Section A: Clarification on effectiveness data

1a. **Priority request:** Please provide the complete clinical study report (CSR) for the AXIS study.

Please find attached the clinical study report.

1b. **Priority request:** Please also provide the supplemental report with the final OS analyses (see ref 63, page 192 of the manufacturer submission): Pfizer Ltd. Final supplemental clinical study report. Axitinib (AG-013736) as second-line therapy for metastatic renal cell cancer: AXIS trial. 2011; Data on file.

Please find attached the file with the supplemental report for the final OS analyses.

2. **Priority request:** Please provide the actual trial data to go with the WinBUGS code from section 10.14 (appendix 14 of the manufacturer submission).

Please find attached the file with the trial data along with the WINBUGS code from section 10.14.

3. Please provide full references for the 25 RCTs found through the RCT search (see flow chart on page 39 of the manufacturer submission) and, if possible, full papers.

Please find attached the references for the 25 RCTs found through the RCT search. Full papers are also attached.

4. Please provide full references for the 4 publications found through the search in Appendix 15 (see flow chart on page 353 of the manufacturer submission) and, if possible, full publications.

Please find attached the references for the 4 publications found through the search in Appendix 15. The relevant publications are also attached.

5 On page 82 of the manufacturer submission, it is stated that: *"Similar methodologies have been accepted in recent HTA appraisals to overcome gaps in the evidence network which rule out a standard indirect comparison approach, including NICE TA171 (Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy."* The ERG have looked at the submission and the ERG report for lenalidomide (TA171) and this does not seem to contain a simulated treatment comparison (STC). The actual meta-analysis in the systematic review is based on a pooled analysis of 2 trials comparing the same treatments (using all the IPD, and using summary measures) and there is a mixed treatment comparison.

- Please clarify which aspect of the analyses used in TA171 is being used as an example of an STC in an appraisal?

- Please clarify whether the manufacturer is aware of STCs being used in any other NICE appraisals?

The methodology is described in detail on pages 120-121 of the manufacturer submission:

Cost and outcomes are extrapolated beyond the follow-up period of the MM-009 and MM-010 trials. The post-progression survival among patients randomised to dexamethasone in the trials includes a strong lenalidomide effect. Therefore, to reflect the correct post-progression survival with dexamethasone, a factor was added to the equation for dexamethasone, calibrated in such a way that modelled median overall survival matches the median overall survival derived from Medical Research Council (MRC) Myeloma trials IV, V, VI, and VIII (2). The MRC Myeloma trials were selected to calibrate the equations because they provide long term follow-up (minimum 7.5 years), are UK specific, reflect a large patient population (1,372 patients were considered in overall survival analyses), are multi-centre and consider treatment options (Melphalan, ABCM, VAD and Cyclophosphamide) comparable to dexamethasone (no significant difference in overall survival between treatment options was found in the MRC trials).

Parametric survival analysis was carried out to derive a prediction equation for time to death, based on the subset of patients in the MRC trials starting on second-line treatment. Age, performance status, M-protein level, Beta-2M level and time to progression with first-line treatment were predictors in this equation. The values of these predictors were then set to the corresponding mean values in the dexamethasone arm of the MM-009 and MM-010 trials to derive the expected median survival for these patients under MRC conditions. The post-progression survival equation derived from the MM-009 and MM-010 trials was then calibrated, by iteratively varying a term added to the equation until the predicted median matched the one obtained from the MRC equation.

As is evident from this paragraph, the methodology used in the lenalidomide *submission is equivalent to that used in the axitinib submission The confusion may have arisen from the fact that in the* lenalidomide *submission, the method was used to incorporate information from another trial to account for bias resulting from cross-over, rather than to compare with another trial, as was done in the Axitinib submission.*

In the case of the lenalidomide *submission, the methodology used was accepted by the appraisal committee. On page 19, paragraph 4.9 of TA 171 it is stated that trial results resulted in a crossover and that the committee considered 'whether the method of using data from historical MRC trials to predict survival for people treated with dexamethasone is appropriate in the absence of an unbiased estimate from the trials of lenalidomide.' It is further stated that 'The Committee (...) accepted that these data represent the best available survival data for people with multiple myeloma to be used in extrapolation of overall survival in the current analysis.'*

Further description of the method can be found in Ishak et al, 2011 Adjusting for patient crossover in clinical trials using external data: a case study of Lenalidomide for advanced multiple myeloma, Value in Health, 14, pp. 627-678. The full publication is attached.

We are not aware of STCs being used in any other NICE appraisals.

6. **Priority request:** From the AXIS trial, please provide full QoL data (FKSI-15, FKSI-DRS and EQ-5D) in a table for each treatment arm and differences between treatment arms with corresponding confidence intervals separately for the cytokine refractory and sunitinib refractory subgroups.

   Please find attached the QoL data based on FKSI-15, FKSI-DRS and EQ-5D separately for the cytokine refractory and sunitinib refractory subgroups.

7. **Priority request:** Section 6.9 of the manufacturer submission reports on the adverse events from the AXIS trial. Please provide data by treatment arm as reported in tables 30-32 separately for the cytokine refractory and sunitinib refractory subgroups.

   Please find attached the adverse event tables for the cytokine refractory and sunitinib refractory subgroups.

Section B: Clarification on cost-effectiveness data

Section 7.2

1. Please clarify why a time horizon of 15 years was chosen in a scenario analyses, and why this time horizon was not used in the base case.

   A 10 years time horizon of 10 years was chosen as the base case in keeping with previous technology appraisals in mRCC. *This a conservative assumption as the scenario with a time horizon of 15 years horizon which was explored in sensitivity analysis resulted in more favourable ICERs for axitinib.*

Section 7.3

2. **Priority request:** It appears from the model that each cycle, patients may discontinue treatment with axitinib. However, it also appears that the only difference between the patients who withdraw and the patients who stay on treatment is the cost; no treatment costs are applied to patients who withdraw from treatment. Please clarify the rationale for assuming that patients who withdraw from treatment continue to follow the PFS and OS curves for axitinib, rather than following the PFS and OS curves of the BSC group after withdrawal. The implication of the approach currently in the model is that more favourable ICERs will be found if more patients withdraw from treatment.

   In AXIS, a number of patients on axitinib discontinued treatment before progression due to adverse events. Patients who discontinued were still followed up in the trial and included in the estimation of the PFS and OS curves for axitinib. Therefore, the PFS and OS curves reported in the trial include patients who discontinued and reflect the actual axitinib dose administrated to these patients. Thus, dosing, OS and PFS estimates currently incorporated in the economic model are related directly to the AXIS study data.

Assuming that axitinib patients who discontinue treatment would have similar PFS and OS to BSC patients would not be appropriate as patients who discontinued were still followed up in the trial and included in the estimation of the PFS and OS curves for axitinib. Thus, assuming that these patients should follow the PFS and OS curves of the BSC (lower progression free and overall survival compared to axitinib) would artificially underestimate the true axitinib benefit.

Moreover, not including an adjustment factor for costs to reflect discontinuation would result in a modelled drug cost higher than that administered in the AXIS study, and likely substantially higher than the expected cost once the drug is introduced in UK clinical practice.

Section 7.3.2

3. Please clarify the rationale for not including the gamma distribution as part of the set of distributions used for analysis.

   The gamma distribution was not explored in the extrapolation for several reasons. First, a gamma distribution is very difficult to implement in the Excel 2007 model framework, and would have required complex VBA coding to incorporate a probabilistic analysis. In addition, gamma distribution is an accelerated time failure model and would not be applicable when the proportional hazard assumption was required.

4. Please provide log-cumulative hazard plots for all distributions considered (both for PFS and OS, for both subgroups).

   Please find attached the log-cumulative hazard plots for all distributions considered (both for PFS and OS, for both subgroups).

5. Please provide more details about the procedure to select the base case model. For example:

   - When AIC and BIC rank ordering are not the same, how are the 3 best fits selected?

   - The three distributions with the best fit were included, with the base case representing the most plausible survival estimate: how is the plausibility of the survival estimate determined?

   - The best fit is determined based on 3 criteria: how are these three combined to come to a selection. From the descriptions later in that section it appears that expert opinion was always dominant in the model selection.

   In keeping with NICE DSU recommendations, no one factor was viewed as dominant to another when choosing extrapolation options. However, as the long-term survival trends are a key driver of the model results, the plausibility of long-term survival estimates was an important factor and in many cases overrode other factors.

Plausibility of survival estimate was determined based on clinical opinion, knowledge of the natural history of renal cell carcinoma, examples from previous NICE appraisals and other HTA appraisals for late-stage metastatic solid tumours, and clinical and product knowledge of sunitinib and axitinib. When several distributions demonstrated similar fits for all criteria, "high, medium and low" survival estimates were chosen for the economic model, to allow for examination of the impact of different survival assumptions on the model outcome.

Additionally, in the cases when survival in the other treatment arm was modelled through the use of a hazard ratio (as was the case for the cytokine refractory subgroup), only the best fitting of the two accelerated failure time models was retained in the scenario analysis.

Cytokine Refractory Overall Survival curves

6. In the description of the model selection it is stated that the exponential and lognormal distribution showed poor fit (pg 140). However, in Appendix 19 according to AIC the Gompertz is ranked 4th and according to BIC ranked 5th. Therefore, the lognormal distribution appears to be a better candidate than the Gompertz. Please clarify the reasoning behind the choice of distributions.

As stated above when several distributions demonstrated similar fits for all criteria, "high, medium and low" survival estimates were chosen for the sensitivity analysis, to allow for examination of the impact of different survival assumptions on the model outcome. Additionally, in the cases when survival in the other treatment arm was modelled through the use of a hazard ratio, the list of 3 best fitting distributions has to include at least 2 proportional hazard models.

7. The manufacturer submission states that the loglogistic distribution provided the best fit in statistical term (page 141). However, this does not seem to be consistent with table 34, where the Weibull appears to have the best fit. Please clarify this apparent inconsistency.

This is a mistake in the text. The relevant section should read as follows:

"Additionally, the Weibull model allows for the incorporation of a hazard ratio to model the BSC arm, in keeping with the indirect comparison framework used for the cytokine refractory population (as described in Section 7.3.1 and later in Section 7.3.2). While the loglogistic model provided the second best fit in statistical terms (AIC and BIC), it did not allow for the application of the indirect comparison hazard ratio as it is an accelerated failure time model. Therefore, the loglogistic model was not chosen as base case where the application of a proportional hazard was required. The Gompertz model was retained and explored in a scenario analysis."

8. Please clarify why, if in the base case the application of proportional hazard was required, accelerated time failure models were considered?

Accelerated failure time models were explored as they were previously performed for a comparative analysis of axitinib vs. sorafenib in the cytokine-refractory population. As described in the statistical appendix, while application of a proportional hazard model is theoretically flawed, some accelerated failure time models provided fits which were felt to present

plausible extrapolation scenarios. Thus, application of proportional hazard models were retained in several instances as scenario analyses.

Cytokine Refractory Progression Free Survival curves

9. The manufacturer submission states that the *lognormal* distribution provided the best fit in statistical term (pg 142). However, this does not seem to be consistent with table 35, where the Weibull distribution appears to have the best fit. Also, it is noted that the exponential distribution gives the best BIC (appendix 19) but is not considered one of the 3 candidates. Please clarify the reasoning behind the choice of these distributions.

This is a mistake in the text and should be amended to have stated "the lognormal distribution provided the second best fit in statistical term …".

As stated above when several distributions demonstrated similar fits for all criteria, "high, medium and low" survival estimates were chosen for the sensitivity analysis, to allow for examination of the impact of different survival assumptions on the model outcome.

10. The manufacturer submission states that *similarly to the OS data*, the lognormal distribution provided the best fit (pg 142). Please explain this statement, as the lognormal distribution is not considered for the OS data.

This is a mistake in the text and should be amended to have stated "similar to the OS data, where the loglogistic provided the best fit, the lognormal…".

11. The manufacturer submission states that the lognormal model predicted a higher proportion of non-progressed patients at 10 years, which was felt to be clinically implausible by the experts and a reference is made to table 35 (pg 142). Please clarify why this was considered to be clinically implausible and how table 35 is seen to support this.

The lack of plausibility of this distribution was due to the proportion of non-progressed patients predicted by the model. Clinical opinion and company experience with axitinib and other mRCC products indicates that, a small proportion of mRCC patients may survive for long periods due to the heterogeneous nature of the disease, meaning that a distribution with a tail at 10 years may be plausible for OS. For PFS, it would not be expected for patients to continue on treatment with axitinib for a time period as long as 10 years. Thus the assumption of a distribution showing a proportion of non-progressed patients at 10 years was not felt to be likely.

The reference to table 35 is in the wrong place – it should be at the end of the previous sentence "Similarly to the OS data, the lognormal model provided the best fit in terms of AIC-BIC and fit to the trial portion of the Kaplan Meier curve."

Sunitinib Refractory Overall Survival curves

12. In the description of the model selection it is stated that the exponential and loglogistic distributions showed poor fit (pg 143). However, in Appendix 19 the ERG notes that according to AIC and BIC the Gompertz is ranked 4th whilst the loglogistic is ranked 2nd. Thus, the loglogistic distribution appears to be a

better candidate than the Gompertz. Please clarify the reasoning behind the choice of distributions

This text may not have accurately reflected the process of selecting the choices in the economic model. In this case, the loglogistic and lognormal distributions provided very similar fits. As the Gompertz model provided a lower survival estimate it was included to provide a scenario analysis demonstrating the impact of a more conservative survival estimate in the model.

13. In the manufacturer submission it is stated that the sunitinib refractory subgroup and the cytokine refractory subgroup are considered by many clinicians to comprise different subgroups. In light of this, please explain why it is plausible that the results of the fitted lognormal model for OS in the *sunitinib refractory* subgroup are similar to the results of the *cytokine refractory* 5-year follow-up from the axitinib phase II trial as stated on pg 143.

This is a mistake in the text and should be amended to have stated "similar to the lower 95% CI from the axitinib phase II trial."

The 5-year survival from the cytokine refractory subgroup axitinib phase II trial was 20.6%, 95% CI (10.9%-32.4%). The fitted lognormal model for OS in the sunitinib refractory subgroup predicted a survival probability of 11.3% at 5 years. This difference in survival probabilities at 5 years further supports that sunitinib and cytokine refractory patients are considered by many clinicians to comprise different patient populations.

Section 7.4

14. Please explain why for the post progression utility estimate only the mean utility at the end of treatment was used instead of also including the utility measurement at the 28 days follow-up.

The utility measurement at the 28 day follow-up was not included as it is likely to be confounded due to responder bias. Compliance was low (~40% in each treatment arm) and patients that were doing better, were more likely to have returned for their day 28 follow-up visit contributing to higher scores.

15. **Priority request:** Please provide the utility estimates for progression free and post progression survival for the prior sunitinib and the prior cytokine subgroups separately. Please also test the hypotheses that these utilities are the same in each subgroup.

The utility estimates for progression free (PF) and post progression (PP) survival are showed in table below.

	Overall	[redacted]	[redacted]	[redacted]
PF	0.692	[redacted]	[redacted]	[redacted]
PP	0.61	[redacted]	[redacted]	[redacted]

[redacted]

16. Please clarify which patients were used for the estimation of utility post progression, is this based on only patients receiving axitinib or also patients receiving sorafenib?

The utility post progression used in the submission is based on patients previously receiving axitinib or sorafenib.

17. In the manufacturer submission it is stated that while patients receiving axitinib may expect to experience some reduction in health-related quality of life related to the treatment, they will also receive HRQoL benefit in terms of symptomatic control and disease stabilisation. However, from the study by Swinburn (2010) it is clear that grade III diarrhoea, grade III fatigue and grade III hypertension influence the utility score for stable disease from 0.795 to 0.534, 0.591 and 0.642 respectively [TTO with UK members of the general public]. Also the study by Zbrozek (2010) shows the influence of serious toxicity on the utility score. In the light of these findings, please provide further justification of the assumption that patients receiving best supportive care would experience the same utility as patients receiving active treatment with axitinib.

The study by Swinburn et al, 2010 found considerable disutilities for selected adverse events when compared to likely utility of patients on stable disease receiving first line mRCC treatment. However, one limitation of the study was the development of the health state descriptions. As the stated by the authors "The process used in this study was to adapt already existing metastatic disease health states. Ideally the initial process undertaken would have been to conduct extensive qualitative research with mRCC patients currently undergoing such therapies."

However, these findings do not contradict our assumption that patients receiving best supportive care would experience the same utility as patients receiving active treatment with axitinib.

The impact of adverse events on the mean utility value per patient on treatment would be substantially lower than the differences described above as not all patients receiving mRCC treatment will experience AEs. Also, for patients who did experience AEs the impact on utility is expected to be applicable only for the period where the AE is experienced. As most grade 3-4 AEs will be actively managed and resolved either through urgent clinical intervention or dose reduction/interruption it is expected that the duration of the utility decrement due to the AE will be short. In addition, Swinburn et al, 2010 estimated utility values for adverse events compared to estimates for the utility of patients receiving first line treatment of mRCC. Baseline utility is expected to be lower in the second line treatment and therefore the differences described in the question might be less apparent.

This is further supported by the utility data reported in AXIS, where the mean utility of patients receiving axitinib was 0.692 over the duration of treatment compared to a mean baseline utility for these patients of 0.732 before treatment initiation. These estimates demonstrate that on average axitinib treatment had a utility decrement of 0.04.

In addition, patients on best supportive care would experience a negative impact in their HRQoL due to disease symptoms and actively progressing uncontrolled disease. This negative impact might be less significant when compared to that of some serious adverse events but it might have the same overall impact on the mean utility per patient as it is likely to affect more patients. This is further supported by QoL evidence comparing placebo with active treatment in 2nd line mRCC, which suggests that QoL is similar to placebo despite the presence of AEs.

Therefore, we believe that the assumption that patients receiving best supportive care would experience the same utility as patients receiving active treatment with axitinib is sufficiently justified.

Section 7.5

18. In the NICE specification section 7.5.3, NICE requests a systematic search of relevant source data for resource identification. In the submission it is stated that a systematic review was not completed and that evidence for this section comes from clinical opinion, published sources, the manufacturer's submission for the everolimus STA and the PenTAG model developed for the NICE bevacizumab, sorafenib, sunitinib and temsirolimus MTA. An initial examination of these sources shows publication dates of 2009 & 2008 respectively.

    a) Please provide further justification as to why no systematic review of resource use in the treatment of renal cell carcinoma was conducted.

    b) Please clarify the steps made to ensure that the information used in the submission is up to date.

    c) Please provide a list of all the published sources used and how these were identified. Please include the details of any search strategies used.

    As multiple recent appraisals have been carried out recently in mRCC, with several opportunities for consensus and input from NICE ERGs and appraisal committees, it was felt than an updated systematic review would not be required. Furthermore, assuming common resource utilisation assumptions with previous NICE mRCC appraisals ensures consistency in decision-making. To ensure the validity of the previous NICE assumptions with current UK practice, resource utilisation assumptions referenced from previous appraisals were tested with UK clinical experts in mRCC treatment to ensure that they were still relevant and reflective of clinical practice prior to their being incorporated into the submission.

19. **Priority request:** Please provide the dose intensity for the patients who were sunitinib refractory and cytokine refractory in the AXIS trial separately and clarify why in the base case analysis the overall dose intensity was used

instead of sub-group specific. Please provide ICERs with the sub-group specific dose intensities.

[redacted]

The ICERs with the sub-group specific dose intensity for sunitinib refractory patients were £40,639 and [redacted] for with [redacted] PAS scenario [redacted]. For cytokine refractory patients the ICER with the sub-group specific dose intensity was £66,955 and [redacted] for with [redacted] PAS scenario [redacted].

20. Please provide further justification for the assumption that no hospitalisations take place in the progressed disease state.

In our model, a cost of death was assigned in the progressed disease state, which included hospitalisation costs for palliative care costs as described in the response of question 21 below. Therefore, we did not include additional hospitalisation costs in the progressed disease state as this potentially would have resulted in double counting.

21. **Priority request:** Please clarify what the costs of death represent and how the estimate for these costs (before inflating to 2011 costs) was derived from the Coyle paper.

Using individual patient information collected from eight 'district health authorities' located in England and Wales in 1994, Coyle et al (1999) estimated the mean cost of palliative care in the community, in hospitals and in hospices in the UK. Appropriate inpatient data was available for 231 hospice patients and 95 hospital patients who were recruited into the study within three days of admission to the inpatient setting or within three days of transfer to palliative care. Cost data were collected at baseline, after one week and at monthly intervals for two months. After the third follow up there were no inpatients remaining in the study. To estimate the cost of inpatient palliative care, information on length of stay, procedures received, the number and type of tests conducted and other treatments delivered was recorded for each patient. The resource use items included bed-day costs, surgical procedures, chemotherapy, radiotherapy, blood transfusions, nasogastric tube insertion, blood tests, ECG, X-rays, ultrasound scans, bone scans, CT and MRI scans. Coyle et al (1999) estimated the mean cost of palliative care to be £2285.88 (SD £2096.8) in the hospital and £3049.91 (SD: £1791.7) in the hospice setting respectively (see Table 12). To estimate the 'cost of death' in the model, the weighted average cost (weighted by patient numbers in the study) of inpatient palliative care delivered in either the hospital or the hospice setting was calculated and inflated from 1999 to 2011 using the PSS Pay & prices inflator.

22. Please explain why the Mickisch study was not used for the AE costs of hypertension and diarrhoea. Please also explain the current assumptions underpinning the AE costs related to hypertension and diarrhoea.

Similarly to other health state costs, adverse event cost estimates for hypertension and diarrhea were based on the resource use assumed in the PenTAG economic model and these assumptions were validated with expert clinical opinion to ensure consistency with current clinical practice.

The adverse event cost for anaemia was based on the everolimus STA which used the Mickisch study, as this was in included in the PenTAG economic model. Please note that the anaemia AE cost estimate based on the Mickisch study was not included in the base case analysis (see response to question 24 below).

The use of Mickisch study to estimate the adverse event costs of hypertension and diarrhoea would have a negligible impact on the model results due to relatively small mean AE costs per patient.

23. Please clarify the difference between the costs of AE in table 40 and in table 45.

Table 40 includes the unit costs estimates used to estimate the cost per AE episode as shown in Table 45. More specifically, the cost of hypertension (£424) in table 45 was derived by adding the cost of 2 GP visits (£36 per 11.7 minute visit), 2 district nurse visits (£38) and the medication cost for hypertension (£276). The unit costs for GP visits, district nurse visits and the inflated to 2011 medication cost for hypertension are provided in Table 40. In addition, the cost of diarrhoea (£544) was estimated by multiplying the unit cost of inpatient day for anaemia in Table 40 (£272) by 2. Finally, the cost of anaemia in table 45 represents the unit cost in table 40 (£1,958) inflated to 2011 values (£2,068.47),

24. **Priority request:** Please clarify the adverse event rates associated with best supportive care. In the manufacturer submission (table 45) adverse events associated with best supportive care includes a percentage of anaemia of 5.1% while in the model 2% hypertension is used and no anaemia.

The 5.1% value stated in the submission was an incorrect reference based on a previously-examined scenario. We examined two potential sources to inform the AEs for best supportive care. In the RECORD-1 study 5.1% of patients receiving best supportive care experienced anaemia and 0% hypertension, while in TARGET study 2% of patients receiving best supportive care had hypertension and 0% in anaemia. The TARGET study was used in the base case.

This is a conservative assumption as the inclusion of AEs from the RECORD-1 study for BSC would have resulted in higher costs for these patients and as a result more favourable ICERs for axitinib.

Section 7.6

25. **Priority request:** Figures 36 and 37 present the results of the univariate sensitivity analysis in tornado diagrams. For these analyses ranges of +/- 20% were used. However, such a range could be much larger or much smaller than the confidence interval of a specific parameter. In order to get a sense of the realistically possible variation in the outcome, please provide univariate sensitivity analyses (both with and without PAS) with ranges

based on 95% confidence intervals (as also used in PSA) instead of a general +/- 20%.

The results of the univariate sensitivity analysis with parameter variation based on 95% confidence intervals (as used in the PSA) are presented below as tornado diagrams for both with and without PAS scenarios. As some scenarios produced negative ICERs, the graphs have been generated using incremental net benefit (assuming willingness to pay = £50,000) instead of cost/QALY figures to allow for better interpretability.

The updated univariate sensitivity analysis based on 95% confidence intervals showed that results were most sensitive to utility value estimates. However, these results should be interpreted with caution as some univariate scenarios could be clinically implausible, for example, scenarios where utility estimates for one intervention were set to the lower 95% CI value (which was close to zero) in the univariate analysis while for the other intervention the base case value was still used.

Figure 1: Tornado diagram: sunitinib refractory population (with PAS)

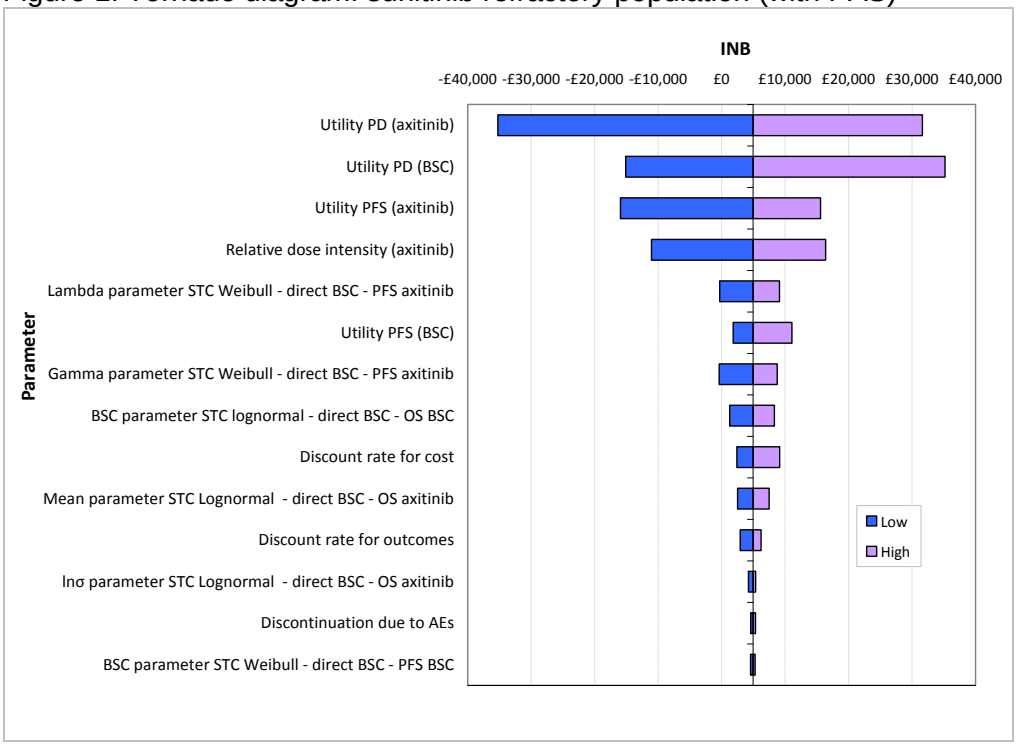
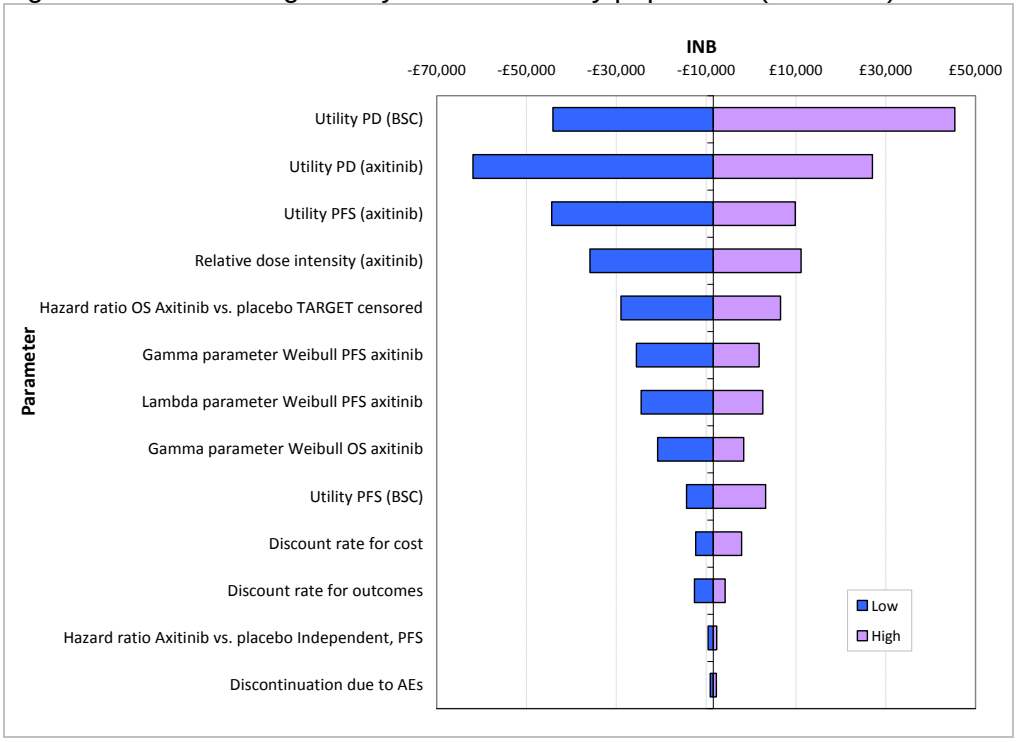


Figure 2: Tornado diagram: cytokine refractory population (with PAS)



[redacted]

Section 7.8

26. **Priority request:** Please provide the spreadsheet used for the validation process that is mentioned in the text of the manufacturer submission.

Please see attached the spreadsheet used for the validation process attached.

Appendix 19

27. Please provide further justification for the derivation of the survival curves for best supportive care (using the hazard ratio), either by providing a mathematical proof that this is a reasonable approach or by providing references.

The equations in question can all be derived from the definition of the probability of survival and the proportional hazard assumption. Using the following notation:

S(t) the survival function

H(t) the cumulative hazard function

HR the hazard ratio of axitinib versus BSC (i.e. the hazard ratio of BSC versus axitinib, which is required in the model, is 1/HR).

By definition: $S(t) = exp\{-H(t)\}$

Therefore:

$$S_{BSC}(t) = exp\{-H_{BSC}(t)\} = exp\left\{-\frac{1}{HR}H_{AXI}(t)\right\} = exp\{-H_{AXI}(t)\}^{\frac{1}{HR}} = S_{AXI}(t)^{\frac{1}{HR}}$$

Other equations on pages 346-7 take the same approach just using the functional forms of the given distributions.

Section C: Textual clarifications and additional points

1. Please could you confirm the following details for the Clinical effectiveness searches for the Web of Science (10.2) searches:

- The ERG does not recognise the search syntax as being ISI Web of Knowledge, in some lines it appears to be Ovid, but there appear to be mixed use of adjacency operators i.e. “adj” and “near”. Please can you confirm which host was used?

The search was carried out using DataStarWeb, therefore it is using the Datastar search syntax. In the Datastar search syntax the “adj” operator means that the words must be next to each other, the “near” operator means the words are in the same sentence

- Within the Web of Science, please can you confirm which indices were searched? i.e. Science Citation Index etc

The indices searched were the Science Citation Index

- Please can you provide the date range searched?

  The strategy presented is up to 2010. Was an update search undertaken as with the other searches in this section? Please confirm the search dates.

  The search was carried out on 8th July 2010, and there were no date restrictions on the search, therefore the data retrieved were from 1900 – present (i.e. 8th July 2010).

  The search strategy has not been updated since then.