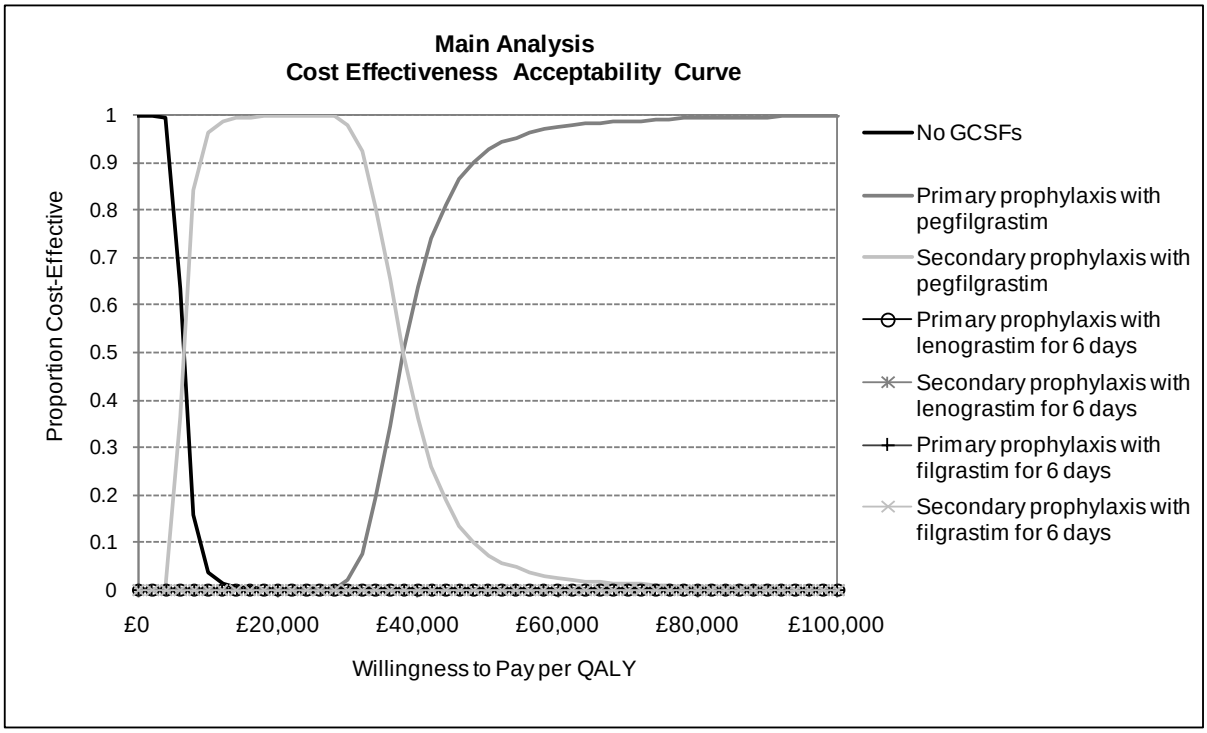
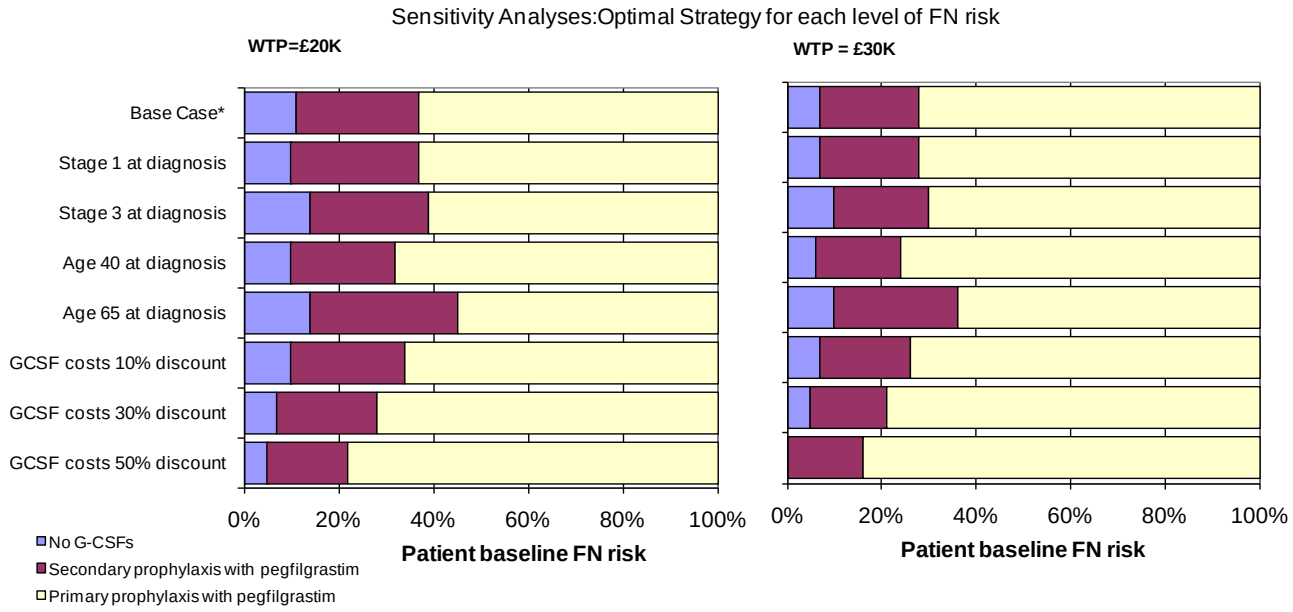


Figure 4: Sensitivity Analyses: The G-CSF strategy with highest NMB for different levels of baseline FN risk



*Base case is WTP of £20,000 per QALY gained, stage 2 at diagnosis, age 52 at diagnosis.

Figure 5: Tornado diagram for primary prophylaxis with pegfilgrastim compared to secondary prophylaxis with pegfilgrastim

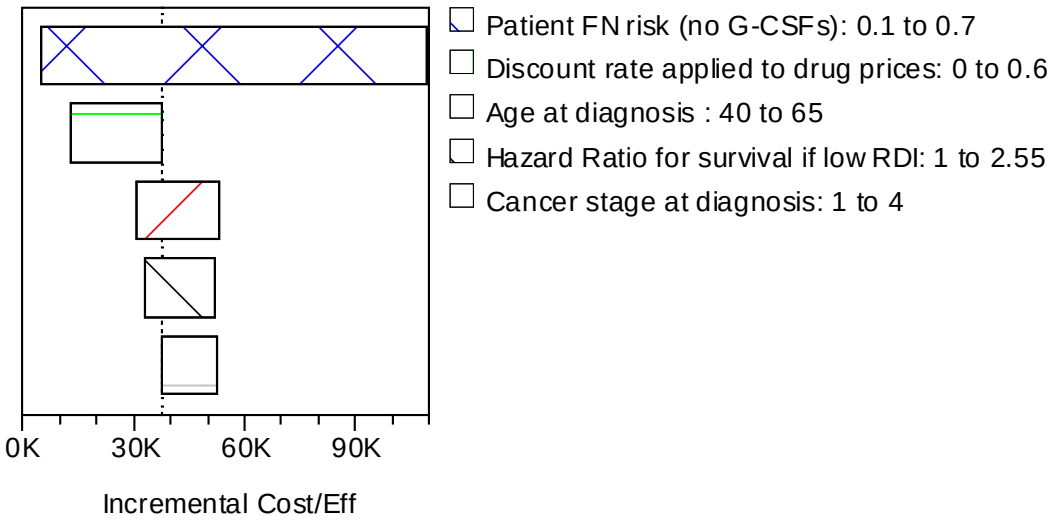


Table 1: Relative risk of febrile neutropenia incidence with G-CSF prophylaxis

G-CSF prophylaxis	Source	Relative risk of FN compared with no G-CSF prophylaxis, (95% CI), p-value
Pegfilgrastim	Vogel 2005(6), Balducci 2007(46), Romieu 2007(37), Hecht 2009(47)	0.30 (0.14 to 0.65), p=0.002
Filgrastim (11 day)	Kuderer 2007(23), del Giglio 2008(48)	0.57 (0.48 to 0.69), p<0.00001
Filgrastim (6 day)	Assumed same as 11 day	0.57 (0.48 to 0.69), p<0.00001
Lenograstim (11 day)	Kuderer 2007(23)	0.62 (0.44 to 0.88), p=0.007
Lenograstim (6 day)	Assumed same as 11 day	0.62 (0.44 to 0.88), p=0.007

Table 2: Relationship between age, prior febrile neutropenia (FN) and relative dose intensity (RDI)

Proportion of patients with RDI <85% *	
All patients (n=3707)	29.7%
Age <65 (n=2998)	26.9%
Age ≥ 65 (n=709)	41.4%
FN (n not reported)	36.0%
Odds ratios for risk of reduced RDI*	
Age ≥ 65 vs. age <65	1.51 (95% CI 1.24 to 1.83)
Prior FN event vs. no prior FN event	1.58 (95% CI 1.20 to 2.10)
Probability of having a low RDI based on age and prior FN events	
Aged < 65 years , No prior FN (BR)	24.7% (95% CI 14.9% to 34.5%)
Aged < 65 years, Prior FN	34.1% **
Aged 65 years or over, No prior FN	33.1% **
Aged 65 years or over, Prior FN	43.9% **

* Data from Shayne et al. 2006 (2)

**Calculated using odds ratio and formula: BR/ (OR (1-BR) +BR) where BR=baseline risk, OR=odds ratio

Table 3: Summary of parameters used in model: deterministic values, distribution used in PSA, and references

Variable	Value	Distribution	Source
Costs			
Cost of pegfilgrastim per injection	£ 686.38	Assumed fixed	BNF (43)
Cost of filgrastim per injection	£ 98.39	Assumed fixed	BNF (43)weight based dose 5mcg/kg/day
Cost of lenograstim per injection	£ 111.83	Assumed fixed	BNF (43)weight based dose 5mcg/kg/day
Cost of administrating a G-CSF injection	£ 21.00	Assumed fixed	Curtis 2007 (49)
Cost of TAC chemotherapy per cycle	£ 1,234.00	Assumed fixed	Ward et al 2007 (39)
Cost of hospitalisation per day	£ 235.00	Assumed fixed	Curtis 2007 (49)
Cost of IV antibiotics during hospitalisation	£ 47.23	Assumed fixed	BNF(43)
Cost of daily investigations (per day of hospitalisation)	£ 9.27	Assumed fixed	Sweetenham et al 1999 (50) uplifted to 2007
Cost of once-per-FN investigations (per FN)	£ 47.86	Assumed fixed	Sweetenham et al 1999 (50) uplifted to 2007
Average duration of hospitalisation for an FN event in days – breast cancer	8	Normal(Mean = 8, Std Dev = 0.2041)	Kuderer et al 2006(1)
Rate used for discounting costs and QALYs	0.035		NICE (15)
RDI and mortality inputs			
Probability of dying from an FN event	0.036	Normal(Mean = 0.036, Std Dev = 0.00357)	Kuderer et al 2006 (1)
Risk of RDI<85% if <65 years and no FN	0.247	Normal (Mean = 0.247, Std Dev = 0.05)	Shayne et al 2006(2)
Odds ratio for RDI<85% if patient >65 years	1.51	Log-normal (mean of logs=0.4072, sd of logs=0.0993)	Shayne et al 2006 (2)
Odds ratio of having RDI<85% if patient has had FN event	1.58	Log-normal (mean of logs=0.4472, sd of logs=0.1428)	Shayne et al 2006 (2)
Hazard Ratio if low RDI (<85%)	1.73	Log-normal (mean of logs=0.5284, sd of logs=0.1987)	Chirivella et al 2009 (31)
FN risk			
Relative risk of an FN event with pegfilgrastim primary prophylaxis vs. no G-CSF	0.30	Log-normal (mean of logs=-1.2807, sd of logs=0.3917)	See Table 1
Relative risk of Neupogen (filgrastim) 11 days compared with no G-CSF	0.57	Log-normal (mean of logs=-0.5664, sd of logs=0.0926)	See Table 1
Relative risk of Lenograstim compared with no G-CSF	0.62	Log-normal (mean of logs=-0.4886, sd of logs=0.1754)	See Table 1
Relative risk of an FN event if patient has already had an FN event	9.089	Log-normal (mean of logs=2.1878, sd of logs=0.1961)	Calculated from data in von Minckwitz et al 2008 (21)
Relative risk of an FN event in cycles 2-6 compared with cycle 1	0.213	Log-normal (mean of logs=-1.5621, sd of logs=0.1635)	Calculated from data in von Minckwitz et al 2008 (21)
Utility multipliers (these are multiplied by an age-specific average utility value from Kind et al 1998 (32))			
Breast cancer; undergoing chemotherapy treatment	0.7	Range 0.5-1	Hillner et al 1992 (33)
Breast cancer; undergoing chemotherapy treatment - **multiplier**	0.843	Beta(9.9, 1.8) 95% CI 0.6-0.98	
FN event hospitalisation	0.33	Range 0.24-0.42	Brown et al 2001 (35); Brown & Hutton 1998 (34)
FN event hospitalisation - **multiplier**	0.398	Beta(30.7, 46.5) 95% CI 0.29-0.51	
First year post chemo and subsequent years 2-5	0.855		Hind et al 2007 (36)

Cancer survivors after year 5	0.879		Hind et al 2007 (36)
Years 20 onwards (from diagnosis), Utility	0.94		Hind et al 2007(36)
multiplier for disease free survival		Beta(3.44, 0.21)	
Utility multiplier for local regional BC	0.74	Beta(1.36, 0.48)	Hind et al 2007 (36)
Utility multiplier for metastatic BC	0.5	Beta(2.75, 2.75)	Hind et al 2007 (36)

Table 4: PSA results

	Cost (£)	QALYs	Incr. Cost (£)	Incr. QALYs	Incr NMB (£), WTP=£20K	Incr NMB (£), WTP=£30K	ICER*
Base Case: TAC chemotherapy, FN risk level 24%, age 52, stage at diagnosis 2							
No GCSFs	8,282	10.060	-	-	-	-	
Secondary prophylaxis with lenograstim for 11 days	9,250	10.083	968	0.023	- 509	- 279	dominated
Secondary prophylaxis with lenograstim for 6 days	8,744	10.083	462	0.023	- 3	227	dominated
Secondary prophylaxis with filgrastim for 11 days	9,134	10.084	852	0.024	- 382	- 147	dominated
Secondary prophylaxis with filgrastim for 6 days	8,679	10.084	397	0.024	73	308	dominated
Secondary prophylaxis with pegfilgrastim	8,556	10.103	274	0.042	570	992	£ 6,500
Primary prophylaxis with lenograstim for 11 days	16,607	10.136	8,326	0.075	- 6,816	- 6,061	dominated
Primary prophylaxis with lenograstim for 6 days	12,637	10.136	4,355	0.075	- 2,846	- 2,091	dominated
Primary prophylaxis with filgrastim for 11 days	15,715	10.138	7,434	0.077	- 5,891	- 5,120	dominated
Primary prophylaxis with filgrastim for 6 days	12,147	10.138	3,865	0.077	- 2,322	- 1,551	dominated
Primary prophylaxis with pegfilgrastim	11,841	10.188	3,559	0.128	- 1,008	268	£ 38,482
Second Example Analysis: ET chemotherapy, FN risk level 31%, age 52, stage at diagnosis 2							
No GCSFs	8,658	9.989	-	-	-	-	
Secondary prophylaxis with pegfilgrastim	8,910	10.059	253	0.069	1,131	1,823	£ 3,651
Primary prophylaxis with pegfilgrastim	11,910	10.170	3,252	0.181	368	2,178	£ 26,824

* ICERs are only presented for strategies on the cost effectiveness frontier. The ICER is calculated compared to the next less effective strategy on the cost effectiveness frontier.