Pazopanib – Responses to ERG questions		
Section A: Clarification on effectiveness data - GENERAL		
Question		**Response**
A1	**Priority request:** P68 – Table 5.11, in answer to the question 'Was the concealment of treatment allocation adequate? It is stated 'Yes. Adequate blinding was achieved…' However blinding is not the same thing as allocation concealment. Please provide the information reported by the study that was the basis for classifying the concealment of treatment	Please see excerpt below from CSR which addresses the ERG question on allocation concealment. **5.4.5. Treatment Assignment** Upon completion of all the required baseline assessments, eligible subjects were registered into the GSK interactive voice response system (IVRS) called RAMOS (Registration And Medication Ordering System), by the investigator or authorised site staff for stratification and central randomisation. The randomisation schedule was generated by GSK Biomedical Data Sciences Department. Subject number and the following subject information for stratification were entered into the system in order to obtain the blinded treatment assignment: 1. Baseline ECOG PS: 0 vs. 1. 2. Prior nephrectomy: yes vs. no. 3. Prior systemic therapy for advanced RCC: cytokine-pretreated versus treatment naïve. All calls to RAMOS were confirmed with a FAX, which was sent to the site upon completion of each call. Study-specific instructional worksheets were provided for the use of RAMOS. The process described above shielded those involved in the trial from knowing upcoming assignments.
A2	**Priority request:** pp22-23 - The statement 'Thus approximately 3.4 per 100,000 patients are estimated to be eligible to receive first-line treatment with pazopanib per year in the UK, equating to around 2120 patients in England and Wales annually.' This is based on the information given in the table on p22, which states '…approximately 40% of those treated for localised disease relapse..' However the source given for this statement (Lam 2005) does not state that this is an annual figure. Please give the rationale for this figure	There is a paucity of epidemiological data in terms of the annual proportion of patients relapsing after treatment of localised RCC. The ERG is correct in highlighting that the quoted paper does not state that the 40% figure is in fact an annual rate. However, this figure is not dissimilar to the one used in the NICE costing tool for sunitinib.

	being taken as an annual figure.	
A3	If possible, please provide available data on file for the studies VEG107769, VEG108844 and VEG113046	Studies VEG108844/VEG113046 have not reported out yet so there is currently no data available.. The CSR for VEG107769 was included in our original submission (a copy is attached to this email). GSK is also providing additional data from this study as part of our responses to ERG queries on the treatment naïve population.
A4	P43 – Table 5.1 – 'Studies which are presented at conferences are usually published in full within 3 years of presentation.' Please provide support for this statement.	A Cochrane review demonstrated that the mean time to full publication ranged from 9 to 36 months with a median of 17.9 months [1]. Therefore we have conducted conference searching to encompass this time period, by searching each conference proceeding for 3 years prior to the date of the database searching. Further, it was determined that about 60% of randomised controlled trials initially presented as an abstract at a conference are subsequently published in a peer-reviewed indexed journal [2]. Hence, it is assumed that following 3 years, this study is unlikely to be published. [1.] Scherer RW, Langenberg P, von Elm E. Full publication of results initially presented in abstracts. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: MR000005. DOI: 10.1002/14651858.MR000005 [2.] See 1
A5	P65 – Bulleted list of factors adjusted for in the multivariate analysis. Please explain the rationale for including 'presence of liver metastases' in this list.	Presence of liver metastases has been identified as a predictor of rapid disease progression [1.] Furthermore, pazopanib data supports this statement as VEG105192 subjects treated with pazopanib with no liver metastases had a median PFS of 12.9 months as compared to a median of 5.6 months in those with liver metastases (log rank p=0.005). [1] Negrier S, Gomez F, Douillard JY, e tal; Groupe Français d'Immunothérapie. Prognostic factors of response or failure of treatment in patients with metastatic renal carcinomas treated by cytokines: a report from the Groupe Français d'Immunothérapie. World J Urol. 2005 Jul;23(3):161-5. Epub 2005 Feb 12.)
A6	P127 – 'The causes of the remaining deaths are reported as 'other' or 'unknown', with the exception of an additional three deaths where the cause of death was only recorded in the parent study.' What was the cause of death for these additional three deaths?	These additional three deaths were all due to the disease under study. Subjects were not required to enter death data into the VEG107769 eCRF if the death was not due to an AE and it occurred more than 28 days after the last dose of therapy. These deaths were only required to be entered into the EG105192 eCRF in order to analyze OS for both studies.
A7	Please clarify why sorafenib, bevacizumab and temsirolimus were considered as comparators in the submission when they were not listed as comparators in the scope	The systematic review and economic model included other targeted agents used in the treatment of RCC (sorafenib, bevacizumab and temsirolimus) as relevant interventions for completeness. However, the clinical and cost-effectiveness sections of our submission focus on the relevant comparators (i.e. sunitinib, interferon and BSC) as per the scoping document.

	document.	
A8	P33-35 – In the Decision problem table, please explain why, in the 'Comparators' row, interleukin-2 is listed in the 'Scope' column but is not listed in the 'Decision problem addressed in the submission column'.	Interleukin-2 does not have a licence in the UK.
A9	P141 - 'These demographic and disease characteristics...are likely to be representative of patients with advanced/metastatic RCC in the UK.' However in study VEG105192 the percentage of patients with prior nephrectomy was 83% in the pazopanib arm and 84% in the placebo arm (Table 5.7). Please explain the rationale for this statement, as independent advice suggests that the vast majority of patients presenting with advanced/metastatic renal cell carcinoma in the UK have not undergone nephrectomy.	Cytoreductive nephrectomy in patients presenting with advanced/metastatic renal cell carcinoma is associated with improved survival outcomes. The best evidence for performing cytoreductive nephrectomy, before the era of targeted therapy, came from two prospective randomised clinical trials, Southwest Oncology Group (SWOG) 8949 and European Organization for Research and Treatment of Cancer (EORTC) 30947 [1,2] which revealed a survival benefit for nephrectomy followed by IFN-α compared with IFN-α alone (median survival of 11.1 and 8.1 months, respectively, in the SWOG trial and 17 and 7 months, respectively, in the EORTC trial). Flanigan et al.[3] did a combined analysis of these two trials, which yielded a median survival of 13.6 months for nephrectomy plus IFN-α versus 7.8 months for IFN-α alone. Cytoreductive nephrectomy seemed to improve overall survival in patients with metastatic RCC treated with subsequent IFN-α independent of patient performance status, site of metastases, and presence of measurable disease. The pivotal sunitinib trial investigating the efficacy and safety of sunitinib versus IFN-α included 750 patients with advanced/metastatic RCC. 91 and 89% of patients receiving sunitinib and IFN-α had undergone nephrectomy, respectively.[4] The fact that most patients in the UK undergo nephrectomy is supported by experts in the field including Dr Thomas Powles, Consultant Oncologist, St Barts, who has stated that "Nephrectomy is the standard of care for patients in the UK with metastatic clear cell renal cancer. It is associated with an overall survival advantage in randomised phase III studies. Deviation from this approach is against the best evidence and guidelines." Cancer Research UK states on their website that "In patients fit for surgery presenting with metastatic disease, nephrectomy controls the primary tumour most effectively and may also control symptoms such as haematuria and renal pain"[5] Therefore the statement that the disease characteristics of the VEG105192 trial are likely to be representative of patients with advanced/metastatic RCC in terms of UK patients with metastatic RCC undergoing nephrectomy is supported by RCT data and expert opinion. 1. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon α-2b compared with interferon α-2b alone for metastatic renal-cell cancer. N Engl J Med 2001;345:1655–9. 2. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-α-based

immunotherapy compared with interferon α alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 2001;358:966–70.
3. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004;171:1071–6.
4. Motzer RJ, Hutson TE, Tomczak P, *et al.* Sunitinib versus interferon alfa in metastatic renal cell carcinoma. New Engl J Med 2007; 356: 115-24.
5. http://info.cancerresearchuk.org/cancerstats/types/kidney/symptomsandtreatment/index.htm. Accessed 25th May 2010.

Pazopanib – Responses to ERG questions

Section A: Clarification on effectiveness data - Treatment-naïve patient population

Question		Response
A10	**Priority request:** It appears as though only a selection of tables from the clinical study report on pazopanib have been provided for the population of interest (treatment naïve patients). Please provide additional tables for the treatment naïve population; a list of the required tables is appended (**Appendix 1**).	Please refer to attached folder which contains most of the requested tables. As requested, it would be extremely beneficial to have a teleconference with the ERG (and the NICE technical team) so that we can clarify some of the requests (see table below) and perhaps discuss other relevant issues associated with the appraisal.

Analysis	Provided?
Table 6.1	The current table already lists the appropriate information for the treatment naïve ITT and safety populations.
Table 6.4	✓
Table 6.8	✓
Table 6.26	✓
Figure 7.1	✓
Figure 7.6	Clarification required
Figure 7.11	Clarification required
Figure 7.14	This would not provide any additional information beyond what is in the table and graphical representation does not add to the interpretability.
Figure 7.29	This would not provide any additional information beyond what is in the table and graphical representation does not add to the interpretability.
Table 7.8	✓
Table 7.9	✓
Table 7.15	✓
Table 7.16	✓
Table 7.25	✓
Table 7.26	✓
Table 7.27	✓
Table 7.49	✓
Table 7.102	✓
Table 8.10	✓
Figure 8.101	✓
Table 8.11	✓
Table 8.12	✓
Table 8.13	✓
Table 8.16	✓

			Table 8.17	✓
			Table 8.2	✓
			Table 8.26	✓
			Table 8.27	✓
			Table 8.28	✓
			Table 8.63	This is duplicate information. Please see tables 8.8 and 8.5 in the safety data source tables and figures in the VEG105192 CSR.
			Table 8.69	✓
			Table 8.54	✓
			Table 13.4	✓
			Table 13.5	✓
			Table 13.6	✓
			Table 13.8	✓
A11	**Priority request:** P7 '…these data are made available to the committee as soon as possible – expected to be in 3Q 2010'. Would it be possible to provide any additional overall survival data at this point, prior to its release in Q3 2010?	GSK will submit final OS data by mid July 2010. .		
A12	**Priority request:** For the treatment-naïve group of the VEG105192 study it was stated on page 35 that the evidence available does not allow sub-groups to be considered, but no further details have been provided. Please provide the results for pazopanib and placebo for the primary and secondary outcomes for the three subgroups: • Resected versus unresected primary tumour • Clear cell component versus no clear cell component	Response to this query will be provided by 9th June 2010		

	Performance	
A13	**Priority request:** P113 – Table 5.47 - Overall best response and response rate (VEG102616). Please also provide the data (n (%)) for the response categories (CR, PR etc) for the treatment-naïve group, for both independent review and investigator assessment.	Response to this query will be provided by 9th June 2010
A14	**Priority request:** P114 – Table 5.48 – Response at week 12 (VEG102616). Please also provide the data (n (%)) for the response categories (CR, PR etc) for the treatment-naïve group, for both independent review and investigator assessment.	Response to this query will be provided by 9th June 2010
A15	**Priority request:** P115 – Table 5.49 – Secondary efficacy endpoints (VEG102616). Please also provide the data (n (%)) for Duration of response and Time to response for the treatment-naïve group, for both independent review and investigator assessment.	Response to this query will be provided by 9th June 2010
A16	**Priority request:** P116 – Table 5.51 – Summary of efficacy endpoints (VEG107769). Please also provide these data for the treatment-naïve group	Response to this query will be provided by 9th June 2010
A17	**Priority request:** P125 – Table 5.61 – Treatment /emergent AEs occurring in ≥ 10% subjects (VEG102616).	Response to this query will be provided by 9th June 2010

	Please also provide these data for the treatment-naïve group.	
A18	**Priority request:** P125, subsections 'Deaths', 'SAEs', 'AEs leading to permanent discontinuation of study medication', 'AEs leading to dose reductions or interruptions'. Please also provide this information for the treatment-naïve group.	Response to this query will be provided by 9th June 2010
A19	**Priority request:** P126 – Table 5.62 – On-therapy laboratory abnormalities reported in ≥ 10% subjects (VEG102616). Please also provide these data for the treatment-naïve group.	Response to this query will be provided by 9th June 2010
A20	**Priority request:** P127 – Table 5.63 – AEs reported for ≥ 5% subjects (VEG107769). Please also provide these data for the treatment-naïve group	Response to this query will be provided by 9th June 2010
A21	**Priority request:** P127, subsections 'Deaths', 'SAEs', 'AEs leading to permanent discontinuation of study medication', 'AEs leading to dose reductions or interruptions'. Please also provide this information for the treatment-naïve group.	Response to this query will be provided by 9th June 2010
A22	**Priority request:** P128 – Table 5.64 – Summary of worst-case toxicity grade increase from baseline for haematology and clinical chemistry parameters (VEG107769). Please also provide these data for the	Response to this query will be provided by 9th June 2010

	treatment-naïve group	
A23	**Priority request:** P53, Table 5.5 – VEG105192, 'Location' row. How many of the 28 subjects randomised by the UK centres were treatment-naïve? How many were randomised to the pazopanib and placebo groups? Which four centres in the UK were involved in the study?	7 out of the 28 subjects from the UK enrolled in VEG105192 were treatment naïve and all had undergone nephrectomy. Of these 7 subjects, 5 were randomized to pazopanib and 2 to placebo. The following investigators were involved in the study: Hawkins (centre 025673 The Christie Hospital, Manchester), Sheehan (centre 025674 – Royal Devon & Exeter Foundation Trust), Marshall (centre 025675 – Clatterbridge Centre for oncology), and Wagstaff (centre 026758 – Singleton Hospital, Swansea).
A24	**Priority request:** P104 – Table 5.41 – VEG102616, 'Location' row. Were there any UK sites and if so how many patients did they enrol and how many of these patients were treatment-naïve? Which UK sites were involved?	There were no UK sites involved in study VEG102616.
A25	**Priority request:** P104 – Table 5.41 – VEG107769, 'Location' row. How many of the 5 UK patients were treatment-naïve?	3 of the 5 UK patients enrolled were treatment naïve.
A26	**Priority request:** P80 - Table 5.26, Quality of life. Please provide, for the treatment-naive group, a detailed breakdown of results for the pazopanib and placebo arms for each of the three instruments.	This information is provided in an attached file.
A27	P119 – 'Deaths resulting from AEs was reported in 12 (4%) subjects in the pazopanib arm and 4 (3%) of subjects in the placebo arm for the total study population.' In each of these arms how many of the subjects were treatment-naïve? 'Four	Exactly half of the deaths resulting from AEs reported in each arm were from treatment naïve subjects (6 and 2 subjects respectively). Likewise 2 of the 4 subjects with fatal AEs that were assessed by the investigator as attributable to study treatment were treatment naïve. This is consistent with the fact that approximately half of the subjects were treatment naïve (54%). Fatal SAEs were considered related to investigational product for 4 of the subjects in the pazopanib arm including abnormal hepatic function and rectal hemorrhage (Subject 160), abnormal hepatic function (Subject

	patients (1%) in the pazopanib arm had fatal AEs that were assessed by the investigator as attributable to study treatment…' How many of these subjects were treatment-naïve? What were the fatal adverse events that were assessed by the investigator as being attributable to study treatment?	912), peritonitis (Subject 398) and ischemic stroke (Subject 77). Subjects 77 and 912 were treatment naïve.
A28	P118 – Section 5.9.2.1.1 Extent of exposure. Could you provide the values for the median reduced dose (mg) for treatment naïve participants in the pazopanib trial, and the duration of dose reduction for those treatment naïve participants who received a reduced dose?	Response to this query will be provided by 9th June 2010

Pazopanib – Responses to ERG questions		
Section A: Clarification on effectiveness data - Statistical issues		
Question		**Response**
A29	**Priority request:** P61 – Table 5.9 - The use of a pike estimator is mentioned in the statistical analysis section. What was the rationale for using a pike estimator in the Kaplan-Meier analyses and what effects did its use have on the results?	The Pike estimator is a non-parametric estimator of the hazard ratio. Therefore the only effect is in the hazard ratio estimation. The hazard ratio estimates using the Pike estimator are consistent with the results from a similar Cox analysis. Kaplan-Meier analysis and log-rank tests are non-parametric, so it is more appropriate to summarize the hazard ratio with a non-parametric hazard ratio as well. The Pike estimator is a function of the log-rank test statistic and the observed number of deaths in each arm. The alternative, a Cox hazard ratio, is semi-parametric and involves a proportional hazards assumption.
A30	P77 – It is stated 'RPSFT does, however, have some limitations when applied to immature data due to the degree of re-censoring required.' Given this, what adjustments were made in the RPSFT analyses to address these limitations?	No adjustment was made to the RPSFT analyses to address this limitation as it is inherent to the methodology.
A31	**Priority request:** P95 - Table 5.32 - Is the reported confidence interval for overall survival correct, as it appears to be inconsistent with the 0.086-1.276 reported elsewhere in the submission?	The correct confidence interval is 0.086-1.276. The CI reported in table 5.32 is an error.
A32	**Priority request:** P101 – 'It should be noted that the indirect comparison utilising the MRC RE01 trial presented in the systematic review report uses an HR for OS from VEG105192 that is not adjusted for cross-over.' What rationale was employed in deciding when to use adjusted	Adjusted cross over data was not available when the systematic review was conducted. Once available the adjusted HR was used.

	cross-over data and ITT data?	
A33	P62-5 – Section 5.3.6.1 – How were the IPCW and RPSFT analyses carried out in practice (i.e. which statistical packages were used)?	Both analyses were conducted using SAS Statistical Analysis Software, SAS Inc., Cary, NC.
A34	P75 & 77 – Section 5.5.1.2 - For the IPCW analyses, please explain why the univariate results were not reported in tables 5.20 and 5.22? Please could you provide the results of the unadjusted IPCW analysis?	The use of weights calculated using multivariate logistic regression analysis is a fundamental element in the analysis. "Unadjusted" IPCW analysis is not feasible.
A35	P81-103 – Section 5.7 (indirect and mixed treatment comparisons) – Please explain why mixed treatment analyses were not included in either the submission or the systematic review?	There were no treatment comparisons (in treatment naïve patients) for which both direct and indirect evidence were available (i.e., either direct or indirect evidence was available, but never both). Hence mixed treatment comparisons were not feasible.
A36	P99 – Table 5.35 – Please comment on whether an unadjusted-for-crossover hazard ratio from the pazopanib trial should be used, perhaps as a sensitivity analysis, in the indirect treatment comparison so that it is consistent with the estimated hazard ratio from the sunitinib trial? Please clarify how this would affect the results?	As treatment with placebo followed by treatment with pazopanib is not one of the comparators in the evaluation, analyses based on HR for OS without adjustment for cross-over are generally inappropriate, as the results of such an analysis are not consistent with the treatment strategy under consideration. Nevertheless, for completeness, a sensitivity analysis was conducted in which the HRs for OS for pazopanib vs. IFN was based on the HR for pazopanib vs. placebo in VEG105192 without censoring on cross-over or adjustment for baseline covariates (HR=0.930) (#32). There was no RPSFT analysis of OS conducted for sunitinib and there was no analysis of OS with patients who received post-study treatment excluded for pazopanib. Further because the extent and nature of the cross-over was different in the two trials, any analysis with censoring on cross-over (except those such as IPCW), or cross-over as time-dependent covariate, may yield a biased comparison across trials. An analysis based on "consistent" methods is therefore not feasible.
A37	P99 - Table 5.36 – Please clarify why there is a major discrepancy between the methods used to estimate the 95% confidence interval around median overall survival	Table 5.36 presents CIs for the median using two alternative approaches. The "percentiles" estimates are based on the 0-.25 and 97.5% tiles of the simulated values. The "normal approximation" estimates were obtained by calculating the SD of the simulated values and calculating the 95%CI as Estimate +/- 1.96 x SD. The negative lower bound on the CI is based on the normal approximation suggesting that the normality assumption may not be appropriate and that the CIs based on percentiles of the simulation should be used. The CI on the median for IFN is exact because it is based on the fitted lambdas and gammas. These were

	for pazopanib? Please explain how it is possible to have negative survival as suggested by this confidence interval? Can you confirm whether this estimated interval is correct, or if it is a typo, and a misspecification in the model. If the confidence interval is correct, please could you explain what this means in terms of survival (as this wide CI reflects extreme uncertainty and does not qualify the statement on median OS in the paragraph below the table). Also, why are the median progression free survival estimates for IFN reported as being exact (e.g. the CIs for PFS is 5.4-5.4)?	obtained by OLS regression on the reported S[t] from the sunitinib trial report. This approach does not yield a SE for these parameters. The values are therefore constant in the simulation. It might be more appropriate to report these CIs as “not evaluable” rather than exact values.

Pazopanib – Responses to ERG questions		
Section B: Clarification on cost-effectiveness data - GENERAL		
Question		**Response**
B1	**Priority request:** P169, Table 6.10 Summary of model inputs. Can you provide a detailed explanation of how the cost of pazopanib was generated?	The list price for pazopanib was based on price parity with the sunitinib list price (based on a per day basis). The list price of sunitinib is £112.10 per daily 50mg dose. One cycle of sunitinib consists of 28 days on treatment followed by 14 days off treatment. Thus the average daily cost of sunitinib and therefore pazopanib (for which treatment is continuous) is £74.73 ([£112.10 x 28] / 42).
B2	**Priority request:** P9 - The decision to use RPSFT for the economic base case was based on expert opinion from leading academics in this field. Please provide details of which academics, the process by which they were selected, whether they were remunerated, and whether they had any competing interests in relation to their involvement with GSK.	UK: Dr Paul Nathan (consultant medical oncologist at Mount Vernon Cancer Centre). Dr Nathan has taken part in an advisory board and some additional activities related to pazopanib clinical development. Honoraria related to these activities have been covered by GSK. US: A US clinician provided US–specific clinical input for mRCC. This clinician has also been involved in several clinical advisory boards in the US and his professional fees have been covered by GSK for his expert opinion.
B3	P8 Please confirm whether the regular liver function test (every 4 weeks) has been included in the costings (blood tests are subsumed in outpatient cost but this may underestimate this element of cost)?	The costs of these tests were not considered explicitly but were assumed to be included in the cost of visits.
B4	P21 It is stated that 5 year survival with metastatic disease is 9.5%. Please comment on how consistent this estimate is compared with the model predictions.	The five-year overall survival for treatment-naïve patients receiving BSC from the model is approximately 7%.
B5	P29 It is stated that hypertension and thyroid dysfunction should be monitored; periodic urine	These costs are not explicitly included in the analysis. Hypertension and thyroid dysfunction are class effects of anti-VEGF TKIs, therefore sunitinib patients would require similar monitoring (this is also listed in the sunitinib prescribing information). The impact of including periodic urine analysis and electrocardiograms on cost effectiveness results would be minimal. Urinalysis would cost approximately £1 and an electrocardiogram

	analysis and electrocardiograms are also advised. Please confirm whether these costs are included? In addition, please clarify whether these tests (and hence costs) are required for other treatments?	£33 (assumed to be every 3 months) (NHS reference costs) resulting in an additional monthly monitoring cost of £12. Cost effectiveness results are not sensitive to changes in monitoring costs (see sensitivity analyses 9 and 10). The monitoring costs used in this submission are consistent with those used by PenTAG for the MTA of treatments for advanced/metastatic RCC.
B6	P145 Please provide details on the patient groups used to estimate the EQ-5D scores	In the Remak study EQ-5D scores were taken from the sunitinib pivotal trial (Motzer 2007). To model the change in QOL over one sunitinib treatment cycle, two utility values were used: the weighted average utility on day 28 was assumed to represent utility during the 4 weeks of sunitinib treatment; and the weighted average utility on day 1 of the next cycle was assumed to represent QOL during the 2-week off-treatment period. The utility for IFN-α–treated patients was calculated from the weighted average changes from baseline in EQ-5D scores measured on days 1 and 28 of each cycle (Remak 2008).
B7	P146 - Table 6.2. The value for ICER progression-free does not appear to be correct. Please check whether this is the correct value.	The value of $18,611 per progression free life year gained is correct as per Remak 2008.
B8	P151 Section 6.2.2, para 3. Clinically, please comment on how likely is it that patients who progress will discontinue pazopanib therapy?	Data on the extent to which patients receiving pazopanib might continue treatment post-progression outside the context of the VEG105192 trial are unavailable. The assumption of discontinuation of treatment upon progression used for costing in the model is internally consistent with the effectiveness data employed. We adjusted the projected utilization of pazopanib based on PFS by relative dose intensity (RDI) to account for any difference between the time to progression and time to discontinuation. Clinically speaking, as patients are scanned frequently (usually every 6-12 weeks) to assess response, there should not be a protracted period of time that patients remain on therapy post-progression. There is no clinical evidence at this stage of treatment benefit beyond progression.
B9	P151. Section 6.2.3. How was the cut off date chosen for the interim trial? What reassurance can the company give that this cut off date was not favourable to pazopanib?	The interim analysis of OS (ITT population) was pre-specified to occur at the same time as the final PFS analysis, so that this data could be submitted as a part of the regulatory submissions. The final PFS analysis was pre-specified to occur when there was at least 90 PFS events (per IRC) had accrued in each of the treatment naïve and cytokine pre-treated subgroups and after at least 160 deaths had accrued. The PFS requirement was defined to ensure adequate power in the sub-populations. The interim death requirement (minimum 160 deaths) was required to make sure that the interim analysis of OS was based on enough data to be meaningful (>50% of the required number of deaths for the final analysis). When these criteria were confirmed to have been met, a final data cut-off date was set.
B10	P152 Section 6.2.5. In the analysis it is assumed that	As noted above, the data on the extent to which a patient receiving pazopanib might continue treatment post-progression outside the context of the VEG105192 trial are unavailable. The assumption of discontinuation of

	patients cease treatment immediately if they progress. Please comment on how realistic this assumption is? Also, how long clinically would a patient be monitored before a decision that progression had occurred is made?	treatment with progression used for costing is internally consistent with the effectiveness data employed. We adjusted the projected utilisation of pazopanib based on PFS by RDI to account for any difference between the time to progression and time to discontinuation. Progression would be identified either due to a symptomatic relapse and subsequent scan or due to incidental routine scanning. This would be dependent on scanning frequency which varies between 6 and 12 weeks.
B11	P159. How would the results of the economic evaluation have changed had the data from VEG105192 been used as the reference treatment for the Weibull survival functions?	This was included as a sensitivity analysis (#39 and #40) Using the pazopanib arm of VEG105192 as the reference resulted in an ICER versus sunitinib of £12,970/QALY. Using an independent Weibull from the pazopanib arm of VEG105192 for pazopanib and an independent Weibull from the placebo arm of VEG105192 as the reference for other comparators, resulted in pazopanib being dominated by sunitinib. However, this may not be an appropriate approach as the placebo arm of VEG105192 was confounded by patients crossing over to pazopanib upon progression.
B12	P154 - Clinical continuation rule. Could treatment be discontinued due to adverse effects?	Treatment may have been discontinued as a consequence of AEs. We did not model this explicitly but rather captured any affects of treatment discontinuation due to AEs by the application of the RDI.
B13	P157 - Last paragraph on page states 'It should be noted that the HR used for OS from the sunitinib trial was not adjusted for post-study therapy in the same way as the OS data in VEG105192 and was taken from a sub-group analysis in subjects with no post-study therapy (Motzer 2009)' Was any sensitivity analysis performed around this estimate?	Several sensitivity analyses were conducted including • HR for OS for sunitinib vs. IFN based on final analysis (HR=0.820) • HRs for PFS and OS for pazopanib vs. IFN = HRs for sunitinib vs. IFN (PFS HR=0.539, OS HR=0.647) • HR for OS for pazopanib vs. IFN = HR for sunitinib vs. IFN (HR=0.647) • HR for OS for pazopanib vs. IFN to make PPS equal to that of sunitinib (HR=0.629)
B14	P158 - Table 6.8, Effectiveness estimates used in the economic model, the first two lines of IFN Weibull distribution. Why were two different sources used for PFS	Please refer to explanation on page 159. Parameters for OS for IFN (lambda=0.07, gamma=0.83) are based on estimates derived by PenTAG (assessment group) by fitting to OS data provided by Pfizer excluding patients who received non-study therapy (TA 169). These figures were validated using the Kaplan-Meier (KM) data for the analysis excluding patients who received non-study therapy as reported by Figlin at ASCO 2008. These parameters were used

	and OS values?	to approximately replicate the estimated LYs for IFN obtained by PenTAG using the Appraisal Committee (AC) preferred assumptions (~2.2 LY), which were used as the basis of the AC final decision regarding sunitinib. Weibull parameters for PFS were obtained by fitting data to KM curves for investigator assessed PFS for IFN patients in the sunitinib pivotal trial as reported in the Motzer 2007 ASCO presentation. Weibull parameters for PFS from the DSU/PenTAG's report using the AC's preferred assumptions were not employed because of concerns regarding the validity of these estimates. Our main concern is related to the fact that in the Sunitinib DSU's report using the AC's preferred assumptions, the PFS curves provided by Pfizer are used. Presumably, both of these are based on the final ITT analysis of PFS. However, the median IRC assessed PFS for sunitinib and IFN goes from 11.0 and 5.1 months respectively (10.8 and 4.1 months based on investigator assessment) as reported in the ASCO 2007 presentation to 20.88 months and 12.72 months as reported by Pfizer in their revised submission and used as the AC's preferred assumptions. Looking at the KM curves, it is clear that the number of censored observations prior to the median (as indicated by tick marks on the curves) are limited, and it's unlikely that additional follow-up for these patients would explain the approximate doubling of PFS. Note that the median PFS in the ASCO presentation is similar to that reported in the latest publication reported in JCO (11 and 5 months). Finally, OS data was not taken from Motzer 2007 as this was interim data.
B15	P168 Section 6.3.5. Who were the experts, were they paid and do they have any declared conflicts of interest?	UK: Dr Paul Nathan (consultant medical oncologist at Mount Vernon Cancer Centre). Dr Nathan has taken part in an advisory board and some additional activities related to pazopanib clinical development. Honoraria related to these activities have been covered by GSK. US: A US clinician provided US–specific clinical input for mRCC. This clinician has also been involved in several clinical advisory boards in the US and his professional fees have been covered by GSK for his expert opinion.
B16	P168 Section 6.3.6. Please explain why all costs of grade 3 adverse events were not reported in appendix 16?	Only those events that met the criteria for costing were assigned costs. The estimated incidence of the events is included in the model nevertheless to permit sensitivity analyses on costs/utility effects associated with these events.

<table>
<tr><td>B17</td><td>P169 - Table 6.10 Summary of model inputs. Please clarify whether the value reported as the ‘utility value’ is actually the decrement rather than the actual utility value? Please clarify how the decrement of 15% was obtained?</td><td>The value is a utility decrement. Parasuraman reported utility values (apparently medians) for health states including baseline, no progression or toxicity, toxicity (time with any grade3 or 4 AE prior to progression), and relapse (post-progression). Utility for no progression or toxicity was 0.689. Utility for relapse was 0.587. Progression was therefore associated with an absolute (percentage) decrement in utility of 0.102 ~15%.</td></tr>
<tr><td>B18</td><td>P170 Table 6.11. How was the 15% utility decrement for movement to PPS arrived at?</td><td>See above.</td></tr>
<tr><td>B19</td><td>P174 Please can the authors provide a copy of Swinburn 2010-05-07?</td><td>See attached file.</td></tr>
<tr><td>B20</td><td>P177 Please can you conduct sensitivity analysis around decrement for PPS utility obtained from the Oxford Outcomes study?</td><td>A sensitivity analysis was conducted using the utility decrement from the Oxford Outcomes study (#28). (File is attached to the email)</td></tr>
<tr><td>B21</td><td>Page 6.18. Please clarify why some rates e.g. fatigue grade 3+ are not available but rates for fatigue grade 1-2 are (when no data were available).</td><td>The table had some rows misaligned. A revised table is provided below.

Table 6.18: EQ-5D utility values for persons with and without adverse events in VEG105192
<table>
<tr><th rowspan="3">Adverse Events</th><th colspan="8">Unadjusted</th><th rowspan="3">Adjusted Difference</th></tr>
<tr><th colspan="3">With Event</th><th colspan="3">Without Event</th><th colspan="2">Difference</th></tr>
<tr><th>N</th><th>Mean</th><th>SE</th><th>N</th><th>Mean</th><th>SE</th><th>Mean</th><th>SE</th></tr>
<tr><td>Anemia</td><td>23</td><td>0.58</td><td>(0.01)</td><td>1,488</td><td>0.70</td><td>(0.01)</td><td>-0.12</td><td>(0.01)</td><td>-0.17</td></tr>
<tr><td>Bleeding</td><td>9</td><td>0.61</td><td>(0.12)</td><td>1,502</td><td>0.70</td><td>(0.01)</td><td>-0.09</td><td>(0.12)</td><td>-0.03</td></tr>
<tr><td>Diarrhea grades 3+</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>-0.02</td></tr>
<tr><td>Diarrhea all grades</td><td>293</td><td>0.76</td><td>(0.01)</td><td>1,218</td><td>0.69</td><td>(0.01)</td><td>0.07</td><td>(0.01)</td><td></td></tr>
<tr><td>Fatigue/asthenia grades 1-2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>-0.10</td></tr>
<tr><td>Fatigue/asthenia Grade 3+</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>-0.19</td></tr>
<tr><td>Fatigue/asthenia All Grades</td><td>207</td><td>0.59</td><td>(0.02)</td><td>1,304</td><td>0.72</td><td>(0.01)</td><td>-0.13</td><td>(0.02)</td><td></td></tr>
<tr><td>Fever</td><td>4</td><td>0.62</td><td>(0.09)</td><td>1,507</td><td>0.70</td><td>(0.01)</td><td>-0.08</td><td>(0.10)</td><td>0.00</td></tr>
<tr><td>Flu like symptoms</td><td>4</td><td>0.71</td><td>(0.07)</td><td>1,507</td><td>0.70</td><td>(0.01)</td><td>0.01</td><td>(0.07)</td><td>-0.34</td></tr>
<tr><td>PPE syndrome</td><td>51</td><td>0.76</td><td>(0.03)</td><td>1,460</td><td>0.70</td><td>(0.01)</td><td>0.06</td><td>(0.03)</td><td>-0.05</td></tr>
<tr><td>Hypertension</td><td>248</td><td>0.72</td><td>(0.02)</td><td>1,263</td><td>0.70</td><td>(0.01)</td><td>0.02</td><td>(0.02)</td><td>-0.07</td></tr>
<tr><td>Low WBC</td><td>44</td><td>0.73</td><td>(0.04)</td><td>1,467</td><td>0.70</td><td>(0.01)</td><td>0.03</td><td>(0.04)</td><td></td></tr>
</table></td></tr>
</table>

Mucositis/stomatitis	26	0.65	(0.05)	1,485	0.70	(0.01)	-0.05	(0.05)	-0.02
Nausea/vomiting	168	0.65	(0.02)	1,343	0.71	(0.01)	-0.06	(0.02)	-0.09
Non-PPE Rash	42	0.79	(0.04)	1,469	0.70	(0.01)	0.10	(0.04)	-0.01
Thrombocytopenia	61	0.71	(0.03)	1,450	0.70	(0.01)	0.01	(0.04)	

The reason for the missing cells is that the unadjusted means for G3+ diarrhoea and for G1-2 and G3+ fatigue/asthenia were not reported in the analysis originally conducted by the agency, whereas the regression that was used to obtain the adjusted differences included as covariates G3+ diarrhoea and fatigue/asthenia by grade (G1-2 and G3+) were. Adjusted differences were calculated based on the regression coefficients and the means for all persons without the event (any grade). We have contacted the agency who undertook this analysis and we will provide the missing values by June 9th.

We would like to inform the ERG that there was an error in the utility decrements for AEs that were utilised by the model. These values are currently incorrect and are not consistent with those reported in table 6.18. Although sensitivity analysis has shown that the model is not sensitive to changes in utility values, we have provided updated base case results using the correct utility decrement values (as reported in table 6.18; Table A). It should be noted that this will be corrected in the cost effectiveness results that GSK intend to provide which will include updated OS results.

Table A: Revised base case cost effectiveness results using utility values reported in table 6.18

	Strategy				Diff. Pazopanib vs		
	Pazopanib	**Sunitinib**	**IFN**	**BSC**	**Sunitinib**	**IFN**	**BSC**
Life years	4.058	3.018	2.020	1.598	1.040	2.039	2.460
QALYs	2.514	1.864	1.230	0.979	0.650	1.284	1.535
Total Costs	43,082	36,228	8,404	4,094	6,854	34,679	38,989
Cost/LY					6,591	17,011	15,850
Cost/QALY					10,545	27,007	25,396

B22	P178 Sect 6.4.9. What is the justification for requiring that post-progression utility scores should be consistent with Remak and Parasuraman?	The decrement in utility with progression was obtained from the Parasuraman study, which was consistent with that from Remak. The utilities from Parasuraman were based on EQ-5D assessments, the NICE preferred method for obtaining utilities. Because EQ-5D assessments were not collected routinely post-progression in VEG105192, the post-progression utility from the VEG105192 trial was deemed to be potentially biased. The decrement in utility from the Swinburn study was based on community preferences for hypothetical health states which is not a preferred method.
B23	P179 The SE for the duration of AEs has been assumed to be 0.25 by the mean duration. What is the justification for this assumption?	Estimates of the SEs of the durations of AEs were not available at the time of the submission. The assumption of 0.25 was arbitrary. The assumption that SE=0.25 x mean was arbitrary, and consistent with a normal random variable with 95%CI ~equal to +/- 50% of the mean. This is likely a conservative (i.e., wide) range (e.g., if the SD of a random variable is equal to the mean (coefficient of variation [CV]=1.0), an SE = 0.25 x mean implies that the number of subjects upon which the estimate was based was <20; if the CV=2.0,

		the implied N is <20). The model results were not sensitive to the AE duration so this did not likely materially impact the PSA findings.
B24	P180 - Were EQ-5D utility values for persons with and without adverse events incorporated into the model analysis?	The utilities for PFS and for the decrements in utilities with AEs were based on EQ-5D values from VEG105192. The decrement in utility for PPS was based on Parasurman, which also used EQ-5Ds.
B25	P181 - Table 6.19 Summary of quality-of-life values used in the cost-effectiveness analysis. Please explain why it was assumed that the utility values would be the same for all interventions? Table 6.16 gives a summary of EQ-5D values for IFN and Sunitinib. Were these values used in any analysis?	Utility values conditioned on progression and AEs were assumed to be the same across treatments because analyses of EQ-5D data suggest that independent of progression and AEs, treatment with pazopanib had no effect on utility compared with placebo. Also, utilities by disease state and treatment from a direct comparison or robust adjusted indirect comparison were unavailable for sunitinib or IFN. The value in Table 6.16 were provided for illustration and to inform the decision regarding the value used in the model and were not used in the model per se (as this represents an unadjusted indirect comparison).
B26	P183, section 6.4.14. Please clarify what the statement means " HRQL is assumed to differ for time in PFS and PPS states. Please clarify whether this means that the values used for the states differs but that the value for a state remains the same over time?	The utility value for all time in the PFS sate (no AEs) was 0.70. The utility value for all time in the PPS state was 0.59. Decrements in utilities for AEs were calculated by multiplying the duration of the AE by the utility decrement.
B27	P184 What is the justification for assuming that all patients with progressive disease will be discharged to management in primary care?	This was based on the assumption that was used in the PenTAG report for TA169 and was deemed appropriate by clinical experts.
B28	P185 Table 6.24. Can you please provide details about how the costs presented in this table are calculated? From the text of the report it is not clear for all cost lines	The cost in each month is equal to the visit cost plus 1/3 the cost of the scan (£140.4/3=£46.80). The cost in the first month is therefore £241+£46.80 = £287.80. The cost in subsequent months is £99+£46.80=£145.80. To avoid double counting, treatment initiation (one-off) costs are calculated as the first month costs minus the subsequent month costs (£287.80-£145.80=£142).
B29	P186 Table 6.26. Please	All AEs costs, including the costs of anti-hypertensive therapy are calculated as one-off costs without

	clarify at which point anti hypertensive therapy will be initiated? Please confirm whether there are costs (other than the medication) involved in initiating and monitoring the use of this medication?	discounting (i.e., they are assumed to occur in the first year). The mean duration of G3+ hypertension was ~40 days—therefore, only one prescription for antihypertensive medication was assumed to be required. No additional costs were considered. Model results are not sensitive to the assumed cost of antihypertensive therapy (8% incidence of G3+ hypertension with pazopanib; even assuming £1000 per event, incremental cost is only £80 ~0.26% of the additional medication costs of pazopanib vs. IFN).
B30	P187 – Table 6.23, Assumed services and costs of monitoring during PFS and OS. Are these based on current practice?	These are based on the assumptions used by PenTAG in TA169 and were deemed appropriate by clinical experts.
B31	P187 - Table 6.24, What is the justification that the SE of cost-estimates such as cost estimates for routine follow-up and AE costs used in the model will be 25% of their mean values?	Information on the SEs of these inputs was unavailable. The assumption that SE=0.25 x mean was arbitrary, and consistent with a normal random variable with 95%CI ~equal to +/- 50% of the mean. This is likely a conservative (i.e., wide) range (e.g., if the SD of a random variable is equal to the mean (coefficient of variation [CV]=1.0), an SE = 0.25 x mean implies that the number of subjects upon which the estimate was based was <20; if the CV=2.0, the implied N is <20).
B32	P187 - Adverse events costs. Why were only 'costs of grade 3 or more and had an incidence of 5% or more' considered? Was any sensitivity analysis performed on these estimates?	AEs considered in the model included those that were identified prior to the conduct of the evaluation as being of particular interest (diarrhoea, nausea/vomiting, fatigue/asthenia, hypertension, heart failure, gastrointestinal (GI) perforation, palmar plantar erythrodysesthesia (PPE, hand and foot syndrome), mucositis/stomatitis, and non-PPE rash) or those with a combined incidence of grade 3 and 4 events greater than or equal to 5% or with a combined incidence of all grades greater than or equal to 20%, in any arm of any RCT of any comparators. AEs were estimated separately by grade (grades 1 or 2 and grades 3 or more). Only the costs of treatment of AEs that were grade 3 or more and had an incidence of 5% or more for any treatment based on the indirect comparison were considered. Costs of grade 1-2 AEs were not considered as these events are likely to require little or no intervention/incremental health care resource utilisation. There were many unique G3+ AEs reported in the VEG105192 trial and developing reliable estimates of costs for all these events would not be feasible. Furthermore, not all the AEs were reported in trials of the other comparators. The threshold value of 5% was used as an objective criterion to limit the number of AEs considered to a reasonable set. The 5% threshold is conventional and was reported in the studies for other comparators used in the adjusted indirect comparison. It should be noted that extensive sensitivity analyses were conducted on the incidence, costs, and decrement in utilities with the AE. The model was insensitive to these parameters. Increasing the cost of AEs by 50% vs. the baseline estimates increased the expected lifetime cost of pazopanib by £51. Increasing these costs by 10 times vs. the baseline would therefore increase costs by ~£1000, which represents an increase in the expected lifetime cost of pazopanib of only ~2%. It is unlikely therefore that additional refinements to the

<table>
<tr><td></td><td></td><td>estimation of the costs of AEs would materially affect model results</td></tr>
<tr><td>B33</td><td>p188 – Table 6.26, expected costs per grade 3+ adverse events. Why were the values of some of the assumed services such as anaemia, HFS/PPE and neutropenia added up. Is it not the case that each item is a separate event?</td><td>This is an error. They are treatment alternatives and a patient would receive one or the other. Base case cost effectiveness results are provided in table B where this is corrected. An average cost of the treatment alternatives was used. The model is not sensitive to changes in the cost of treating AEs and therefore the cost effectiveness results are not significantly impacted by these changes.

Table B: Revised base case results using corrected costs for treating adverse events
<table><tr><th></th><th colspan="4">Treatment</th><th colspan="3">Diff. Pazopanib vs</th></tr><tr><th></th><th>Pazopanib</th><th>Sunitinib</th><th>IFN</th><th>BSC</th><th>Sunitinib</th><th>IFN</th><th>BSC</th></tr><tr><td>Life years</td><td>4.058</td><td>3.018</td><td>2.020</td><td>1.598</td><td>1.040</td><td>2.039</td><td>2.460</td></tr><tr><td>QALYs</td><td>2.533</td><td>1.898</td><td>1.249</td><td>0.990</td><td>0.635</td><td>1.284</td><td>1.543</td></tr><tr><td>Total Costs</td><td>43,058</td><td>36,139</td><td>8,356</td><td>4,081</td><td>6,919</td><td>34,702</td><td>38,977</td></tr><tr><td>Cost/LY</td><td></td><td></td><td></td><td></td><td>6,653</td><td>17,023</td><td>15,845</td></tr><tr><td>Cost/QALY</td><td></td><td></td><td></td><td></td><td>10,889</td><td>27,017</td><td>25,256</td></tr></table>
Cost effectiveness results obtained using the revised utility decrements for AEs (see response to Q B21) and corrected costs for treating AEs are provided in table C.

Table C: Revised base case results using revised utility decrements for AEs and corrected costs.
<table><tr><th></th><th colspan="4">Treatment</th><th colspan="3">Diff. Pazopanib vs</th></tr><tr><th></th><th>Pazopanib</th><th>Sunitinib</th><th>IFN</th><th>BSC</th><th>Sunitinib</th><th>IFN</th><th>BSC</th></tr><tr><td>Life years</td><td>4.058</td><td>3.018</td><td>2.020</td><td>1.598</td><td>1.040</td><td>2.039</td><td>2.460</td></tr><tr><td>QALYs</td><td>2.514</td><td>1.864</td><td>1.230</td><td>0.979</td><td>0.650</td><td>1.284</td><td>1.535</td></tr><tr><td>Total Costs</td><td>43,058</td><td>36,139</td><td>8,356</td><td>4,081</td><td>6,919</td><td>34,702</td><td>38,977</td></tr><tr><td>Cost/LY</td><td></td><td></td><td></td><td></td><td>6,653</td><td>17,023</td><td>15,845</td></tr><tr><td>Cost/QALY</td><td></td><td></td><td></td><td></td><td>10,645</td><td>27,025</td><td>25,388</td></tr></table></td></tr>
<tr><td>B34</td><td>P192 - Table 6.28, Summary of model results compared with clinical data. Was sensitivity analysis performed assuming that the trend of outcomes remained the same?</td><td>This requires clarification from the ERG</td></tr>
<tr><td>B35</td><td>P195 and P196. The results of clinical outcomes indicate much higher life year gain in PPS state for pazopanib. Is there any</td><td>We are not aware of any evidence to support this. It should be noted that results for pazopanib were based on interim data.</td></tr>
</table>

	biological evidence that tumours that progress after treatment with pazopanib are different to tumours that progress after any of the other treatments?	
B36	P200-203 - Why is BSC labelled as BSC2L?	This is a typographical error.
B37	P203 Figure 6.10. It would be helpful if the results of the probabilistic analyses were represented as CEACs based on a net-benefit statistic rather than on the ICER.	The CEACs are calculated by first calculating a net-health-benefit statistic for each threshold value/simulation and then determining for each threshold value the proportion of simulation for which each treatment is preferred.

Pazopanib – Responses to ERG questions		
Section B: Clarification on cost-effectiveness data - Treatment naïve population		
Question		**Response**
B38	**Priority request:** P 180 – Table 6.18, EQ-5D utility values for persons with and without adverse events in VEG105192. Are the data in Table 6.18 for the treatment naïve group of patients? If not, please provide these data for the treatment-naïve group.	These data are for all patients in the VEG105192 trial. They are based on multivariate analysis which included treatment group and line of therapy as covariates. Data on the treatment naïve population will be provided by 9th June 2010
B39	**Priority request:** P 181 – Table 6.20, Mean duration of AEs (days) in VEG105192 trial. Are the data in Table 6.20 for the group of treatment naïve patients? If not, please provide these data for the treatment-naïve group.	These data are for all patients in the VEG105192 trial. Because of the small number of events, and without any prior rational to expect duration of AEs to differ by line of therapy, results for the treatment naïve subgroup were not calculated. Data on the treatment naïve population will be provided by 9th June 2010
B40	Where additional information has been provided for treatment naive patients please revise the economic evaluation to reflect these data. If this is not possible please provide a justification as to why these data have not been used	Cost-effectiveness results were not sensitive to changes in the duration or utility values associated with adverse events. See deterministic sensitivity analyses 24-28.

Pazopanib – Responses to ERG questions		
Section C: Textual clarifications and additional points		
Question		**Response**
C1	P78 – 'The overall response rate…' Should the first instance of 'placebo' be 'pazopanib'?	Yes this is a typographical error.
C2	P128 – Table 5.65 – Should 'N=315' be 'N=351'?	It should read N=351
C3	P140 – 'VEG105192 was a multi-national study involving 5 sites in the UK…' However Table 5.5 (p53) states '4 centres in the UK.' Please clarify the number of UK centres.	5 sites were set up in the UK of which 4 sites recruited patients into the study.
C4	P145 - '…for which the model structure is shown in figure 6.3.' Should this state 'figure 6.1' rather than 'figure 6.3'?	Yes this is a typographical error and should read figure 6.1.

Pazopanib – Responses to ERG questions		
Section C: Systematic review document		
Question		**Response**
C5	P15 – In section 3.1.1 it is stated that a summary version of the original study protocol can be found in Appendix A1. Could the full protocol be provided please?	See appendix 1 for clinical protocol
C6	P20 – Section 3.1.4 Data extraction strategy. Please clarify whether the data extraction "grid" for the systematic review was pre-designed? The appendix provides this data extraction grid with pre-specified adverse events. Can you confirm that no additional adverse events were reported by the included studies aside from those listed in the rows of the data extraction grid?	The data extraction grid was partially pre-designed; however outcomes were checked according to the included studies, i.e. to determine if any key outcomes were reported in the included studies which were not present in the extraction grid. This was particularly important for the adverse event list
C7	P21 – 'Studies excluded during data each stage, along with rationale for exclusion are provided in a separate MS Excel document…' Could you provide this Excel file please?	Provided in appendices 2 and 3
C8	P21-22 – Section 3.1.5, Quality assessment. Please explain the rationale for using all of these three quality assessment tools in the systematic review.	Qualitative appraisal was conducted as per NICE's recommendation. However for additional information and as a further summary of the "quality" of studies, the Jadad scoring and Allocation Concealment grades were also applied. Both of these additional quality assessment tools are commonly used in the review of RCTs
C9	P25 – In section 3.2.1 it is stated that a summary version of the original study protocol can be found in Appendix A2. Could the full protocol be	Provided in appendix 4

	provided please?	
C10	P63 – '…from personal communication with Motzer RJ…' Would it be possible to provide a copy of this correspondence?	Provided in appendix 5
C11	P78-79 – Table 36, Specific AEs experienced by randomised patients (across all grades). Can you confirm that all of the adverse events reported by the included studies are included within the groupings in the table. If not, which adverse events are not listed here?	An excel spreadsheet (appendix 6) is provided that shows the data availability of the AE outcomes (excluding the pazopanib trial owing to the very number of AE outcomes which are present in the CSR). It also shows those AEs which were extracted and those which were not.
C12	P98-99 – Table 45, Result of meta-analysis – AEs (all grades) versus IFN. Can you confirm that all of the adverse events reported by the included studies are included within the groupings in the table. If not, which adverse	See above.