NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patient/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee. Where clinical specialists and patient experts make comments on the ACD separately from the organisations that nominated them, these are presented alongside the consultee comments in the tables below.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Bayer Healthcare	In response to the ACD we are pleased to see that the Committee recognises that sorafenib has demonstrated both clinical and statistical significance in terms of overall survival, progression-free survival and tumour response. However, we are very disappointed that such a clinically effective treatment option, the first to demonstrate clinical effect in this patient group for over a decade, will be denied to NHS patients, despite it being able to extend their life expectancy by 50%. The proposed recommendation will mean that patients with advanced RCC, a rare cancer, will now only be able to receive cytokine therapy or supportive care as part of routine clinical practice in England and Wales, severely limiting the clinical options available to oncologists. The proposed recommendation from the Committee will have a devastating impact on both patients and their family. If this recommendation stands the NHS will be denying life extending treatments to vulnerable people at a point in their lives when they rely on the NHS the most. Essentially, the decision will mean that the Committee and the NHS will have let these patients down and cut any final hope they may have during their valuable last few months of life.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about sorafenib.
Bayer Healthcare	There is both rising incidence and rising mortality due to renal cell carcinoma in the UK. The decision by the Committee to not recommend use of these important therapies for patients who have either limited or non-existent alternatives is contradictory to the Department of Health's commitment to ensure that the NHS provides world class cancer care, as outlined in the recent Cancer Reform Strategy.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus. See the FAD 'sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' section 1 for guidance relating to the first-line use of sunitinib.

Consultee	Comment	Response
Bayer Healthcare	The UK already has one of the lowest expenditure per capita for sorafenib within Europe, with 13 countries having higher expenditure, including Greece, the Czech Republic and Slovakia. The UK position will continue to fall as a result of the proposed guidance. Decisions such as this will also mean that the UK continues to rank poorly in cancer survival compared to our European counterparts.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus. See the FAD 'sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' section 1 for guidance relating to the first-line use of sunitinib.
Bayer Healthcare	The guidance poses several questions in light of the recently published End of Life Care Strategy. By denying these life extending drugs, the guidance provides no recommendation on what clinicians should do and what patients should expect from the NHS in preparation for their end of life. The guidance makes no attempt to estimate what would be a cost-effective end of life package that represents optimal care whilst remaining within the Committee's judgement on what constitutes value for money for the NHS, leaving patients with an uncertain last few months of life. Furthermore, the guidance offers no proposed education or training to health care professionals in explaining to patients why they are deemed not worth treating by the NHS and how they will now be managed.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus. The remit for this technology appraisal did not include recommendations on an optimal care package for end of life care. See the FAD 'sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' section 1 for guidance relating to the first-line use of sunitinib.

Consultee	Comment	Response
Bayer Healthcare	The Strategy states that "it is difficult, if not impossible, to calculate the cost of end of life care in this country". The academic group assumed a minimal supportive care package would be provided to patients, contrary to the aims of the End of Life Care Strategy. Ironically, the proposed guidance now means that the Department of Health and NICE should begin to consider whether providing high quality supportive care at the end of someone's life will be a cost-effective use of public money given that it may not have sufficient impact on quality of life to achieve a favourable incremental cost/QALY ratio. Our own cost estimates of supportive care for advanced RCC patients show that, even without the cost of sorafenib being included in the calculation, extending life in the way that sorafenib has proven to do, would only just be deemed cost-effective by NICE based on a £20,000 per QALY threshold.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus. The remit for this technology appraisal did not include recommendations on an optimal care package for end of life care. See the FAD section 1 for guidance relating to the first-line use of sunitinib as a life-extending, end-of-life treatment.
Bayer Healthcare	Whilst we recognise that the Committee has to be mindful of the need to take into account the effective use of NHS resources, we disagree that the QALY is the appropriate outcome to measure the benefit of oncology products, particularly in advanced stage disease. Although the health state utility attempts to adjust time by modifying it for the preference (or fear) of a health state, it does not account for people's valuation of their time. When people have less time available, for example, if they have short life expectancy, they will value any time available much more highly than if they have more many years of life left. Unfortunately, the QALY approach, even accounting for discounting based on Treasury financial investment recommendations, does not take this into account. This therefore results in a perverse situation where the NHS values the addition of 6 months of life to someone with only a few months to live the same as if it were given to someone with 30 years to live. The implication of this is that the NHS is implicitly devaluing the benefit of time these life extending drugs provide for advanced stage disease at a point when patients value their time most highly.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus. See the FAD section 1 for guidance relating to the first-line use of sunitinib as a life-extending, end-of-life treatment. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness.

Consultee	Comment	Response
Bayer Healthcare	Throughout the ACD, the document mentions that the Phase III sorafenib trial, TARGET, was terminated early. In the way that it is written, readers may interpret this as the manufacturer's decision and that this may have compromised the results of the trial. Please can you add that the cross-over decision was based on ethical grounds, and recommended by the independent monitoring group after sorafenib had demonstrated a clinically significant increase in progression free survival over placebo. The pre-planned secondary analyses with the placebo arm censored did show a statistically significant overall survival advantage.	Comment noted. This has been amended throughout the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' accordingly.
Bayer Healthcare	The ACD comments on further possible research areas within the RCC field. We would like to bring to the Committee's attention that Bayer has remained committed to investing in and undertaking research on sorafenib in the UK, including a large scale (n=1656), UK specific phase III trial, SORCE.	Comment noted.
Bayer Healthcare	Please find below a list of additional comments relating to specific sections of the ACD that we would like the Committee to take into account for the wording of the FAD. 4.1.21 Bokowski et al. (2007; JCO Vol 30 (3)) reported that the median time to health status deterioration was significantly greater for subjects on sorafenib than those on placebo ($p<0.0001$ by log rank test). Health status deterioration was defined as a greater or equal than four point drop in FKSI-10 total score, progression or death).	Comment noted. This has been amended in the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Bayer Healthcare	4.1.24 Please change "appears" to "demonstrated" Please add "on ethical grounds" i.e. "terminated early on ethical grounds"	Comment noted. This has been amended in the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Bayer Healthcare	4.2.6 Title should be unsuitable for immunotherapy	Comment noted. This has been amended in the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Bayer Healthcare	Please remove the statement "although the precise range of ICERs is not reported numerically in the manufacturer submission" as these were available to PenTAG within the fully enabled and transparent economic models provided. Otherwise, please add that Tornado diagrams were provided in the submission to demonstrate the results of the one way sensitivity analysis. It was not our intention to not provide these values numerically.	Comment noted. This has been amended in the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'

Consultee	Comment	Response
Bayer Healthcare	4.4.7 Sorafenib is licensed for patients unsuitable for cytokine therapy. By not allowing this group to receive any of the clinically effective treatments available, NICE is denying patients the ability to both relieve symptoms and extend their lives. As this group has no other treatments available they have the highest unmet clinical need of all advanced RCC patients; denying them treatment when nothing else is available is unjust.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about sorafenib.
Bayer Healthcare	4.4.15 Please add "on ethical grounds" i.e. "…was terminated early on ethical grounds and people…"	Comment noted. This has been amended in the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Bayer Healthcare	4.4.15 The Committee believe that in clinical practice patients will receive additional therapies. The Committee should be mindful that, as a result of denying these new drugs to patients, that this statement will no longer be correct in England and Wales, although it is highly appropriate for all the other countries who regularly fund treatment with sorafenib. Only patients recruited into clinical trials will be able to receive other therapies and this is not reflective of clinical practice throughout the NHS.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus. See the FAD section 1 for guidance relating to the first-line use of sunitinib as a life-extending, end-of-life treatment.

Consultee	Comment	Response
Bayer Healthcare	We would therefore ask the committee to reconsider their proposed decision in denying sorafenib to patients where no further treatment options available to them. In particular: • We do not believe that that using the QALY for advanced RCC patients is a suitable and sound basis for making recommendations to the NHS in this patient group.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about sorafenib. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness.
Bayer Healthcare	The decision will be inequitable to those patients who are unsuitable for cytokine therapy and therefore will not be eligible for any treatment at all.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about sorafenib.
Bayer Healthcare	Finally, Bayer believes that sorafenib should be available to clinically eligible RCC patients. We are currently in discussions with the Department of Health about schemes that may allow patients access to sorafenib in the event that NICE rejects the use of sorafenib in the NHS.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about sorafenib.
Pfizer	**Summary** Pfizer believes that sunitinib is both clinically efficacious and cost-effective, compared to other systemic therapies, when used to treat patients with metastatic Renal Cell Carcinoma (mRCC) in England and Wales. We are therefore disappointed that the Committee has not recommended sunitinib, a drug that has now become the standard of care in treating this condition across the rest of Europe.	Comment noted. See detailed responses below.

Consultee	Comment	Response
Pfizer	We understand that one of the major impediments to reaching a positive decision lay around understanding the applicability and robustness of a key analysis within the final study results presented to the Institute. This analysis, which excluded patients who received additional systemic treatment, is most reflective of relative drug efficacy in settings where clinicians will not realistically have the opportunity to prescribe, or individual patients receive, more than one systemic therapy. Further data obtained by Pfizer in relation to this analysis, presented here, support the applicability of the data to help guide decision making regarding the use of sunitinib.	Comment noted. The updated evidence that was submitted was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.
Pfizer	Pfizer also highlighted a number of issues in our response to the Assessment Report (TAR) around the approach taken to the clinical data and the relative cost-effectiveness of sunitinib, which significantly modified the Assessment Group base case, that are not reported on in the ACD and we are therefore unclear whether they have been considered.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment report and the Appraisal Consultation Document.
Pfizer	Pfizer is in discussion with the Department of Health in relation to formalising our commitment to offering the first cycle of treatment free to all patients commencing treatment for mRCC with sunitinib. We hope that discussions will be concluded promptly and will advise NICE when they are completed. In the interim we would request that the free cycle is reflected in any re-analyses undertaken in response to feedback regarding the ACD.	Comment noted. The patient access scheme was agreed by the Department of Health in time for the second appraisal Committee meeting and was incorporated into the analyses and considered fully by the Committee. See FAD section 3.1.3.
Pfizer	This failure to recommend sunitinib is particularly disappointing given that the drug was given the first ever positive opinion on the granting of a conditional marketing authorisation (designed to facilitate early access to medicines) by the CHMP effective July 2006 for second line use in mRCC and GIST. This decision is strongly aligned with the proposals in the Cooksey Report, subsequently adopted by the UK Government, for Conditional Licensing to be granted to medicines which demonstrate evidence of appropriate efficacy and safety, especially in patient populations with significant unmet clinical need	Comment noted. Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See section 1 of the FAD.
Pfizer	We believe that a re-appraisal of evidence, incorporating these points, explored in more detail below, should conclude that sunitinib is not only clinically efficacious in relation to other systemic therapies available but also cost-effective when applying the threshold used by the National Institute for Health and Clinical Excellence.	Comment noted. See detailed responses below.

Consultee	Comment	Response
Pfizer	**Clinical efficacy** The clinical efficacy of sunitinib has been significantly underestimated in the ACD because of a failure to accept the validity of the survival analysis excluding patients who received further systemic treatment post study discontinuation. The validity has been questioned under three broad headings: 1. The applicability of post hoc analyses. 2. The appropriateness of the specific analytical approach. 3. The availability of sufficient information regarding demographics and patient characteristics.	See detailed responses below.
Pfizer	*The applicability of post hoc analyses* In the study, overall survival OS) was a pre-specified secondary endpoint; the primary endpoint being progression free survival (PFS) where sequential treatment with multiple systemic therapies is generally not regarded to have been a confounder. Pfizer acknowledges that the OS intention to treat (ITT) analysis of the full trial population is reflective of the study protocol and accepts that the statistical analysis plan failed to incorporate the need to develop strategies to handle confounding events that could reasonably be expected to occur, so as to enable application of the study results to the needs of patients, UK clinical practice and HTA bodies.	The Committee understood that there had been both crossover after disease progression, but also participants had had second-line treatment after the study had ended. This could be expected to exaggerate overall survival estimates for people in the UK receiving IFN-α in the future, as the Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.

Consultee	Comment	Response
Pfizer	The European Medicines Evaluation Agency (EMEA) has recognised that there are significant issues with clinical trial design and measuring overall survival in the sphere of oncology, stating recently, *"While it is generally acknowledged that the aim of treatment is to improve quality of life and survival, restraints on the conduct of clinical trials may make these goals unattainable. It is thus recognised that investigators, patients and ethics committees may require, e.g. optional cross-over at time of tumour progression. Similarly, the use of active next-line therapies must be accepted. This may affect the possibility of detecting differences in OS as well as symptoms related to tumour progression." (EMEA 2005)*	See detailed response above.
Pfizer	Previous NICE Committees have also acknowledged the inadequacies of Randomised Controlled Trials (RCTs) where cross-overs or multiple treatments have played a part; the Appraisal Committee reporting on the use of RCTs in TA30 (Breast cancer - taxanes (review)) stated, *"Conducting and interpreting randomised controlled trials of anti-cancer drugs is complicated by a number of issues; including protocol defined and undefined cross over to alternative treatment where there is evidence of disease progression on randomised treatment, unblinded studies and differential toxicity profiles".* and have gone further to question how the findings should be interpreted, *"The evidence base for the management of advanced colorectal cancer includes a number of randomised controlled trials. However, results for overall survival from RCTs need cautious interpretation because the disease is often managed with sequences of either mono- or combination therapy, with the frequent use of unplanned second- or third-line salvage chemotherapy."* *(TA93 (Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer (review of TA33))* and we would strongly argue that similar caution needs to be applied to interpreting the recent sunitinib RCT data relating to the current appraisal.	See detailed response above.
Pfizer	*The appropriateness of the analytical approach* Discussion relating to the overall survival (OS) benefit of sunitinib centres on the validity of alternative final analyses to that of the full Intention To Treat (ITT). The full ITT analysis incorporates patients who were permitted to cross over from interferon alfa (IFN-α) after the first interim analysis as well as including patients who received further treatment post study discontinuation.	See detailed response above.

Consultee	Comment	Response
Pfizer	An analysis was performed in which patients who crossed over from IFN-α to sunitinib were censored at the time of crossover. Allowing crossover in a study has the potential to confound any demonstration of improvement in OS with censoring at the point of cross-over a legitimate means of addressing it. This analysis demonstrated a statistically significant benefit in OS for patients treated with sunitinib but still failed to fully explain the value of sunitinib to clinical practice in the UK.	Comment noted. See detailed response above.
Pfizer	This ITT analysis, with cross overs censored, appears to demonstrate a survival benefit for IFN-α significantly greater than that reported in other clinical trials or experienced in clinical practice. This has been attributed solely to the overall improvement in management of patients with cancer which is simplistic and not supported by the evidence. Table 1 below shows the median survival with IFN-α for a number of studies. The Escudier 2007 (19.8m) and Figlin 2008 (20m) are the two highest. These are both confounded by the significant number of patients who went on to receive second or third line systemic therapy, as clinical trial data demonstrates that second line treatment improves overall survival in patients who have progressed on their initial systemic therapy (Escudier et al, 2007[1] Motzer et al, 2005). *Table not reproduced here*. To explore the potential confounding influence of post-study cancer treatments, the systemic treatments patients received post A6181034 study discontinuation were reviewed and analysed as shown in Table 2. Of the 359 IFN-α patients who discontinued from the study, 59% received post-study cancer treatments with 33% receiving sunitinib. The inclusion of such patients confounds any analysis of survival benefit[1]. *Table not reproduced here.*	The Committee noted the relatively high median overall survival associated with IFN-α from the ITT analyses and considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate. The Committee considered it was reasonable to accept the reduced overall survival estimate that these data implied for the control (IFN-α) group. See FAD sections 4.3.7 and 4.3.9.

[1] There is work ongoing using Marginal Structural modelling to handle time dependent variables such as the use of additional systemic therapies in the A6181034 study because of problems such as this (Hernan et al, 2000; Wang et al, 2008).

Consultee	Comment	Response
Pfizer	In the UK, outside of participation in clinical trials, patients do not routinely receive sequential treatment with a number of systemic therapies; as happened to a majority of patients in the sunitinib study (Table 2). Unless the guidance to be published by the Institute on the management of patients with mRCC specifically recommends sequential therapy, the likelihood will decrease even further. Therefore, to be applicable to the UK, a revised study analysis needs to exclude patients who have received more than one systemic agent. This additional analysis (Figure 1), already presented to NICE, importantly appears to offer a more accurate interpretation of the efficacy of the two drugs with the median value for IFN-α of 14.1 months corresponding well to the value from the Cochrane systematic review of 13.3 months (Coppin et al, 2005). Figure 1 not reproduced here. Patients who crossed over to sunitinib in the study (I.e. did not receive sequential therapy other than sunitinib on study) are included in this additional analysis. This will have marginally increased the median value for IFN-α.	The Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that investigation of the 'no post-study treatment' group was appropriate. See FAD section 4.3.7.
Pfizer	*The availability of sufficient information regarding demographics and patient characteristics.* The Committee commented on the need for further information regarding the patients included in the analysis that excluded patients who received systemic therapy post discontinuation, to understand its relevance and also to understand how representative these patients were of the overall study population. We have generated a breakdown of the demographics and patient characteristics for patients included in this analysis. This has been incorporated into a table (Table 3) that includes the demographics and patient characteristics for the overall study population. This serves to demonstrate that there is no systematic difference in patient characteristics between the treatment groups (sunitinib vs. IFN-α) both in the overall population as well as in patients who did not receive post study systemic therapy. *Table 3 not reproduced here.*	Comment noted. This information was submitted in time for the second Appraisal Committee meeting and was considered fully by the Committee. See FAD section 4.3.7.

Consultee	Comment	Response
Pfizer	The Assessment Group commented, *" On the subgroup data presented for individuals who did not receive any post study treatment, whilst the information provided is interesting, we feel it is important to highlight that this sub-group of patients was not pre-defined within the study protocol and we are unsure how such a subgroup would be identified prospectively (pre-selection?) in the clinical setting".* and Pfizer agrees that whilst identifying these patients prospectively would be difficult it is in fact unnecessary. This analysis is of a representative sample of the overall population requiring treatment and, in a clinical setting where multiple systemic drugs are not available for use on a routine basis; the efficacy values from this analysis are more likely to reflect actual results in practice. This is supported by the comparison of demographics and patient characteristics presented in Table 3 that demonstrates no systematic difference between the analysis groups. Further support for the representative nature of this analysis compared with the total study population can be gained by examining progression free survival. *Table not reproduced here*.	Comment noted. See detailed responses above.
Pfizer	As stated in a previous communication, had this analysis been available at the time of the original submission, we would have presented the case for it being the more appropriate for use to both position sunitinib within the care pathway and to drive any cost-effectiveness analysis. The views of clinicians expert in treating patients with mRCC support the appropriateness of this approach and is captured in the response to NICE from the Royal College of Physicians: *"An analysis in which patients who crossed over or received 2nd line treatment with other agents was presented confirming a huge median overall survival benefit (increased from 14months to 28months). This is the "purest" population in which it is possible to establish the survival benefit of sunitinib."* The feed back received from UK oncologists who have seen all three analyses of the final data (ITT, ITT cross overs censored, and no systemic therapy post study discontinuation) is that the latter is the most applicable to the clinical setting in England and Wales.	Comment noted. See detailed responses above.

Consultee	Comment	Response
Pfizer	**Cost-effectiveness** The Committee has concluded that sunitinib is not cost-effective, with the reasons lying under four broad headings: 1. The choice of clinical data used to inform the model. 2. The modelling of the clinical data selected. 3. The failure to incorporate into a revised base case previously highlighted concerns regarding model assumptions, inputs around utility values, cost of supportive care, and death. 4. The failure to incorporate the free cycle offered by Pfizer into the base case.	Comment noted. See detailed responses below.
Pfizer	*The choice of clinical data used to inform the model* As discussed above, the analysis of final OS data that excludes patients who received systemic treatment post study discontinuation would have been used as the base case had it been available at the time of the original submission. We did however provide a revised cost-effectiveness analysis based on this data on June 27th 2008 as soon as the data was to hand. It would appear from the comment by PenTAG, *"We suggest that such a survival profile would lead to a lower cost per QALY in this subgroup, all else equal. However the PenTAG modelling framework is structured to use data on both progression-free-survival and overall survival from the same source – consistent across all cost-effectiveness analyses undertaken for the broader review – to estimate cost-effectiveness. We believe this to be the correct approach given the modelling framework used. Therefore we are unable to provide cost-effectiveness estimates using this additionally supplied data on OS for either sub-group." (PenTAG response to comments on the TAR. Pg.2)* that there are concerns related to the source of the efficacy data used to generate these cost-effectiveness results, which prevented the Group from developing their own cost-effectiveness estimate from this analysis. While the PFS curves for the exploratory analysis have not been published alongside the OS curves, we would like to clarify that the efficacy data used to model the sub-group population was **all** derived from the exploratory analysis.	Comment noted. The revised cost effectiveness analyses were submitted in time for the second appraisal Committee meeting and were appraised by the Assessment Group and the DSU and considered fully by the Committee. See FAD sections 4.2.4, 4.2.5, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8 and 4.3.9

Consultee	Comment	Response
Pfizer	*The modelling of the clinical data used* In modelling the OS and PFS for this analysis, the IFN-α survival data was extrapolated using regression techniques to estimate the parameters of the Weibull survival curve. The sunitinib survival curves were then modelled using the revised hazard ratios and the extrapolated IFN-α survival curve. The resulting curves and the empirical data from the exploratory analysis are shown figures 2 and 3. *Figures not reproduced here* The above curves were generated from a regression that used all available data points to estimate the Weibull parameters, this approach is consistent the approach taken in our original submission. However, as in the original submission, the survival analysis for PFS is heavily influenced by the first few data points in the Kaplan-Meier trial data and results in the model underestimating the PFS for IFN-α.	Comment noted. See detailed response below.
Pfizer	In our original model, PenTAG corrected this underestimation by fitting a Weibull curve to fewer data points (one per month). We have adopted this approach to improve the fit of the IFN-α curve shown in figure 2 and generated the survival curves for IFN-α and sunitinib as shown in figure 4. While adjusting the regression improves the fit of the IFN-α curve, applying the hazard ratio to this IFN-α curve to estimate the sunitinib curve generates one that does not fit the sunitinib trial data. When the curve for sunitinib is fitted independently (sunitinib survival data is extrapolated using regression to estimate the parameters of a Weibull curve), the modelled curve is shown to fit the data very well. *Figures included, but not reproduced here*	Comment noted. The revised cost effectiveness analyses and modelling approaches were appraised by the Assessment Group and the DSU and considered fully by the Committee. The Committee then agreed their preferred assumptions for the 'no post-study treatment' group. See FAD sections 4.2.4, 4.2.5, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8 and 4.3.9.
Pfizer	The survival analysis for OS is also heavily influenced by the first few data points in the Kaplan-Meier trial data. The transformation of the Weibull survival function S(t) for regression, In(-In(S(t)) is very large and negative where S(t) is below 1. Adjusting the regression by fitting one data point per month (the approach used by PenTAG) alters the shape slightly, by reducing the underestimate observed at the end of the curve (figure 5). *Figure included, but not reproduced here* To estimate cost-effectiveness of sunitinib compared to IFN-α, mean survival times have been calculated from the Weibull curves shown in figure 4 (for PFS) and figure 5 (for OS). Using the costs and utilities from our original submission, this gives the following cost effectiveness result. *Figure included, but not reproduced here*	Comment noted. See response above.

Consultee	Comment	Response
Pfizer	Probabilistic sensitivity analysis was undertaken to explore the impact of second-order uncertainty surrounding mean parameter values on marginal costs and health effects. The probabilistic analysis was carried out by allowing parameters to vary according to the uncertainty specified in their probability distributions, with 2,000 sets of random numbers used to generate 2,000 sets of cost-effectiveness results. The results of these simulations are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). Figure 6 presents a cost effectiveness plane showing the marginal costs and QALYs associated with sunitinib compared to IFN-α. Figure 7 shows the cost effectiveness acceptability curve. The CEAC shows that at a willingness to pay threshold of £30,000 the probability that sunitinib is cost effective is 51%. *Table included, but not reproduced here*	Comment noted.
Pfizer	The Committee appear confident that the approach taken to modelling the data is sound but that it could not be *'…considered a robust basis for decision making as the estimates had not been critiqued by the Assessment Group and no details about the post-hoc subgroup were provided'*. Pfizer has addressed the concerns about missing details elsewhere in this response as well as the argument for the utility of the analysis. We have also attached to this response a fully executable version of the model used to derive cost-effectiveness results for this analysis. Should any further data be required over and above that present in the model we will provide it on request. *Figures included, but not reproduced here*	Comment noted. The revised cost effectiveness analyses were submitted in time for the second appraisal Committee meeting and were appraised by the Assessment Group and the DSU and considered fully by the Committee. See FAD sections 4.2.4, 4.2.5, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8 and 4.3.9
Pfizer	*The failure to incorporate into a revised base case previously highlighted concerns regarding model assumptions and inputs around utility values and cost of supportive care and death.* In our response to the TAR, we raised the concern that the Assessment Group base case ICER represented an inflated estimate of the ICER for sunitinib compared to IFN-α. We felt that their assumptions concerning utility values and costs associated with supportive care and death were not representative of clinical practice. The further scenario analysis we presented in response to the TAR demonstrated that the cumulative effect of changing assumptions related to baseline efficacy data, supportive care costs, 1st free cycle, inclusion of death costs resulted in a much lower ICER for sunitinib compared to IFN-α.	Comment noted. See detailed response below.
Pfizer	The Assessment Group, in their response to comments on the TAR; acknowledge the accuracy of this multi-way sensitivity analysis, however there is no evidence within the ACD that this alternative base case figure has been considered. That PenTAG have accepted the validity of a number of the sensitivity analyses, leaves Pfizer with the concern that, where there is acknowledged uncertainty within each of the two approaches, the Committee defaults to that of their Assessment Group, without exploring the validity of the arguments raised by Pfizer. This is especially concerning as some of the PenTAG assumptions are clearly built around subjective opinion within their team.	Comment noted. The Assessment Group also highlighted the paucity of evidence on utility values for people with advanced and/or metastatic RCC. The Committee considered the possible effect of the change in utility values on the 'no-post study treatment group'. See the FAD section 4.3.10.

Consultee	Comment	Response
Pfizer	Utility values In relation to the utility values used we note that our comments have been acknowledged and that PenTAG conducted further sensitivity analyses to explore in greater detail the uncertainty around the values used in their base case. As discussed above there is no evidence that this has been considered by the Committee as valid to modify the PenTAG base case.	Comment noted. The Committee considered the possible effect of the change in utility values on the 'no-post study treatment group'. See the FAD section 4.3.10.
Pfizer	In our revised analysis, presented above, we have modelled using the trial based utility values as in our original submission. These values are problematic as the values derived from the Motzer study are 'within trial' values and therefore unlikely to be an accurate reflection of the 'true' utility associated with being either progression free or progressed with a diagnosis of metastatic RCC as reflected in real world practice. In addition, as we have previously commented, there are significant concerns that the 'progressed' values within the trial were taken at the point where the patients entered the progressed state.	Comment noted. The Committee considered the possible effect of the change in utility values on the 'no-post study treatment group'. See the FAD section 4.3.10.
Pfizer	*The failure to incorporate the free cycle offered by Pfizer into the base case.* In line with Pfizer's ongoing commitment to ensure the widest possible access to clinically effective drugs the cost of the drug was reduced by 5% in May 2007 making the UK price of Sutent the lowest within Europe. In addition, Pfizer commenced offering the first cycle free on 08/05/2007, having confirmed with the MHRA that this revised pricing scheme did not constitute a prohibited "gift, pecuniary advantage or benefit in kind" to persons qualified to prescribe or supply medicines. In response to the comments in the ACD regarding the scheme we have contacted the Department of Health and made them aware of its structure and function. We have answered the questions that the department had and now anticipate endorsement for the first cycle free scheme within the UK in the near future. The cumulative effect of the price reduction and offering the first cycle free is estimated at being an effective total price reduction of 18.5%.	Comment noted. The patient access scheme for sunitinib was agreed by the Department of Health in time for the second appraisal Committee meeting and was incorporated into the analyses and considered fully by the Committee. See FAD section 3.1.3.

Consultee	Comment	Response
Pfizer	**Conclusion** Pfizer believes that sunitinib is both clinically efficacious and cost-effective when used to treat patients with metastatic renal cell carcinoma in England and Wales.	Comment noted. Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See section 1 of the FAD. See detailed responses above.
Pfizer	The supporting data presented by Pfizer in relation to the final study results, demonstrates that there is no systematic difference between the patients in the analysis undertaken in those who did not receive any post study systemic therapy and the general study population. This supports the use of the analysis for demonstrating efficacy and modelling cost-effectiveness. In using this analysis, it has been shown that sunitinib can offer a doubling of overall survival benefit (28.1m) vs IFN-α (14.1m).	Comment noted. See detailed responses above.
Pfizer	It appears that the Committee, in making the provisional recommendation in the Appraisal Consultation Document (ACD), have failed to take into account a number of key issues raised in previous correspondence around the Technology Assessment Report. This unfortunately has the effect of perpetuating inconsistencies in the approach to the sunitinib clinical data and also the drugs relative cost-effectiveness.	Comment noted. See detailed responses above.
Pfizer	Pfizer has initiated discussion with the DoH regarding the offer of the first cycle of therapy free. This, along with the original five per cent price cut, has effectively reduced the cost to the NHS of sunitinib by 18.5%.	Comment noted. The patient access scheme for sunitinib was agreed by the Department of Health in time for the second appraisal Committee meeting and was incorporated into the analyses and considered fully by the Committee. See FAD section 3.1.3.
Pfizer	It is our view that a re-appraisal of evidence, incorporating the points above, should conclude that sunitinib is not only clinically efficacious in relation to other systemic therapies available, but also cost-effective when applying the threshold used by the National Institute for Health and Clinical Excellence.	Comment noted. Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See section 1 of the FAD. See detailed responses above.

Consultee	Comment	Response
Roche Products	Thank you very much for sending us the Appraisal Consultation Document (ACD) for the above technology appraisal. Roche welcomes the provisional clinical findings of the Appraisal Committee in relation to establishing the effectiveness of bevacizumab, recognising its ability to address significant unmet clinical need for patients with renal cell cancer. However, the ACD presently concludes that bevacizumab is not cost effective when based on either Roche's submission or on the analysis performed by the Assessment Group (AG).	Comment noted. See responses below.
Roche Products	Roche would like to request that the Appraisal Committee when reconsidering the ACD, evaluate further and deliberate on several key parameters currently included within the AG's economic model which we believe presently compromise the accuracy and validity of the final base case estimate of the bevacizumab ICER. In this context, we would also point out that the ACD is currently not clear regarding which of the alternative assumptions reported are considered to be most robust by the Appraisal Committee in establishing the base case ICER and we would like to request that these are made explicit to us.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for a description of the alternative assumptions accepted by Committee.
Roche Products	We also present in this response to the ACD what Roche considers to be a more appropriate hazard ratio from the AVOREN trial for use in the AG's model in relation to appropriately taking into account post progression treatments and also present details of the actual dosing observed from the AVOREN trial because we believe the AG's treatment duration assumptions for bevacizumab are inaccurate.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Roche Products	Roche would like to request that if the points raised below are considered valid by the Appraisal Committee that they are incorporated into the AG's economic model cumulatively rather than as part of any univariate analysis in order to report a revised base case ICER for bevacizumab. Alternatively, if any of the points raised are not considered valid then we would like to request that the Committee provide a clear explanation and rationale as to why alternative assumptions are preferred.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'

Consultee	Comment	Response
Roche Products	**1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT** It is unclear from the ACD as to whether or not Roche's response to the Assessment Group's Report discussing the validity of some of the assumptions used in their analysis was considered by the Committee. There are a number of differences between the clinical and economic analyses performed by Roche and those conducted by the AG which have a very significant impact on the final ICER and therefore it is important that each of these points be considered in turn:	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Roche Products	**A) Overall survival / post-progression treatment effect** In this section we provide a further analysis of the AVOREN pivotal trial that adjusts overall survival for second-line treatments. Roche's original submission used an overall survival hazard ratio based on the safety population (HR 0.709) whereas the AG's analysis was based on the ITT population (HR 0.75). Roche maintain that the safety population is the relevant population to consider in the analysis since this represents the population that actually received at least one dose of the study drug. AVOREN was a double-blinded trial and therefore the reason for a patient not receiving drug would not be related to which arm they had been randomised to. Additionally there is no incremental cost prior to the first dose between the two arms so the likelihood of patients not receiving treatment post randomisation is irrelevant. Hence patients that did not receive the study drug do not contribute to informing the decision problem and merely dilute the average costs and outcomes of the patients that did receive the study drug.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Roche Products	None of the analyses undertaken however account for the confounding effects of second-line treatments. This has previously been summarised in a publication by Tappenden et al *"The central difficulty in interpreting overall survival data from many existing cancer trials concerns the number of patients who crossover to alternative therapies following disease progression or treatment failure."…. "The implication for clinical effectiveness is that outcomes observed within the comparator treatment group may be exaggerated, leading to the underestimation of the incremental treatment benefit, whilst the implication for cost-effectiveness analyses is that the cost of achieving such benefits within the comparator arm will also be underestimated if these are omitted from the model."* (Methodological issues in the economic analysis of cancer treatments, Tappenden 2006) Roche attempted to address the confounding factor of second-line treatments by including the cost of these treatments in our submission, as observed within the AVOREN trial.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'

Consultee	Comment	Response
Roche Products	However PenTAG noted in their response to comments on the AG report *"that whilst the published paper includes the statement that "Other neoplastic agents were allowed subsequent to progression or toxicity", we are unaware of any published evidence to suggest that TKIs or temsirolimus were used as second line therapies. We were therefore unable to adjust the IFN baseline overall survival data to reflect the use of second line treatment options."* Roche interpret PenTag's comments to suggest that if they had had access to the patient level data from the AVOREN trial then they would have attempted to adjust overall survival for second-line therapies. This represents an alternative and credible method of adjusting for the confounding effect of second line therapy. Roche agree that AVOREN, being a multinational trial, does not fully reflect the decision problem in this appraisal and that adjusting for second-line therapies would therefore represent a more fit for purpose analysis.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Roche Products	Re-analysis of the AVOREN trial adjusting for second-line therapies by censoring patients that received novel treatments second-line (bevacizumab, sunitinib and sorafenib), results in an overall survival hazard ratio for bevacizumab of 0.613 (C.I.: 0.464; 0.811) stratified by Motzer score and region and 0.605 (CI: 0.459; 0.796) un-stratified.	Comment noted. See detailed response above.
Roche Products	There is an inevitable trade off between maintaining randomisation of the resulting cohort versus how well it represents the decision problem of interest. The validity of the revised hazard ratio relies on the assumption that the characteristics of the censored patients are balanced between the arms and are representative of the patient population as a whole. It can be seen from Table 1 below that the baseline characteristics of the censored patients are broadly similar to the ITT population except possibly with regards to Motzer score. The hazard ratio stratified by Motzer score and region takes into account any imbalance between the arms relating to Motzer score and therefore is the most applicable estimate to use. *Table not reproduced here.*	Comment noted. See detailed response above.
Roche Products	Second-line treatments reported in Roche's original submission were based on a table in the AVOREN clinical study report entitled "Summary of subsequent antineoplastic therapy started after disease progression by trial treatment". In the course of estimating a revised hazard ratio it was discovered that this post-progression treatment table does not include any bevacizumab administered post-progression (off licence second-line use) in the bevacizumab+IFN arm. This was because any treatment with bevacizumab had been started prior to disease progression and did not meet the definition of treatments within this specific table. This has been corrected in the re-analysis so that all second-line novel agents are censored.	Comment noted. See detailed response above.

Consultee	Comment	Response
Roche Products	Roche therefore requests that any analysis relating to bevacizumab should now use the overall survival hazard ratio of 0.613 as we believe this best reflects the treatment benefit of bevacizumab within its UK licensed indication, compared with a scenario and consequent outcomes where it is not made available (i.e, the decision problem of interest).	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Roche Products	Analysis utilizing the ITT hazard ratio would in effect be modeling the outcomes of bevacizumab followed by a bundle of other novel agents (many off license and unlikely to be prescribed within the UK NHS) compared to IFN followed by a bundle of novel agents.	Comment noted. See detailed response above.
Roche Products	**B) Average cumulative dose administered per patient** For patients who received bevacizumab there is presently a discrepancy between the cumulative dose recorded in the AVOREN trial and that estimated by the AG. This results in a cost difference between the two models of £12,535 (and an approximate difference in the ICER we estimate of approximately £47,000).	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Roche Products	Roche used the actual mean cumulative dose as observed in the AVOREN trial to calculate drug acquisition cost. We consider this the optimal method of calculating drug acquisition costs as it is a precise reflection of drug consumption that resulted in the health benefits observed in the trial.	Comment noted. See detailed response above.
Roche Products	The AG used an estimated average cumulative dose based on the assumption of treatment until progression and an average dose intensity taken from the Escudier *et al* 2007 paper. As can be seen in Table 2 below, the AG have also overestimated the treatment duration of first-line bevacizumab by approximately 70% and hence the drug acquisition cost is also vastly overestimated. Table not reproduced here.	Comment noted. See detailed response above.
Roche Products	Roche would like to request that a re-analysis of the economic model is performed for bevacizumab to include the costs based on the average cumulative dose as observed in the AVOREN trial itself. (We note that the clinical outcomes of bevacizumab at the dose assumed by the AG are unknown).	Comment noted. See detailed response above.

Consultee	Comment	Response
Roche Products	**C) Administration costs (number of administrations)** As per point B above regarding the assumed dose administered, the AG assumed treatment until progression at the per protocol treatment frequency when estimating the number of administrations provided.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Roche Products	The number of administrations of IFN and bevacizumab as observed in the AVOREN trial were considerably less than those estimated by the AG as the average treatment duration was only 7.36 months compared to 12 months assumed by the AG. Additionally on average, bevacizumab administrations actually occurred every 16.5 days as opposed to the per protocol cycle length of every 14 days, further contributing to the present overestimate.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Roche Products	Roche would like to request that a re-analysis of the economic model is performed for bevacizumab to include the costs based on the actual number of administration observed in the pivotal trial.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'

Consultee	Comment	Response
Roche Products	**D) Administration costs (cost per administration)** The administration of bevacizumab is more rapid than for chemotherapy regimens and as such applying the cost of an average chemotherapy administration (£189 in 2006/7 reference costs (HRG code SB15Z), uprated to £197 for 2007/8 by the Assessment Group) places an inappropriately high cost on the administration of bevacizumab. Roche suggests that it would be more appropriate to consider the lower interquartile range figure for the relevant reference cost (£95 in 2006/7 reference costs, uprated to £98 for 2007/8). This is appropriate given the average administration time of bevacizumab of approximately 30 minutes (from the second administration) compared to commonly administered agents such as irinotecan, leucovorin, and other combination therapies which take an average of two hours to infuse (see relevant Summaries of Product Characteristics). Applying this more appropriate administration cost would further reduce the treatment cost of bevacizumab + IFN whilst ignoring this we believe biases the results against bevacizumab + IFN.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Roche Products	**Conclusion** Roche believes that the cumulative impact of all of these model parameter refinements upon the final ICER of bevacizumab is highly significant. However, it has not been possible for us to estimate a revised ICER ourselves as we only have access to the "read-only" version of the AG's Economic Model which has limited our ability to understand the impact of these changes and to respond fully to this consultation.	Comment noted. See detailed response above.
Roche Products	We would therefore like to request that the AG's economic model is re-run with our proposed revised assumptions and that the results are shared in a fully transparent manner, along with details of all of the final assumptions relied upon by the Committee in determining a revised base case ICER which can subsequently be used as the basis for continued engagement and dialogue going forwards.	Comment noted. See detailed response above.
Roche Products	**2 WHETHER YOU CONSIDER THAT THE SUMMARIES OF CLINICAL AND COST EFFECTIVENESS ARE REASONABLE INTERPRETATIONS OF THE EVIDENCE AND THAT THE PRELIMINARY VIEWS ON THE RESOURCE IMPACT AND IMPLICATIONS FOR THE NHS ARE APPROPRIATE** Please refer to our response to question 1 above.	See detailed response above.

Consultee	Comment	Response
Roche Products	**3 WHETHER YOU CONSIDER THAT THE PROVISIONAL RECOMMENDATIONS OF THE APPRAISAL COMMITTEE ARE SOUND AND CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS** Roche would like to request that the issues raised in response to question 1 are addressed by the Appraisal Committee and appropriate changes incorporated into a re-analysis of the baseline ICER of bevacizumab which is shared transparently with stakeholders.	Comment noted. This additional analysis was conducted by the Decision Support Unit (DSU) in time for the second appraisal Committee meeting and was considered fully by the Committee. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
Roche Products	Roche would also like to point out that for this particular appraisal of bevacizumab in renal cell cancer we believe that other relevant factors (such as those listed in Section 6 of the revised Guide to Methods) should be explicitly taken into account by the Appraisal Committee. These factors include "severity of disease" and the "degree of clinical need of patients with the disease". We would like to request that the position of the Appraisal Committee is made clear and transparent in relation to whether and how these factors have been considered when interpreting the final ICER for bevacizumab.	Comment noted. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations.
Roche Products	**4 ARE THERE ANY EQUALITY RELATED ISSUES THAT NEED SPECIAL CONSIDERATION THAT ARE NOT COVERED IN THE ACD?** We believe there are none.	Comment noted. No actions requested.
WYETH	Wyeth has reviewed the Appraisal Consultation Document (ACD) for the above appraisal and is extremely dismayed by its conclusion that Torisel (temsirolimus) should not be made available to patients with advanced renal cell carcinoma (aRCC) on the basis that it would not be a cost-effective use of NHS resources. The conclusion of the ACD has been reached despite the unequivocal evidence demonstrating the clinical effectiveness of Torisel and the Appraisal Committee's own acknowledgement of the significant clinical benefits this drug has to offer patients with aRCC. Wyeth believes that denying this group of patients access to the real and measurable benefits of Torisel in extending survival is unconscionable. It is a devastating and cruel blow to patients and their families.	Comments noted. See detailed responses below.

Consultee	Comment	Response
WYETH	It is Wyeth's opinion that this preliminary recommendation is fundamentally misguided on two counts: • Firstly, as an ultra-orphan drug, Torisel, has been subject to an inappropriate appraisal methodology. • Secondly, critical feedback submitted by Wyeth in response to NICE's earlier assessment report has largely been ignored. As a consequence Wyeth does not consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.	Comment noted. See detailed responses below.
WYETH	**Inappropriate appraisal methodology** We remain extremely concerned that this appraisal has been carried out in the absence of any clear NICE framework for appraising ultra-orphan drugs and identifying what the appropriate decision rules should be. Wyeth first raised these concerns when originally notified of NICE's intention to include Torisel in this appraisal and indicated that it would not be appropriate to appraise the drug through the institute's existing process.	Comment noted. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness.

Consultee	Comment	Response
WYETH	NICE itself has previously acknowledged that ultra-orphan drugs present special difficulties for appraisers and has highlighted the need to identify an appropriate appraisal methodology. The majority of the institute's Citizens Council members came to a conclusion that it is sometimes, or always, justified for the NHS to pay premium prices for ultra-orphan drugs[2]. To this end, NICE has even indicated that "at current prices, indicative ICERs for ultra-orphan products are in the range of £200,000 to £300,000 per QALY (i.e. a ten-fold increase on the decision rules currently applied in conventional appraisals)"[3]. Nevertheless, despite this recognition, temsirolimus has still been appraised subject to NICE's standard cost-effectiveness measures. Yet, despite the lack of appropriate appraisal methodology, Torisel has remained in scope. Unsurprisingly, Torisel has failed to meet NICE standard cost-effectiveness threshold	Comment noted. See above.
WYETH	By applying its standard appraisal criteria, NICE has produced an ACD that, if implemented, will seriously disadvantage and discriminate against a small and vulnerable group of patients, i.e. aRCC patients with the poorest prognosis. Contrary to the spirit and aspirations of the NHS, NICE will have succeeded at denying a group of patients with the greatest clinical need potentially life-extending treatment.	Comment noted. See above.
WYETH	The underlying fallacy of this approach is demonstrated by the fact that, as an ultra-orphan drug, temsirolimus would have a very limited impact on the overall NHS budget. Annually, approximately 390 patients with newly diagnosed poor prognosis aRCC in England and Wales are eligible for treatment at an additional £22,000 lifetime cost (from the PenTAG model). The total cost of providing all of these patients with Torisel treatment would thus amount to an additional £8.6 million per annum, which needs to be seen within the context of an annual NHS budget for England of over £100 billion per year[4]. However, not all patients would be suitable for such a treatment, thus the actual NHS spending could be considerably lower.	Comment noted. See above.
WYETH	The total potential patient population for current and future indications for temsirolimus is anticipated to be less than 1,000 patients in the UK. Concessions within the regulatory approval process for orphan drugs adopted by government agencies are in recognition of the economic difficulties associated with the development of treatments for rare conditions. The failure to take into account such factors during health technology appraisal creates a disconnect between the development and utilisation of such products.	Comment noted. See above.

2 NICE Citizens Council Report – Ultra Orphan Drugs. Available at: http://www.nice.org.uk/niceMedia/pdf/Citizens_Council_Ultraorphan.pdf
3 National Institute for Health and Clinical Excellence. Appraising Orphan Drugs. Available at: http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf; Accessed on 26 August 2008.
4 Department of Health. Departmental report 2008. The Stationery Office, London 2008.

Consultee	Comment	Response
WYETH	**Data from subgroup analyses** Wyeth is also concerned that critical feedback we submitted in relation to the assessment report has not been dealt with appropriately and as a consequence the summary of the cost effectiveness of temsirolimus is not a reasonable interpretation of the evidence.	Comment noted. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations.
WYETH	We are particularly concerned that issues relating to the interpretation of data from subgroup analyses have not been given sufficient attention and have only been addressed superficially. Furthermore, the results of the PenTAG cost-effectiveness analysis of temsirolimus in clear and non-clear cell RCC patients demonstrated inherent errors, casting serious doubts over the robustness of their modelling approach across all populations analysed. Please see the Appendix for further details.	Comment noted. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations.
WYETH	We believe that the Appraisal Committee should have been provided with the best available evidence. Instead, it appears that the Appraisal Committee relied on secondary data sources thus our original data have been compromised. As a result, the ICER for the temsirolimus treatment of aRCC patients with non-clear cell histology has been overestimated. This is especially disappointing since this subgroup of patients is especially disadvantaged as interferon is less effective in this subgroup compared to other patients with clear cell histology RCC. In particular, it should be noted that trials of other new treatments have excluded this subgroup of patients.	Comment noted. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations.
WYETH	**Moving ahead** It is Wyeth's view that NICE should be seeking to put in place appropriate methodologies to appraise ultra-orphan (and orphan) drugs on a fair and equitable basis. To that end, Wyeth would very much welcome the opportunity for Torisel to be used to test the integrity and robustness of any such methodologies NICE is considering for appraising ultra-orphan drugs. As a company, we would welcome the opportunity to work constructively with NICE to facilitate this process.	Comment noted. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness.

Consultee	Comment	Response
WYETH	Wyeth UK has already submitted detailed comments on the Assessment Report. This example focuses on the ability of the different models to replicate the duration of therapy seen empirically in the clinical trial and the impact this has on the estimates of disease progression, overall costs and thus the ICERs generated.	Comment noted. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations.
WYETH	In the subgroup analysis for patients with non-clear cell RCC, the PenTAG model predicts a duration of treatment on IFN of 4.6 months and on temsirolimus of 22 months (Table 1). In comparison to the observed empirical data from the Phase III study, the PenTAG model's predictions are an overestimation of the observed duration of treatment. In the IFN arm this overestimation is by a factor of 2.1 and in the temsirolimus arm the overestimation is by a factor of 3.6. Thus, though the PenTAG model is over estimating treatment duration in both arms it is doing so at a higher rate in the temsirolimus arm. In comparison, the Wyeth model predictions are more in line with the empirical data and the magnitude of the difference is similar in the two arms. *Table included, but not reproduced here*.	Comment noted. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations.
WYETH	We ran the Wyeth model to analyse the base case using the same assumptions as the PenTAG analysis: - IFN self-injection rates: 75% self-injecting; - same drug unit costs; - same drug administration costs. Not surprisingly, the greater PenTAG estimates of treatment duration (Table 1) resulted in greater drug and drug administration costs – see Table 2. The IFN drug costs were 2.4 times greater than the Wyeth estimates, while the temsirolimus drug costs estimated by the PenTAG model were 3 times the corresponding cost prediction of the Wyeth model. *Table included, but not reproduced here*. The base case ICER dropped from £133,848 to £80,681 for the non-clear cell sub-group in the Wyeth model. However, the overestimated treatment durations and costs of the PenTAG model resulted in an ICER which is higher than the base case analysis. (Table 3). *Table included, but not reproduced here*.	Comment noted. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations.

Consultee	Comment	Response
WYETH	Wyeth has not been given access to an executable version of the PenTAG model and therefore is not in a position to ascertain the impact of the PenTAG estimated Weibull parameters as well as the other assumptions made on the disease progression and treatment duration being modelled. But it appears that for the non-clear cell sub-group the overall ICER might be much lower than the current PenTAG estimate of £102,457. There are two important messages from this comparison: 1. The sub-group analysis illustrates that the PenTAG model appears to be flawed and the outputs are inaccurate. This could apply more widely than just to the example cited here. The PenTAG model should be revised and the updated results used to inform the recommendation in the FAD. 2. The current practice of providing non-executable models to manufacturers hinders the ability to comment fully on the appraisal process as it does not allow for testing the robustness of models.	Comment noted. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations.
WYETH	3.4.1 4th bullet should read serum lactate dehydrogenase	Comment noted. This has been amended in the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
WYETH	4.1.11 Errors in the following data points, identified and corrected by Wyeth in response to the Assessment Report, have been transcribed into the ACD: OS data, no prior nephrectomy HR 0.61 (not 0.62), 95% CI 0.41 to 0.91 (not 0.42 to 0.93) OS data, prior nephrectomy 95% CI 0.63 to 1.11 (not 0.65 to 1.12) OS data, clear cell carcinoma 95% CI 0.64 to 1.08 (not 0.64 to 0.1.06) It is not clear whether the erroneous values were used in the PenTAG model	Comment noted. This has been amended in the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
WYETH	4.1.12 It is stated that no statistical analysis was reported for interim analysis PFS. However this analysis was provided to NICE at the time of our response to the Assessment Report.	Comment noted. This will be taken into account in the next document for 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' produced by NICE

Consultee	Comment	Response
WYETH	4.2.6 Suspect title above should be 'First-line treatment for people unsuitable for Immunotherapy'	Comment noted. This has been amended in the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'
British Uro-oncology Group	The British Uro-oncology Group (BUG) welcomes the opportunity to reply to this Appraisal consultation document (ACD) for bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma (RCC). The following comments are collated from the responses from individual members of BUG and do not necessarily reflect the opinions of all BUG members. We have retained the wording of responses from individual members, as this reflects in some instances very strong feelings about certain aspects of the document.	Comment noted.
British Uro-oncology Group	BUG would like to thank the NICE Panel for producing this document and inviting our response. The **Appraisal Committee's preliminary recommendations** as outlined in section **1** have caused concern and have been highlighted by our members. The refusal of sunitinib in particular, in treatment naïve patients has generated the most comment and this is detailed in our response. *Bevacizumab, sorafenib, sunitinib and temsirolimus are not recommended as treatment options for advanced and/or metastatic renal cell carcinoma.* *People currently receiving bevacizumab, sorafenib, sunitinib and temsirolimus should have the option to continue therapy until they and their clinicians consider it appropriate to stop.* These recommendations and our subsequent observations are discussed below in the relevant sections. We then specifically address the questions of consideration of the relevant evidence, summaries of clinical and cost effectiveness and whether or not the recommendations of the appraisal committee are sound or not in our concluding remarks.	Comment noted. See detailed responses below.

Consultee	Comment	Response
British Uro-oncology Group	**Clinical need and practice** **2.1-3** *Renal cell carcinoma (RCC) is a type of kidney cancer that usually originates in the lining of the tubules of the kidney and contains many blood vessels. RCC accounts for 90% of kidney cancers and approximately 3% of all adult cancers. In England and Wales, kidney cancer is the 8th most common cancer in men and the 14th most common in women. In 2004, there were 5745 cases of newly diagnosed kidney cancer registered in England and Wales. The incidence of kidney cancer begins to rise after the age of 40 and is highest in people older than 65. In England and Wales the estimated overall 5-year survival rate for RCC is 44%, but there are large differences according to the stage of disease at the time of diagnosis. The worldwide incidence of kidney cancer among both men and women has been rising steadily since the 1970s.* *The American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system is used to grade RCC into stages I to IV. Advanced RCC, in which the tumour is either locally advanced and/or has spread to regional lymph nodes, is generally defined as stage III. Metastatic RCC, in which the tumour has spread beyond the lymph nodes to other parts of the body, is generally defined as stage IV.* *In 2006, of people presenting with RCC in England and Wales for whom staging information was available, an estimated 26% and 17% had stage III and stage IV disease, respectively. About half of those who have curative resection for earlier stages of the disease also go on to develop advanced and/or metastatic disease. The prognosis following a diagnosis of advanced and/or metastatic RCC is poor. The 5-year survival rate for metastatic RCC is approximately 10%.* We agree it is imperative to emphasise the clinical setting of RCC in terms of its relative rarity, but rising incidence. It is seen that the majority of patients present with early disease (of whom around half are cured by surgery), so the actual numbers with advanced tumours in England and Wales, in particular metastatic disease is around only 1500 patients. Neither are all these suitable for further treatment so the actual numbers being considered for systemic therapy are going to be low indeed. This is truly a rare cancer, and needs to be considered as such.	Comment noted.

Consultee	Comment	Response
British Uro-oncology Group	**2.4** *There are currently no treatments that reliably cure advanced and/or metastatic RCC. The primary objectives of medical intervention are relief of physical symptoms and maintenance of function. Metastatic RCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy. People with advanced and/or metastatic RCC are usually treated with either interferon alfa-2a (IFN-α) or interleukin-2 immunotherapy or a combination of IFN-α and interleukin-2. IFN-α (Roferon-A, Roche Products) is the most commonly used immunotherapy in England and Wales and has UK marketing authorisation for treatment for people with advanced RCC. For those people receiving immunotherapies for the treatment of advanced RCC it is suggested that, on average, median survival is increased by 3.8 months compared with those receiving control treatments. Commonly experienced adverse effects of IFN-α include flu-like symptoms, tiredness and depression. There is no standard treatment for people with advanced and/or metastatic RCC whose condition does not respond to first-line immunotherapy, or for people who are unsuitable for immunotherapy.* It is stated that there are currently no treatments that reliably cure advanced and/or metastatic RCC, and that metastatic RCC is largely resistant to chemotherapy, radiotherapy and hormone manipulation. Interferon has a response rate of 10-15%, significant toxicity with at best modest improvements in survival. There has therefore never been a clearer need demonstrated for alternative strategies to treat this disease.	Comment noted.
British Uro-oncology Group	**The technologies** **Sunitinib 3.3.3** *Sunitinib is administered orally. The recommended dosage is 50 mg once daily for four consecutive weeks with a 2-week rest period (that is, a complete treatment cycle of 6 weeks). The price for a pack of 50-mg capsules (30 capsules per pack) is £3363.00 (excluding VAT; BNF edition 55). The average daily cost of sunitinib is £74.74, with an average 6-week cycle costing £3139. Costs may vary in different settings because of negotiated procurement discounts.* The pack is now a pack of 28 and the cost is correspondingly altered. There is, however, a nationally available scheme for making the first cycle available free of charge, and a 5% reduction in pack price (30 capsules) applied from 8th May 2007. This affects cost effectiveness and was fundamental in facilitating agreement of the PCTs in the north east of England to fund sunitinib, the first network to do so, prior to NICE.	Comment noted. The patient access scheme, whereby the first cycle of sunitinib is free to the NHS, was confirmed in time for the second Committee meeting by the Department of Health and incorporated into the analyses and considered fully by the Committee. See FAD section 3.1.3.

Consultee	Comment	Response
British Uro-oncology Group	**Summary of clinical effectiveness 4.1.23** *The Assessment Group concluded from a summary of the data on the clinical effectiveness of first-line treatments for people who are suitable for immunotherapy, that both bevacizumab plus IFN-α and sunitinib as monotherapy appear to have significant benefits compared with IFN-α alone in terms of progression-free survival and tumour response. Although promising, data on overall survival are in general immature. For people with poor prognosis, temsirolimus appears to have significant benefits compared with IFN-α in terms of overall survival, progression-free survival and tumour response rate. There is some evidence to suggest that temsirolimus may have a greater effect on people who have non-clear cell carcinoma and who have not undergone nephrectomy. The frequency of adverse events associated with the first-line treatments is comparable to that associated with IFN-α monotherapy, but the adverse event profiles differ between treatments.* There were data presented at ASCO (albeit a sub group analysis with crossover patients censored) which DID show a survival (OS) advantage for patients on sunitinib vs. interferon, which was statistically significant at 26 vs. 20 months. We express concern that given the timescale of the review that the group published their report before ASCO 2008, or at least undertook their literature search before this. We feel it is incorrect to describe these data as immature as the data is now relatively mature.	Comment noted. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.
British Uro-oncology Group	**Evidence and interpretation** **Cost effectiveness 4.2.1** *No published studies of the cost effectiveness of bevacizumab, sorafenib, sunitinib or temsirolimus were identified. The manufacturers of each of the drugs submitted cost-effectiveness models and the Assessment Group developed a model for each treatment question.* There was a poster at ASCO 2007 (#6607) covering sunitinib vs. interferon which included utility values.	Comment noted. This poster and utility data were identified by the Assessment Group as part of their review of the literature. The Assessment Group highlight that these data have no formal published foundation and also note the paucity of evidence on utility values for people with advanced and/or metastatic RCC and performed sensitivity analyses pertaining to this. See the assessment report p142. The Committee also considered the effect of the sensitivity analyses, see FAD section 4.3.10.

Consultee	Comment	Response
British Uro-oncology Group	**Updated data from Pfizer 4.3.2** *The median overall survival in the final ITT population was no longer significantly different for those who received sunitinib (26.4 months) compared with those who received IFN-α (21.8 months, HR 0.821, 95% CI 0.673 to 1.001, p = 0.0510). The median overall survival in the final ITT population that was censored for crossover did show a statistically significant benefit for those who received sunitinib (26.4 months) compared with those who received IFN-α (20.0 months, HR 0.808, 95% CI 0.661 to 0.987, p = 0.0362). The median overall survival was statistically significantly higher in those who received sunitinib and did not receive any post-study treatment (28.1 months) than those who received IFN-α (14.1 months, HR 0.647, 95% CI 0.483 to 0.870, p = 0.0033).* Clearly all the relevant evidence has not been taken into account. In particular the insistence on overall survival as an end point despite the crossover design, and the then dismissal of the post hoc OS analysis showing 14 vs. 28 month survival in patients who received no further treatment. It should also be noted that progression free survival (11 vs. 5 months, p<0.000001) was the primary end point of this study, an appropriate end point in clinical trials evaluating the treatment of metastatic malignant disease where overall survival is ultimately affected by subsequent treatments. Indeed in this study patients crossed over in February 2006 when the primary end point had clearly been met. PFS as a relevant end point has been recognised previously by NICE.	Comment noted. The Committee understood that there had been both crossover after disease progression, but also participants had had second-line treatment after the study had ended. This could be expected to exaggerate overall survival estimates for people in the UK receiving IFN-α in the future, as the Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.

Consultee	Comment	Response
British Uro-oncology Group	**Consideration of the evidence 4.4.6** *The Committee then considered the estimates of cost effectiveness of sunitinib provided by the manufacturer and the Assessment Group. The Committee noted that the adjustments made to the survival curves by the Assessment Group and their different costing assumptions resulted in a larger ICER than that originally presented by the manufacturer (£71,500 per QALY gained compared with £28,500 per QALY gained, respectively). However, the Assessment Group's estimate was not larger than the updated baseline estimates of cost effectiveness provided by the manufacturer, despite the manufacturer's assumption of a free initial dose of sunitinib. The Committee did not consider that the estimate of cost effectiveness derived from the post-hoc subgroup that received no post-study treatments in the sunitinib trial could be considered a robust basis for decision-making as the estimates had not been critiqued by the Assessment Group and no details about the post-hoc subgroup were provided. Therefore the Committee concluded that sunitinib as first-line treatment for people with advanced and/or metastatic RCC would not be a cost-effective use of NHS resources.* The Evidence review group criticised the immaturity of the data, but when more mature data is available the Evidence Review Group does not appear to have been asked to review it.	Comment noted. Updated evidence was submitted by the manufacturer of sunitinib in time for the second appraisal Committee meeting. This was incorporated into the analyses by the Assessment Group and Decision Support Unit and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.

Consultee	Comment	Response
British Uro-oncology Group	**4.4.18** *Having concluded that bevacizumab, sorafenib, sunitinib and temsirolimus were not cost effective, within their licensed indications for the treatment of RCC, the Committee considered the pricing strategies for bevacizumab and sunitinib proposed by the manufacturers, which include a 'dose cap' scheme and a free first cycle of drug treatment, respectively. The Committee was aware that these pricing strategies had not been considered by the Department of Health to establish whether the proposed discounts are nationally available and how long they will be in place.* It is our understanding is that the 1st cycle scheme is DH approved, available across the whole of the UK and has no end date. This clearly needs clarification as it is integral to the costs incurred. *Sensitivity analyses of the Assessment Group's model taking these pricing strategies into account reduced the ICERs for bevacizumab plus IFN-α to £91,000 per QALY gained and for sunitinib to £57,700 per QALY gained, the latter without taking into account the late data on survival from Pfizer. Therefore, the costs per QALY gained still remained above the levels considered compatible with the best use of NHS resources. The Committee concluded that the use of bevacizumab plus IFN-α and sunitinib as first-line treatments for advanced and/or metastatic RCC, irrespective of the proposed pricing strategies, would still not be a cost-effective use of NHS resources. The Committee suggested that any revised or new pricing strategies, put forward to the Department of Health by the manufacturers, which could result in the use of these drugs being a cost-effective use of NHS resources, would be considered.* In this context it must be stated that this patient group included cross over - therefore the sub group analysis must be taken into account – or the costs of the sunitinib in the crossing over patients must be allowed for. The dose intensity and discontinuations after the first cycle must also be considered in this setting.	Comment noted. The patient access scheme, whereby the first cycle of sunitinib is free to the NHS, was agreed in time for the second Committee meeting by the Department of Health and incorporated into the analyses and considered fully by the Committee. See FAD section 3.1.3. The Committee understood that there had been both crossover after disease progression, but also participants had had second-line treatment after the study had ended. This could be expected to exaggerate overall survival estimates for people in the UK receiving IFN-α in the future, as the Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.

Consultee	Comment	Response
British Uro-oncology Group	We at BUG understand that the Appraisal Committee is interested in receiving comments on the ACD under the following general headings: **Do you consider that all of the relevant evidence has been taken into account?** The ACD has discounted the sunitinib survival data presented at ASCO 2008 in which patients receiving 2nd line therapies were censored. We understand the committee's requirement for more detail on these data so that it can be accurately appraised, but we believe it would be against the interests of patients for a final recommendation to be published without these data being taken into account. A 14 month improvement on overall survival would have a major impact on the cost-effectiveness calculations. We would urge the Committee not to produce a final recommendation without these data being fully appraised. If an extra few weeks are required for the Committee to obtain the evidence it requires from the sponsoring company this would be time well spent. We believe that the risk of not including these data when they are already in the public domain and for the data only to be appraised at the next planned assessment in 2011, would be for clinicians and patients to lose all confidence that NICE was performing assessments based upon the most relevant data.	The Committee understood that there had been both crossover after disease progression, but also participants had had second-line treatment after the study had ended. This could be expected to exaggerate overall survival estimates for people in the UK receiving IFN-α in the future, as the Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.
British Uro-oncology Group	The ACD also appears to make no reference to the views of the clinical or patient experts that were submitted and this should be addressed.	Comment noted. The Committee considered the views of the clinical and patient experts that were submitted. See the FAD sections 4.3.1, 4.3.2, 4.3.3 and 4.3.11.
British Uro-oncology Group	We do not consider that the assessment took all relevant data into account, specifically the recently announced overall survival data in the sunitinib vs.interferon trial which was 26 vs. 22 months, 20 months if crossover excluded (p=0.0362 Log- rank, 0.0081 Wilcoxon). Median overall survival was 28.1 vs. 14.1 months p=0.033. (#5024 ASCO 2008) as indicated above in patients who did not receive any post study treatment.	Comment noted. See detailed responses above.

Consultee	Comment	Response
British Uro-oncology Group	We do not consider that the treatment of interferon as the comparator for all groups of patients with metastatic RCC was defensible since we know that it is not appropriate for most patients with the disease.	Comment noted. The appraisal was carried out within the context of the original scope agreed at the scoping workshop. The appraisal considered best supportive care as the comparator for people for whom immunotherapy is inappropriate.
British Uro-oncology Group	Furthermore, the assessment of quality adjusted life was particularly inadequate in a disease like RCC with such variable outcomes. The ACD assumes that clinicians had no ability to select the appropriate treatment for individual patients.	Comment noted. The Committee has a strong preference for expressing health gains in terms of QALYs. However, additional (non-reference case) analyses may be submitted where patients' health-related quality of life has not been adequately captured. See Guide to the Methods of technology appraisal, section 5.5.4. The Assessment Group also highlighted the paucity of evidence on utility values for people with advanced and/or metastatic RCC and performed sensitivity analyses pertaining to this. See the assessment report p142. The Committee also considered the effect of the sensitivity analyses on the 'no-post study treatment group'. See the FAD section 4.3.10.

Consultee	Comment	Response
British Uro-oncology Group	**Are there any equality issues that may need special consideration?** We do not feel equality issues have been addressed. Many colleagues made the point that almost all other cancers are treated by many therapeutic modalities, often multiple lines of therapy, together costing far more than a single option available to renal cancer patients - with the availability of new agents in the rest of Europe and USA and the proposed veto of ANY effective agent in kidney in the UK. Perhaps it can be argued that the QALY calculation should not be about "one drug" but total costs for a cancer type (comparison could be made with the modest response of HERCEPTIN in metastatic breast cancer e.g.) vs. cost over the course of a disease, drawing out the "orphan" drug status of these compounds and the lack of expenditure on lines of chemo and radical treatment options for RCC in particular. The appraisal states the drugs are better tolerated than IFN (except B+IFN obviously), work better than IFN and almost certainly have both a PFS and OS advantage, suggesting this is a purely financial decision and can only be contested on the basis of equality for patients in comparison with other cancers.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13.
British Uro-oncology Group	Other colleagues also voiced concerns about co payment, which is currently under review, with disquiet about the parallel time lines for these.	Comment noted.
British Uro-oncology Group	The provisional recommendations of the committee are inherently unsound. If issued as final guidance the result will be that patients are denied access to drugs which provide significant clinical benefit on the basis of an appraisal using incomplete data within an inappropriate technology.	Comment noted. See detailed responses above.
British Uro-oncology Group	We therefore do not consider that the provisional recommendations of the Appraisal Committee constitute a suitable basis for the preparation of guidance to the NHS. It is recognized that some PCTs already funding these drugs will continue to allow their use in these regions, but there is concern that if this assessment is confirmed the majority of PCTs will indeed deny treatment to patients with this disease. A number of colleagues believe interferon to be inappropriate for the majority of patients. There are serious concerns that NICE will mandate the use of ineffective, toxic, but cheaper interferon. It would be better if they said that most patients should be denied all treatment except palliative care.	Comment noted. See detailed responses above.

Consultee	Comment	Response
British Uro-oncology Group	Patients should expect that guidance to the NHS should be of the highest possible quality. Without such standards, NHS cancer care will inevitably be significantly worse than that provided by health systems in other countries with similar economies and the aspiration for cancer death rates in the UK not to be worse than that seen in other European countries will never be met.	Comment noted. See detailed responses above.
Cancer Research UK	**Summary** Cancer Research UK welcomes the opportunity to respond to this consultation. We are very disappointed with NICE's decision to reject these four kidney cancer drugs. We have outlined our major concerns in more detail below, briefly that: • NICE's appraisal process is not appropriate for all types of cancer drugs; • NICE needs to consider how it can reconcile making recommendations so clearly at odds with current clinical opinion; • these decisions from NICE impact on the public's trust in the NHS and are a potential future threat to medical research in the UK.	Comment noted. See detailed responses for each point below.
Cancer Research UK	We also asked the public to share their views on this decision with us. We believe that it is time now for a government-led public debate about how the NHS is funding treatment and how it can best serve patients' needs now and into the future. Failure to engage with the public could have serious consequences in terms of our ability to raise money and fund research within the UK in the future.	Comment noted.
Cancer Research UK	**Our position** We are disappointed at NICE's view that although these drugs are clinically effective, their high price means that they are not considered to be value for money for the NHS. These drugs have shown a small but definite improvement in an illness where there are few alternative treatments. If this decision stands it will be very frustrating for cancer patients and their clinicians.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus. See the FAD section 1 for guidance relating to the first-line use of sunitinib as a life-extending, end-of-life treatment.

Consultee	Comment	Response
Cancer Research UK	This decision once again raises questions about whether NICE's system of appraisal is appropriate for all types of drugs. It is often difficult to get unequivocal research data in rarer cancers, such as metastatic kidney cancer, which have a small patient population. Although we understand that NICE often has to make difficult decisions, in this case there is a clear separation between what NICE finds to be a valuable treatment and clinical opinion. Action is needed to bring these two positions closer together.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.

Consultee	Comment	Response
Cancer Research UK	We believe that NICE needs to look at whether it is making appropriate allowances to compensate for the lack of uncontaminated large scale trials in these areas. However, we do accept that not all responsibility lies with NICE. We also need to look at the way that pharmaceutical companies are charging the NHS for drugs, and to ensure that further results are sought and that larger trials are carried out. If NICE is to do its job properly then we need to consider what responsibility it should be taking for both of these related issues.	Comment noted. The Committee understood that there had been both crossover after disease progression, but also participants had had second-line treatment after the study had ended. This could be expected to exaggerate overall survival estimates for people in the UK receiving IFN-α in the future, as the Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.

Consultee	Comment	Response
Cancer Research UK	**Specific concerns** The Appraisal Committee has asked us to respond to four specific questions: **i) Do you consider that all of the relevant evidence has been taken into account?** While we accept that all the relevant published data has been taken into account, we are concerned that NICE's methodology is not sufficiently flexible to provide recommendations based on the existing clinical evidence. Metastatic renal cell carcinoma is one of the less common cancers. This low prevalence limits the number of people available for entry into clinical trials. This small population pool is further complicated by the fact that in the majority of cases there are no other treatment options for this type of cancer. Interferon is not considered by clinical colleagues to be an effective alternative treatment for advanced metastatic renal cancer—and in fact is only suitable for use in 30% of patients, leaving 70% untreated.	Comment noted. See detailed responses above.
Cancer Research UK	**ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?** The combination of the above factors leads to significant limitations in the trials presented to NICE. We do not consider that this evidence, which has played a major part in NICE's decision not to recommend the drugs for use in the NHS, is a basis from which reasonable interpretations of cost-effectiveness can be drawn. Where patients were crossed-over from the control into the treatment arm estimations about overall survival cannot be extrapolated effectively enough to make them suitable for NICE's cost-effectiveness calculations. For this reason we think NICE should reconsider whether a more appropriate approach is needed in this situation.	Comment noted. See detailed responses above.

Consultee	Comment	Response
Cancer Research UK	We also understand that the National Cancer Research Institute Clinical Study Group (CSG) on renal cancer has some significant concerns about comparisons with interferon (IFN) in this appraisal. We support the CSGs request that QALY analyses within the appraisal are redone using more appropriate comparative data for IFN with expert oncology input. We also call on NICE to give more consideration to two concerns outlined to us by the CSG that: 1. comparisons with IFN in the appraisal are not appropriate, as data taken from the control arm of the bevacizumab plus IFN vs. IFN alone are considered to over-estimate the effectiveness of IFN and are not in line with clinical experience; 2. emerging results presented at the American Society of Clinical Oncology (ASCO) meeting in June this year, provide evidence that the benefit for interferon in the sunitinib vs. interferon trial was inappropriately enhanced by the high number of patients receiving active second line treatments.	Comment noted. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.
Cancer Research UK	*iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?* For the reasons given above, we do not consider the provisional recommendations sound or suitable for the preparation of guidance to the NHS. We take the council of the renal CSG that bevacizumab, sorafenib, sunitinib and temsirolimus should be recommended for use in metastatic renal cell carcinoma patients on the NHS. We know that the CSG does not make such recommendations lightly.	Comment noted. With regards to sunitinib (first-line) see detailed responses above. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.

Consultee	Comment	Response
Cancer Research UK	**iv) Are there any equality related issues that may need special consideration?** We strongly believe that the lack of a suitable alternative treatment for the majority of patients with metastatic renal cell carcinoma should mean that these patients in particular should not be denied treatments that have shown in trials to be clinically effective. The small patient population for this type of cancer also raises questions about equality, given the impact that this may have on the way these drugs are priced by the manufacturers under our current system of pricing—we think it unfair that these patients should be penalised because of this.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13.
Cancer Research UK	**General comments** As proponents of the NHS, we understand that the reality of having a publicly-funded healthcare system that provides treatments for all members of the population who need it free at the point of delivery often means making difficult choices about those treatments that should be included in the NHS package of care. And we think that NICE is well placed to inform these difficult decisions. NICE is well regarded globally, as a leader in the field of health technology assessment. NICE's methodology has developed over its lifetime to be responsive to the needs of society. However, we believe that cancer still challenges this methodology and that a more flexible approach needs to be developed to ensure that we continue to support innovation and give patients in the UK access to those drugs which we already see benefiting patients elsewhere in the world.	Comments noted. See above.
Cancer Research UK	We also welcome recent efforts by NICE to reach agreements with the pharmaceutical industry which has resulted in otherwise unapproved drugs becoming available on the NHS. We would welcome a greater role for NICE in agreeing appropriate prices for new medicines. If, in the course of the appraisals, NICE consider a drug to be cost-ineffective at the current price, they should also be able to calculate at what price the drug would become cost-effective. This could then form the basis of negotiation with the manufacturers. We do hope that NICE is taking every opportunity to negotiate with manufacturers aimed at similar resolution in the case of these four kidney cancer drugs.	Comments noted.

Consultee	Comment	Response
Cancer Research UK	What the public think Cancer Research UK received an significant response to our call for the public to share their views on this decision with us. Over 100 people submitted comments through our online science blog (http://scienceblog.cancerresearchuk.org) , to a prescribed email address, or alongside a Guardian online article (hhtp://www.guardian.co.uk/commentisfree/2008/aug/07/cancer.health) by Cancer Research UK's Chief Clinician, Professor Peter Johnson. The responses were not wholly surprising. However some salient points outlined below should be of concern to NICE, the Department of Health, politicians and those with a desire to see the science base in the UK continue to prosper.	Comments noted.
Cancer Research UK	<u>The need for public debate</u> It is clear that the public are bewildered by much of the current debate in the media about which drugs are available on the NHS, why, and how, these decisions are made. As expected with this sort of exercise, respondents were mostly unsupportive both of NICE's decision and the organisation as a whole. However, there is clearly sufficient understanding both of the need to manage the limited budget of the NHS and the role that the various stakeholders play in this process. More than ever we believe that it is both timely and essential that the Government, and NICE, engage the public in a debate about healthcare funding in the UK.	Comment noted.
Cancer Research UK	There was much comment about the following areas, in particular: 1. The role of NICE Respondents expressed anger towards NICE in respect of this recent decision. It is clear that many people are confused about the extent of NICE's influence and their responsibilities and how independent they are of Government control. People feel powerless and frustrated.	Comment noted.
Cancer Research UK	2. The cost of cancer drugs in the UK A number of respondents questioned why cancer drugs are too expensive to get through NICE's cost-effectiveness requirements. It appears that the public can't understand why the NHS doesn't have more negotiating power with the pharmaceutical companies. Many expressed the concern that the pharmaceutical companies are holding NICE to ransom.	Comment noted. The Committee is not able to make recommendations on the pricing of technologies to the NHS. See Guide to the methods of technology appraisal section 6.1.8.

Consultee	Comment	Response
Cancer Research UK	3. Funding for cancer drugs in the UK A clear message from the public is that they cannot understand why these cancer drugs are available and being successfully used in other European countries and not the UK. Reference was particularly made to those countries with a lower GDP, including new EU member states, and considered to be in a greater financial predicament than the UK. The ABPI estimate that UK per capita spending on cancer medicine currently stands at just 60% of the European average. The figures advise that, by 2006 rates, additional investment of £403m a year would be necessary for the UK to have parity with the existing average per capita expenditure on cancer medicines in 11 comparable countries. In addition uptake of innovation is slow, with major cancer medicines still being prescribed in the UK at under two-thirds of the European average, five years after licensing. Many respondents expressed strong opinions on how they considered the NHS should be better spending their money to ensure sufficient funding for cancer drugs.	Comment noted.
Cancer Research UK	<u>Loss of public support for medical research</u> The UK is in an enviable and unique position of having a public that is enthusiastically supportive of medical research. Every year people donate in their millions to medical research charities across the UK. Cancer Research UK alone has over 2 million regular givers. Last year we raised £420 million, mostly from individual donors. A report by the European Cancer Research Mangers Forum in 2006 found that public cancer research spend in Europe is evenly balanced between charitable and government organisations with 47% and 53% of spend, respectively. In comparison, USA government organisations are the dominant source of cancer research funding with 96% of all funds coming from ten federal funders. We were therefore very concerned that a significant majority of those submitting comments raised questions about the point of giving money to research when the resulting medicines were not being made available to patients in the NHS. Loss of public support, both financially and in terms of willingness to participate in research, could be very serious for UK science.	Comment noted.

Consultee	Comment	Response
Cancer Research UK	**Conclusion** We hope that NICE reconsiders its preliminary decision not to recommend bevacizumab, sorafenib, sunitinib and temsirolimus for use in metastatic renal cell carcinoma patients on the NHS. We also hope that NICE takes this opportunity to review whether its current process is suitable for all cancer drugs and how flexibility can be introduced into the appraisal process to ensure that patients can get access to drugs where they are likely to benefit. This appraisal also clearly raises some broader questions relating to whether patients in the UK are getting fair and equal access to new medicines on the NHS. We will also be sharing these thoughts with the Secretary of State for Health and await his response on these important issues.	Comments noted. See detailed responses above.
Kidney Cancer UK & James Whale Fund for Kidney Cancer	Kidney Cancer UK and the James Whale Fund for Kidney Cancer are both most disappointed with the Appraisal Committee's preliminary recommendations that none of the drugs appraised should be NHS treatment options for advanced and/or metastatic renal cell carcinoma. In responding to Dr Longson's letter of 30 July we have arranged our comments under the general headings beneath which the Appraisal Committee is said to be interested.	Comment noted. See detailed responses below.
Kidney Cancer UK & James Whale Fund for Kidney Cancer	**Do you consider that all the relevant evidence has been taken into account?** No The ACD contains little or no discussion of the latest empirical evidence on the clinical effectiveness of the new drugs, evidence that was presented at the 2008 Annual Meeting of the American Society of Oncologists. In particular it takes little or no account of the most recent results for sunitinib. These are presented in a paper by Figlin et alia and published in the *Journal of Clinical Oncology,* May 20 supplement, ASCO Abstract 5025. The results demonstrate, very clearly, that median overall survival for patients who received protocol therapy, and no subsequent therapies, was 28.1 months with sunitinib as compared with 14.1 months with interferon-alpha. So, overall survival data representing more than two years has been achieved in the first line setting of advanced and/or metastatic renal cell carcinoma; and this doubling in overall survival is of huge benefit to patients; and so this should be fully reflected in any economic analysis of the new drug.	Comment noted. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.

Consultee	Comment	Response
Kidney Cancer UK & James Whale Fund for Kidney Cancer	Evidence on patient benefits has scarcely been considered in the ACD, compared with the enormous amount of space devoted to discussion of the evidence on costs. In our view the central measure of a QALY is a woefully inadequate measure of patient benefit, calibrated as it on the basis on a number of truly heroic assumptions. Patient benefit encompasses far more than a QALY, something that was argued in the submissions from the patient experts.	The Committee has a strong preference for expressing health gains in terms of QALYs. However, additional (non-reference case) analyses may be submitted where patients' health-related quality of life has not been adequately captured. See Guide to the Methods of technology appraisal, section 5.5.4. However, the Assessment Group highlighted the paucity of evidence on utility values for people with advanced and/or metastatic RCC and performed sensitivity analyses pertaining to this. See the assessment report p142. The Committee also considered the effect of the sensitivity analyses on the 'no-post study treatment group'. See the FAD section 4.3.10. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness.
Kidney Cancer UK & James Whale Fund for Kidney Cancer	It is disappointing that the views of the patient experts have been almost totally disregarded in the evaluation of the new drugs. (Apart from a single oblique reference in paragraph 4.4.2, the ACD contains nothing at all on the views of the patient experts.)	Comment noted. The Committee considered the views of the clinical and patient experts that were submitted. See the FAD sections 4.3.1, 4.3.2, 4.3.3 and 4.3.11.

Consultee	Comment	Response
Kidney Cancer UK & James Whale Fund for Kidney Cancer	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?** No The main reason is that the comparisons do not fully reflect vast differences in the ability to control disease as between the new drugs and the present immunotherapy treatment using interferon-alpha. Only 20 per cent of patients have significant tumour shrinkage on interferon-alpha, whereas modern treatment can reverse this miserable situation with as few as 20 per cent of patients having significant tumour growth on the new drugs. In short, the new drugs both help more people *and* help them for longer. And this major advantage is not really represented in the ACD.	Comment noted. See detailed responses above.
Kidney Cancer UK & James Whale Fund for Kidney Cancer	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** No If adopted, the provisional recommendations would result in large numbers of premature deaths.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus. See the FAD 'sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' section 1 for guidance relating to the first-line use of sunitinib. See detailed responses above.

Consultee	Comment	Response
Kidney Cancer UK & James Whale Fund for Kidney Cancer	They could also have some detrimental effects on incentives to innovate in the treatment of kidney cancer. Calculation of incremental cost effectiveness ratios (ICERs) is in all cases swamped by massive differences in drug acquisition costs. Taking just one example, sunitinib vs interferon-alpha, the £2,952 cost for interferon is playing against a cost of £34,012 for sunitinib (Table 44, page 152 in the Evaluation Report). Why such a large difference? Of course interferon has been in use for a long time and become relatively inexpensive once it was out-of-patent and, after 1980, when some technical advances permitted its mass production from bacterial cultures. By contrast sunitinib is in an entirely new class of drugs, only comparatively recently introduced and still having the burden of recovering substantial R&D expenditures, incurred not just for the drug itself but for all other drugs the company experimented with which did not make the grade. These expenditures have of necessity been large because of the amount of research needed to combat a lethal disease so very difficult to treat with other medications. Huge differences in drug acquisition costs dominate the arithmetic of the incremental analysis, to such a great extent that differences in other factors have only minor effects on calculated ICERs. It might be expected that, in the fullness of time, the costs of the new drugs will fall just as interferon's have. But it is troubling that in the meantime incremental analysis might serve to hold back unduly the march of progress in the area.	Comments noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13.
Kidney Cancer UK & James Whale Fund for Kidney Cancer	When this point is coupled with the point that patient benefits are inadequately represented in the analysis, the basis for the Appraisal Committee's recommendations looks very far from sound. A more academically respectable approach to the evaluation would have involved calculation of net present values (NPVs) in a full-blown cost-benefit analysis. Admittedly, NPV calculations would be much more difficult to make, given that they would require direct valuation of patient benefits. But in this─ as in everything else of course─ there is more to be said for *rough* estimates of the *precise* concept than for *precise* estimates of some *rough* concept. ICER per QALY is a pretty rough concept; and in the ACD, ICERs are solemnly, and most precisely, given down to last £1.	For the reference case, cost-effectiveness analysis is the appropriate form of economic evaluation. However, additional (non-reference case) cost-benefit analyses may be submitted if appropriate See Guide to the Methods of technology appraisal, section 5.3.4. Also see above.
Kidney Cancer UK & James Whale Fund for Kidney Cancer	Kidney Cancer UK and the James Whale Fund urge the Institute to review all the evidence NOW. We are horrified at the proposal for reconsidering the technology in July 2011. This might mean that a reconsidered final report would not be available until December 2013. That would be a unconscionably long time to wait in the circumstance of a very fast rate of development in this field.	Comment noted. The guidance will be considered for review by two years after the publication date. See FAD section 8.2.

Consultee	Comment	Response
Macmillan Cancer Support & Rarer Cancers Forum	We are extremely disappointed that the recently issued ACD on the use of bevacizaumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma is negative and we do not feel that the preliminary recommendation reflects the needs of this small patient group.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus. See the FAD 'sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' section 1 for guidance relating to the first-line use of sunitinib. See detailed responses below.
Macmillan Cancer Support & Rarer Cancers Forum	**i) Do you consider that all of the relevant evidence has been taken into account?** We do not think that interferon alpha is a suitable comparator because the side effect profile is so significant that many patients cannot tolerate this treatment. In the materials for the meeting on 9th July it was deemed inappropriate for interferon to be used in clinical trials. If this is the case then what treatments would be available to renal cell carcinoma patients if NICE does not approve any of the treatments it is currently assessing?	Comment noted. The appraisal was carried out within the context of the original scope agreed at the scoping workshop. The appraisal considered best supportive care as the comparator for people for whom immunotherapy is inappropriate.
Macmillan Cancer Support & Rarer Cancers Forum	Point 2.4 in the ACD states "There is no standard treatment for people with advanced and/or metastatic RCC whose condition does not respond to first-line immunotherapy, or for people who are unsuitable for immunotherapy." Therefore, these treatments provide new options for patients who have exhausted and/or are unsuitable for immunotherapy. We would urge the Committee to re-consider this group of patients in the analysis.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.

Consultee	Comment	Response
Macmillan Cancer Support & Rarer Cancers Forum	The NICE Technology Appraisal process produces barriers to innovation. Whilst we understand that innovation per se is not valued within the NICE system in certain circumstances, like this one, the innovation that these four therapies bring to the treatment of advanced and/or metastatic renal cell carcinoma is significant and should be considered by the Appraisal Committee. It seems to us that because there have been no pharmaceutical developments in advanced and/or metastatic renal cell carcinoma since interferon came to the market these fours treatments are at a procedural disadvantage because the comparator is old and comparatively inexpensive.	Comment noted. The Committee noted both the severity of the disease and the innovative nature of the technologies being appraised in the context of a relatively rare cancer. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Macmillan Cancer Support & Rarer Cancers Forum	We welcome the risk-sharing agreements that the manufacturers of two of these technologies have put forward, and would urge the Committee to reconsider their decision once the Department of Health has concluded its discussions with these manufacturers. In addition we would urge manufacturers to put forward risk-sharing agreements which reduce the QALY to make these treatments more likely to be considered cost effective.	Comment noted. The patient access scheme, whereby the first cycle of sunitinib is free to the NHS, was agreed in time for the second Committee meeting by the Department of Health and incorporated into the analyses and considered fully by the Committee. See FAD section 3.1.3.

Consultee	Comment	Response
Macmillan Cancer Support & Rarer Cancers Forum	**ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?** We are concerned that the EQ5D measure of quality of life does not have a dimension which adequately captures energy or fatigue. These are very important considerations in treatment for cancer patients, particularly as their disease progresses and must be considered by the Appraisal Committee.	Comment noted. The Assessment Group also highlighted the paucity of evidence on utility values for people with advanced and/or metastatic RCC and performed sensitivity analyses pertaining to this. See the assessment report p142. The Committee also considered the effect of sensitivity analyses on the utility values for the 'no-post study treatment group'. See the FAD section 4.3.10.
Macmillan Cancer Support & Rarer Cancers Forum	Point 4.1.23 notes that, "Although promising, data on overall survival are in general immature." A system must be put in place to make appropriate decisions when data is immature. If NICE begins to make decisions quicker and closer to product launch it is important that cancer treatments are not routinely turned down due to immature data, so safeguards must be put in place to reduce the potential for this to happen. We are also concerned that when clinical trials allow patients to cross over to the other arm of the trial because of ethical issues, this degrades the clinical trial data, as described in point 4.1.24. This makes the data less compelling because end points are not reached in the control arm. We would ask the Appraisal Committee to consider this important clinical trial data again.	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus. See the FAD 'sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' section 1 for guidance relating to the first-line use of sunitinib.

Consultee	Comment	Response
Macmillan Cancer Support & Rarer Cancers Forum	**iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** We do not believe that the provisional recommendation constitutes suitable guidance to be implemented by the NHS. This appraisal highlights methodologically flaws in the technology appraisal process. A drug which clinicians believe is effective – when there are no other equivalent treatment options – should be recommended. We have described other methodological concerns above.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Macmillan Cancer Support & Rarer Cancers Forum	**iv) Are there any equality related issues that need special consideration that are not covered in the ACD?** The recent NICE Citizen's Council report recommends that NICE and its advisory bodies should take the severity of a disease into account when making decisions. We would like to see, in the 'Evidence and interpretation' section, whether the Appraisal Committee was persuaded in this instance to take the severity of this condition into consideration alongside the cost and clinical effectiveness evidence.	Comment noted. See detailed responses above.
Macmillan Cancer Support & Rarer Cancers Forum	**Other comments** As a group of charities dealing with patients and their families being denied treatment for kidney cancer, we are more than disappointed that the committee is minded to reject all of these treatments which are vital to patients. We believe that these treatments should be made available to those that would benefit from them, on the basis of clinical decision making, rather than on purely cost-effectiveness grounds.	Comment noted. See detailed responses above.

Consultee	Comment	Response
National kidney federation	The National Kidney Federation is the National Charity (No1106735) representing the interests of some 2.5 million patients with Kidney problems including those with Renal Cell Carcinoma. We have read the above appraisal consultation document and although as a patient body we must leave the technical comments to the Clinicians and Drug companies we do wish to make a number of comment on behalf of the patients we represent.	Comment noted. See detailed responses below.
National kidney federation	We are frankly appalled and extremely concerned at what we consider to be a cold and callous financial decision by NICE completely deviod of patient concern. This decision will leave the patients concerned with few options for treatment. The disease is highly resistant to chemotherapy and radiation treatment. Immunotherapy treatment using the drug Interferon Alpha only has a modest effect in prolonging survival and Interleukin 2 is not proven to increase survival and has substantially negative side effects. There is also a proportion of patients who may be unsuitable for immunotherapy, primarily due to poor performance status and because of the toxicity of interferon (and the even greater toxicity of IL2). This set of patients also include poor risk patients (who are estimated to comprise 28% of advanced RCC cases. The decision seems to abandon the needs of all of these patients leaving them in a desparate situation with little hope for the future and the prospect of an early death.	The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
National kidney federation	It is a decision against all sense, and contrary to the situation in the rest of Europe and in the United States, where these drugs are being made available to such patients. In Sweden particularly where there is a comparable health system to are own, their equivalent organisation to NICE has already approved two of the drugs concerned as suitable for state Finance.	Comment noted. See response above.

Consultee	Comment	Response
National kidney federation	To deprive this small group of patient of access to these new drugs, (that your own ACD accepts are clinically effective), is to totally deprive them of any hope for the future. Their only alternative will be to fall back on what happens at present and that is to find some way of paying for the treatment themselves. Few will be able to achieve this without involving their families in serious hardship and if they should pay privately for NHS denied treatment under present arrangements they may find they will be excluded from further NHS treatment.	Comment noted. See response above.
National kidney federation	Such is the callous nature of this decision, a cost effectiveness judgement as apposed to a cost benefit assessment. The need to consider the severity of the condition, clinical need and other factors that contribute to social value judgement should be weighed alongside cost effectiveness in the context of a compassionate NHS; a view supported by the recent NICE Citizen's Council on Quality Adjusted Life Years and the Severity of Disease.	Comment noted. See response above.
National kidney federation	The Citizen's Councils also questions the EQ-5D which they thought was too blunt to capture all the factors relevant to the definition of a good or bad quality of life. They felt that it should take more account of the views of those who have first hand experience of the circumstances being rated, stating; *the EQ5D measures what people imagine the experience of various health conditions to be like. Clearly most of us never have experienced most of them and never will*. We think these comments are very relevent to the case in consideration and that there is a clear gap in the appreciation of what this decision really does mean to the patients concerned	Comment noted. The Assessment Group also highlighted the paucity of evidence on utility values for people with advanced and/or metastatic RCC and performed sensitivity analyses pertaining to this. See the assessment report p142. The Committee also considered the effect of sensitivity analyses on the utility values for the 'no-post study treatment group'. See the FAD section 4.3.10.

Consultee	Comment	Response
National kidney federation	We feel strongly that the present assessment is flawed. The methodology and the current threshold set by NICE will make it very difficult for these small numbers of patients with metastatic disease to gain any access to any of the new inovative treatments. We have therefore withdrawn from a new proposed Technology Appraisal on two further RCC drugs since we believe the result will inevitable be the same if the methodolgy remains the same. This NICE decision seems to indicate that a substantial number of new highly inovative drugs for diseases of this nature affecting small numbers of patients will fall foul of the NICE threshold level and the rigidity of the cost effectivness assessment.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
National kidney federation	If to many drugs collide with this threshold or are refused assessment then we could see inovative drug development and the availability of variations in treatment to patients being inhibited. As we have previously indicated in our first submission, breast cancers patients survival rates have increased as the range of therapies available increased. We would ask how this NICE threshold was determined and why after a number of years has it remained at the same level despite the fact that NHS spending has risen threefold in that period. *(Health Select Committee report on NICE).* Surely there should be a special category / threshold for diseases of this nature where the number of patients is small perhaps similar to those that should be taken into account with orphan and ultra orphan disease categories.	Comment noted. See response above.
National kidney federation	As we pointed out in our original submission we need to consider budget impact as well as cost effectiveness. Although the individual treatments in this case may be expensive, because the number of people involved is very small, it will have a small effect on the overall NHS budget.	Comment noted. The Committee consider the clinical and cost effectiveness of technologies; it is not part of their remit to take budget impact into account when making decisions.

Consultee	Comment	Response
National kidney federation	We believe fair and equally high standards of care should be available to everyone. To achieve this however, it may be necessary to spend more on some people with more complex problems than on others. We don't feel that this minority should be penalised for the sake of the majority, and we are concerned that once we start to discriminate against a minority of people with a condition such as RCC, who knows which group of essential treatment may be regarded as not cost effective and not affordable next. We have always been assured by Government and the NHS that treatment would be Quality driven not Finance driven.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
National kidney federation	Patients count good days rather than bad days. Good days are when they feel on top of the problems associated with the disease. This decision by NICE will most certainly contribute very few good days to the future of these vulnerable people. The four new drugs in this appraisal are capable of reversing this situation offering Patients and Clinicians important further alternative therapies and advantages in treatment. They will give help and hope to a small group of patients who will otherwise certainly die. We ask not only for a reconsideration of this appraisal but also a review of the methodology to ensure that future decisions made comply with the compassionate, patient centred and egalitarian ideals of the NHS.	Comment noted. See detailed responses above.

Consultee	Comment	Response
Royal College of Physicians	I write on behalf of the National Cancer Research Institute - Renal Cancer Clinical Studies Group, the Royal College of Physicians, the Royal College of Radiologists, the Association of Cancer Physicians and the Joint Collegiate Council for Oncology in response to the above consultation. We would like to make the following joint response under your general headings: i) There has been no account taken of the data presented at the American Society of Clinical Oncology by Figlin et al. earlier this year (available at asco.org) where it is clear from the post-hoc subgroup analysis of patients in the Sunitinib vs Interferon trial that the absolute survival in the Interferon arm is enhanced by the high proportion of patients receiving active second line treatments. ii) The PENTAG QALY analysis is flawed because the group used the data from the bevacizumab trial to model progression with IFN alone; the median survival of the IFN alone group in that trial is far greater that from trials in the pre-TKI era. Using the data from Figlin et al. (ASCO 2008), and a consensus survival estimate from historical controls (either from other trials or from published prognostic models), the overall survival advantage for patients having sunitinib first line is in the order of 9 months. Perhaps the best and most robust data on IFN survival is from the MRC RE04 study (Gore et al. J. Clin. Oncol (ASCO Proceedings) 26,15S Abstract 5039) where median overall survival was 18.7months; this compares with the 26.4 months for sunitinib from the Figlin data. We respectfully ask that the QALY analysis is redone using appropriate comparative data and with expert oncology input.	Comment noted. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.
Royal College of Physicians	Would it not now be possible to take into account proposals submitted by manufacturers relating to drug acquisitions costs? Whilst we understand the constraints under which NICE appraises health technologies we consider the provisional recommendations unsound (see above) and inequitable (see below), and as such does not constitute a suitable basis for guidance to the NHS.	Comment noted. The patient access scheme for sunitinib was agreed by the Department of Health and incorporated into the updated analyses in time for the second appraisal Committee meeting and considered fully by the Committee. See FAD section 3.1.3. Also see responses above and below.

Consultee	Comment	Response
Royal College of Physicians	Renal carcinoma is one of the less common cancers and, as such, must not be discriminated against. There is no other suitable treatment for the majority of patients with advanced/metastatic disease; Interferon is simply not appropriate for these patients. The new treatments under appraisal offer major and evidence-based clinical benefits. They may be more costly but this is first-line treatment and the actual costs to the NHS are small compared with the multiple NICE approved and expensive treatment options available to other more common cancers, such as breast and colorectal carcinoma. It is a shame that appropriate patients with renal carcinoma are to be denied effective treatments which are readily available to similar patients throughout Europe and America.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
NHS Cambridgeshire	**Do you consider that all of the relevant evidence has been taken into account?** Yes: the evidence that the renal oncologists appear most likely to consider critical is the data presented to ASCO week commencing 30 May 2008 giving updated results and information on patients who did not receive any post study treatment for metastatic renal cell carcinoma. The conference data was supplied to us by NICE as the Pfizer HTA from study A6181034.	Comment noted. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.

Consultee	Comment	Response
NHS Cambridgeshire	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?** Agree that the summaries are reasonable interpretations of the evidence but that the evidence base is not yet mature and current research may affect future understanding of which populations to use these drugs for.	Comment noted. The Institute is aware that in providing timely guidance, much of the evidence base will be immature. The NHS need to be informed how to use these new technologies, therefore the Committee must regularly make decisions based on limited evidence available at the time. All decisions will be considered for review at a later stage.
NHS Cambridgeshire	We support the approach taken in this ACD of minimising the impact to the NHS of the (repeated) proposal from the manufacturer to provide one free cycle (treatment for 6 weeks) of sunitinib – as noted on Pfizer HTA p1. We note from the Pfizer HTA that this did not bring sunitinib within the NHS' normal cost effectiveness frame and therefore the absence of this information may affect the understanding of OS with sunitinib but cost effectiveness would not be substantially changed.	Comment noted. The patient access scheme for sunitinib was agreed by the Department of Health in time for the second Committee meeting and incorporated into the analyses and considered fully by the Committee. See FAD section 3.1.3.
NHS Cambridgeshire	One free cycle is also insufficient time in which to expect to see a difference in the disease. The cost to the NHS (both providers and commissioners) of administering the scheme substantially reduces the actual gain for the NHS and is mostly misleading.	Comment noted. The Department of Health considered that the patient access scheme for sunitinib does not constitute an administrative burden to the NHS. See FAD section 3.1.3.
NHS Cambridgeshire	Costing that does not reflect the true cost to the NHS is a great concern at PCT level – the cost of a treatment is often misrepresented and the enduring debate about the treatment fails to address the actual cost to the NHS. The example in this ACD is the manufacturer quoting part vials rather than whole vials. We would ask NICE to consider that all cost calculations should omit free stock or capped scheme. These are principally ways to manipulate the cost per Qualy on the basis of the misunderstanding that it causes away from NICE.	Comment noted. All cost effectiveness analyses are based on full vial price taken from the BNF edition 55. The patient access scheme for sunitinib was agreed by the Department of Health as nationally available in time for the second Committee meeting and incorporated into the analyses. See FAD section 3.1.3.

Consultee	Comment	Response
NHS Cambridgeshire	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a reasonable basis for the preparation of guidance to the NHS?** Patients who have had a nephrectomy and have good or intermediate performance status appear to do better on sunitinib. The cost-effectiveness of selecting a therapy according to performance status appears not to have been explored.	Comment noted. The Committee carefully considered all subgroup analyses where the evidence allowed. For sunitinib there was insufficient data to allow separate exploration of these subgroups. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus' for further details of the Committee's considerations of subgroups
NHS Cambridgeshire	4. **Are there any equality issues that may need special consideration?** There are none that we are aware of.	Comment noted. No actions requested.
Welsh Assembly Government	Following the recent publication of the assessment of bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma, the Welsh Assembly Government would wish the following views to be taken into account during the consultation process. These views are informed by advice obtained from Wales-based oncologists working specifically in the field of renal cancer.	Comments noted. See detailed responses below.
	The response covers a number of issues: It is possible that the Health Technology Assessment used by NICE to evaluate sunitinib was done before the survival data from the pivotal study comparing sunitinib (S) with interferon (IFN) was presented at the Annual American Society of Clinical Oncology meeting at the beginning of June. The drug company provided NICE with these data as soon as they were available, however, it is the impression from reading the ACD published by NICE that they have not used the new data in their evaluation. If that is the case, we believe that the correct response from NICE should have been to delay their decision and ask the Health Technology Assessment team from the Peninsula Medical School to re-do their cost per QUALY calculations based on the real data rather than the modelled data that they used in the draft ACD.	Comment noted. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.

Consultee	Comment	Response
Welsh Assembly Government	The reason that this is important is that many patients in both the S and IFN arms of that study received other treatments after they progressed either on IFN or S. In the group of patients who ONLY received either IFN or S, the average survivals were 14 months for IFN and 28 months for S. A doubling of average survival hardly represents "a few extra months of life" as reported in newspapers at the time of the assessment's publication. Within that study there were some patients who appeared to get long and sustained benefit from sunitinib. This assessment does not seem to take into account this particular group. It is likely that, on a population level, more benefit will be obtained from these drugs if patients are crossed over from one treatment to another if treatment fails, as there is good evidence that second line responses occur. Overall, this is likely to improve the ICER for each drug. However, different approaches are required for patients of differing performance status.	Comment noted. The Committee understood that there had been both crossover after disease progression, but also participants had had second-line treatment after the study had ended. This could be expected to exaggerate overall survival estimates for people in the UK receiving IFN-α in the future, as the Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.

Consultee	Comment	Response
Welsh Assembly Government	While the NICE report makes a reasonable estimate of the cost effectiveness as evident from the clinical trials, it does not predict the situation which will arise if the drugs are denied to patients. The quality of life of a patient who knows that he or she is being denied potentially life-prolonging therapy is extremely poor, particularly when the same treatment is available in other countries. It is likely that the most articulate patients would attempt to acquire the drugs through exceptionality claims through the LHB. The cost of the hundreds of appeals cases and possible further legal action which would result has not been calculated, but could run into millions and divert hospitals and commissioners from more important tasks. This is also a huge drain on health resources, with many extra consultations per patient devoted to explaining the situation. It is vitally important that this potentially chaotic situation is not allowed to continue, as virtually every patient with kidney cancer is now aware of the situation. It is also clear that the drugs are extremely expensive and that the existing resources cannot cover the cost. However, we believe there is no precedent for turning down drugs which have a survival benefit of around 6 months, whatever the cost.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Welsh Assembly Government	With treatment as expensive as this, it is reasonable that it is made available only under strictly regulated conditions. However, as there are many unanswered questions regarding clinical and cost effectiveness, a partnership between Department of Health/WAG research and development, drug company sponsorship and funding from research charities would be a sensible response. Programmes could be developed with NICE to make sure that appropriate clinical and health economic data are collected. Appropriate studies of these drugs may also identify whether surgical intervention is also necessary. Considerable cost saving could be incurred if nephrectomy was avoided (£10,000 per patient).	Comment noted. The Committee have formulated recommendations for future research. See FAD section 6 and the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' section 6.
Welsh Assembly Government	Temsirolimus is accepted as a suitable treatment for poor performance status patients. It is metabolised to sirolimus. There is an oral formulation of sirolimus (rapamune) already in use as an organ rejection drug, which is a fraction of the cost of temsirolimus, and which gives equivalent or higher plasma levels than temsirolimus. Whilst accepting that the drug does not currently have a license for this indication, it again raises an issue of how situations such as this should be dealt with and what actions can be taken when a potentially much cheaper drug could be made available.	Comment noted. The Committee cannot make recommendations regarding the use of a drug outside its current licensed indications. See Guide to the methods of technology appraisal section 6.1.6.

Consultee	Comment	Response
Welsh Assembly Government	Finally, this decision has caused dismay amongst oncologists working with renal cancer patients in Wales and is best expressed by a direct quote: 'All of us who do research into kidney cancer are completely astounded by the decision of NICE. In all the other Western European countries sunitinib is now the standard of care and most patients not only get first line treatment but second and sometimes third line treatment. By not allowing access to any of these new drugs, the survival of patients with advanced kidney cancer in the UK will be the lowest in Europe. I'm sorry that I appear passionate about this but those of us who have used these new treatments have patients who are alive with an excellent quality of life more than 3 years after started treatment. These patients would not be alive now if they had only had access to interferon'.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Expert 1	I have reviewed the Appraisal Consultation Document of July 2008 and I am both disappointed and frustrated at the provisional recommendations of the committee. I wish to make the following points under the headings given in the instructions, (1a) I do not consider that all the clinically relevant data has been taken into account. Firstly, the post hoc subgroup analysis of patients in the Sunitinib vs Interferon Trial who did not proceed to have any second line therapy is highly relevant and while I accept that this was late-breaking news an opportunity should be given for this information to be assimilated by the health economic team and for any further information to be provided by the company before any recommendation is made.	Comment noted. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.

Consultee	Comment	Response
Expert 1	(1b) Secondly, I highlighted that there was "real world" data on Sunitinib available through the Expanded Access Program run by Pfizer and this information, while not randomised clinical trial data, is relevant and important to underpin the efficacy of the treatment.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment report and the Appraisal Consultation Document.
Expert 1	(1c) I do not believe that evidence from the patient groups has been properly considered in the decision making process. It was apparent from the NICE meeting that comments from their representatives would not or could not be taken into account and that cost effectiveness would be the sole criterion. I find it very hard to believe that Professor Littlejohns can say publicly on the BBC that cost-effectiveness was not the sole criterion when it so obviously is.	Comment noted. The Committee considered the views of the clinical and patient experts that were submitted. See the FAD sections 4.3.1, 4.3.2, 4.3.3 and 4.3.11.
Expert 1	(2a) It is not possible for me to say whether the health economic model as presented by PENTAG is valid or not as this is a highly specialist area of statistics. Clearly there are areas of disagreement between the models presented by PENTAG and by the companies. It was not immediately apparent at the NICE meeting why PENTAG's model should be accepted as being the correct one and because this issue is of critical importance it would seem reasonable and logical that a third party adjudicates on the matter.	Comment noted. The Committee considered the cost effectiveness estimates from all of the manufacturers and the Assessment Group. See FAD sections 4.3.6, 4.3.7, 4.3.8 and 4.3.9. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.

Consultee	Comment	Response
Expert 1	(2b) I do not agree that the resource implications for the NHS in its entirety have been addressed. I made the point during the NICE meeting that these drugs have been given orphan drug status because this is still a comparatively rare cancer and that therefore the resource implications for the NHS if these new treatments were to be adopted must be considerably less than if this was a common cancer. This has simply not been factored into any calculations and according to the answer given to me at the time the appraisal committee cannot do so. I would put it to the committee that since they acknowledge that these treatments are clinically effective with significant patient benefit the committee should recommend that the impact on the NHS be reviewed fully and that these drugs should be accorded special status.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Expert 1	(3) I do not agree that these recommendations constitute a sound basis for preparation of guidance to the NHS. It was highlighted at the NICE meeting that all the countries with which the UK should be compared in terms of healthcare have adopted these drugs as the new standard of care for advanced kidney cancer. By denying UK patients these new drugs we will see a significant difference in survival between the UK as a whole and neighbouring countries.	Comment noted, NICE Technology Appraisal Guidance may differ from that of other countries because of different criteria applied.
Expert 1	To add insult to injury we also make the UK less attractive for clinical trials because the forthcoming trials will all assume that these new drugs, as the new standard of care, will be widely available and funded. Patients will have a "double whammy" of being denied both the global standard of care and access to new drugs through clinical trials.	Comment noted. See detailed responses above.

Consultee	Comment	Response
Expert 1	(4) It was highlighted at the NICE meeting that there is already inequality in access to these new drugs in the NHS with the post code lottery because some PCTs have agreed to fund these new drugs. There is further inequality in that these drugs can be prescribed privately. The clinical efficacy of these drugs is such that there will be significant differences in survival between those who can get the drugs over those who can't. The NHS celebrates its 60th year this year and it was created to make healthcare available to all, the most fundamental of equalities. We all recognise the need for cost effectiveness in the NHS, but this "one size fits all" is the ultimate inequality, and surely that is not what NICE should stand for.	Comment noted. See detailed responses above.
Expert 2	**Relevant Evidence** **The evidence of the 3 "patient experts " has been ignored . In their submissions and at the appraisal meeting the patient experts were given almost no opportunity to state their views about their experience of RCC and their opinions about the treatments under review. Their experience of the process was that the NICE committee failed to involve them in the discussions and did not explore or attempt to elicit relevant and important information about the patient and carer evidence on the devastating impact of RCC .** In a 4 hour meeting ,the patient experts were asked no questions by the NICE committee and were restricted to single statements which were curtly dealt with by the Chairman , Professor Stevens. These points are now the subject of a separate formal complaint .	Comment noted. The Committee considered the views of the clinical and patient experts that were submitted. See the FAD sections 4.3.1, 4.3.2, 4.3.3 and 4.3.11. The Institute will respond separately to the formal complaint.
Expert 2	**Summaries of Cost and Clinical Effectiveness** **The evidence was presented in a highly technical manner with no concessions made to involve the "patient experts" and with no attempt to explain the complex and academic debate about statistical method and health economics . The debate as such was limited to a discussion of the interpretation of data and in a style more suited to an academic common-room. It is worth noting that some of the data and method of some of the drug companies was challenged and yet they were not present to defend their work which is both unfair to them and confusing to the "patient experts " who were confronted with evidence which was contradictory and open to very different interpretation.** The information and conclusions presented requires robust and rigorous challenge to ensure the method and the data analysis meets the highest standards. Regrettably the appraisal process was fatally flawed as the necessary expertise was not available--either on the NICE committee or among the patient experts-- to discuss and debate the statistical and methodological issues involved.	The Appraisal Committee relies on the academic groups and its Decision Support Unit to provide advice on the statistical and methodological issues involved. The Institute will respond separately to the formal complaint that was lodged.

Consultee	Comment	Response
Expert 2	**Provisional Recommendations** **It was inevitable that all the treatments investigated would fail the NICE evaluation process for one simple reason . All new cancer drugs are by their nature expensive in view of their long development time . None of these drugs could ever meet the QALY set by NICE nor the willingness to pay level set at £30000. It is a cruel deception to evaluate drugs and treatments which are bound to fail the arbitrary tests set by Department of Health** RCC is a cancer which responds very poorly to standard chemotherapy and radiotherapy. It is not a rare cancer with over 6000 cases per annum in the U.K. and with a rising incidence . The standard NHS approved treatments of interferon or interleukin have largely been discontinued in all other modern states as ineffective and in the light of these newer and more clinically effective drugs, unethical . It is recognised in the report that the data is immature but positive in terms of clinical effectiveness for all of these treatments . What does it say about our NHS if the only treatment supported by NICE for RCC is regarded by the rest of the World as unethical ?	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Expert 2	**Equality Issues** **Current treatments for RCC are determined by the perfect postcode lottery . PCT's are individually deciding whether or not to fund these drug treatments based on the recommendations of their Appeals procedures each with different rules and criteria. This leads to a cruel and exhausting paperchase for patients as they seek treatments prescibed by their clinicians. This analysis does not take into account the quite different systems and outcomes in Scotland Wales and Northern Ireland. It will be a supreme irony if the results of this ACD are to COMPLETELY deny ALL the new and more effective drugs for RCC in England and Wales.** If that is the outcome of this appraisal then NICE can be content that the theoretical equality outcome has been perfect-- no-one gets any of the more effective drugs on the NHS !	Comment noted. See detailed response above.

Consultee	Comment	Response
Expert 3	**I am extremely concerned at the decision reached by the panel. I fear the panel failed on many fronts to address the appraisal in a fair, patient centred manner and showed a real lack of understanding of the current options for kidney cancer patients and the potential significant benefits of the new treatments.**	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Expert 3	**This decision also contradicts the positive commissioning of these treatments in the rest of the western world. This includes both Canada and Sweden where the commissioning structure is comparable. One has to question why you are completely at odds with them.**	Comment noted. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions.

Consultee	Comment	Response
Expert 3	i) Do you consider that all of the relevant evidence has been taken into account? **No, all the relevant evidence has not been taken into account. This includes evidence from the leading clinicians worldwide who are extremely committed to these treatments for rcc patient. They have explained clearly that without these treatments patients are condemned to a premature death. The panel failed to comprehend the current system whereby many oncologists are refusing to prescribe the only available treatment "Interferon" due to its lack of efficacy and appalling side effects.**	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Expert 3	**I am also extremely concerned by comments from employees of NICE made to the press that these drugs offer "just a few weeks" of extra life. This is misleading and incorrect. You were all supplied with the Pfizer data which cites 28 months pfs in the latest clinical trial updates. The "real world" data also suggests that a significant number of patients are living far longer than weeks with a far better quality of life on treatment.**	Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.

Consultee	Comment	Response
Expert 3	**The panel also failed to acknowledge and request the views of the patient experts at the meeting and by doing so failed to consider the damage both physically and psychologically by failing to treat rcc patients with these treatments.**	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment report and the Appraisal Consultation Document. See the FAD sections 4.3.1, 4.3.2, 4.3.3 and 4.3.11
Expert 3	ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate? **The panel has failed to take into account the vast resources spent on supportive care once no further treatment is available to rcc patients. PenTag came up with a totally inaccurate costing for best supportive care factoring it as approximately £85 – a cost for a visit from the community nurse. Many rcc patients will have bone metastases without active treatment. This will be treated with surgical intervention and intensive physiotherapy. This is hugely costly to the NHS and the figures in the appraisal should reflect interventions needed due to the spread of disease such as this.**	Comment noted. The Assessment Group highlighted that there is a paucity of evidence surrounding appropriate costs associated with best supportive care and conducted sensitivity analyses. See Assessment Report pages 148 – 150.

Consultee	Comment	Response
Expert 3	**Without the benefit of a qualification in health economics it is extremely difficult to assess the QALY figure put forward by NICE. However, for these figures to differ so widely from those put forward by health economists from the companies, one has to question the accuracy of the formulas used by PenTag. From the numerous health economists I have consulted with since the ACD it would seem that the argument is based on a failure by NICE to take into account the orphan status of these treatments and thus the fewer beneficiaries. NICE should use a different formula when cost appraising treatments of this nature.**	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Expert 3	iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS? **These recommendations are unsound due to the failures discussed above.**	Comment noted. See detailed responses above.

Consultee	Comment	Response
Expert 3	iv) Are there any equality related issues that may need special consideration? **Special consideration needs to be given to patients with an uncommon cancer, as in kidney cancer.** **Consideration also needs to be given due to the lack of alternatives for these patients.** **It is the role of NICE to look at equality for all patients including those disadvantaged with a terminal illness. This decision punishes them for this very reason.**	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.

Comments received from commentators

Commentator	Comment	Response
NHS Quality Improvement Scotland	All relevant evidence appears to have been taken into account in the NICE Appraisal Consultation Document	Comment noted. No actions required.

Commentator	Comment	Response
NHS Quality Improvement Scotland	The interpretation of the evidence appears to have serious flaws. The Assessment Group has used the data from the bevacizumab trial to model progression with interferon alone. The median survival of interferon alone group in this trial is far greater than from trials in the pre-tyrosine kinase era. The Assessment Group have also not taken into account the effect of crossover in the trials which would have significantly affected the cost-effectiveness calculation. The calculations for first line sunitinib and bevacizumab are only valid if tyrosine kinase inhibitors are available second line. This represents a major flaw in the reasoning used by the Assessment Group.	Comments noted. The Committee understood that there had been both crossover after disease progression, but also participants had had second-line treatment after the study had ended. This could be expected to exaggerate overall survival estimates for people in the UK receiving IFN-α in the future, as the Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.
NHS Quality Improvement Scotland	For the reasons listed in section 2, I think the interpretation of the evidence by the Assessment Committee has been seriously flawed and are not sound enough to form a suitable basis for guidance for the NHS.	Comment noted. See response above.
NHS Quality Improvement Scotland	Whether you consider that all the relevant evidence has been taken into account. The evidence presented appears to have been taken into account. There has been mention in the media of additional evidence which has not been taken into account – I trust the comments will be fed to NICE.	Comment noted. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.
NHS Quality Improvement Scotland	Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. The summaries from the evidence provided appear reasonable.	Comment noted. No actions requested.

Commentator	Comment	Response
NHS Quality Improvement Scotland	Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. The recommendations are in line with current Scottish advice from the SMC.	Comment noted. No actions requested.
Novartis	Thank you for your invitation to comment on the above ACD and accompanying documents which were released on the 30th July 2008. We are disappointed that the draft recommendations do not support the use of any of the new targeted therapies for the treatment of renal cell carcinoma. In particular, sunitinib confers significant benefits as monotherapy when compared to IFN-α alone in terms of progression free survival (11 months vs 5 months) and tumour response. Sunitinib therefore offers an effective alternative to immunotherapy as first-line treatment for patients with metastatic renal cell carcinoma. If the draft recommendations are adopted, patients will be denied access to clinically effective treatments for an indication where current treatment options are extremely limited and generally not well tolerated.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.

Commentator	Comment	Response
Novartis	The "Updated guide to the methods of technology appraisal - June 2008" states that the Appraisal Committee should take into account the degree of clinical need for patients with this disease. We believe that insufficient weight has been given to this aspect of the appraisal. In addition the recently released report, "NICE Citizens Council report *'Quality Adjusted Life Years (QALYs) and the severity of illness'* recommends that severity should be considered in addition to clinical and cost-effectiveness. We therefore urge the Appraisal Committee to re-consider its decision taking into account the severity of the disease and the significant unmet clinical need for metastatic renal cell carcinoma. In summary, the preliminary recommendations do not constitute a suitable or sound basis on which to develop guidance to the NHS as they do not give due consideration to the factors described above.	Comment noted. See response above.

Summary of comments received from members of the public

Theme	Response
Agree with recommendations	Comment noted. No actions requested.

Theme	Response
Lack of/limited alternative treatment options: *"The disease does not respond to standard chemotherapy and radiotherapy and once metastasised has a poor prognosis. The standard immunotherapy treatment has a low response rate and has serious and debilitating side effects as with my husband."* *"It is recognized that these are the only drugs proven to extend the lives of those suffering from the disease and as such are critical to each patient."* *"There are not that many Renal Cancer Patients and this drug is one of the few treatment options they have available."*	Comments noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Evidence on the clinical effectiveness of Sunitinib	Comments noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment report and the Appraisal Consultation Document. See the FAD sections 4.3.1, 4.3.2, 4.3.3 and 4.3.11
Evidence on the clinical effectiveness of Bevacizumab	Comments noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Evidence on the clinical effectiveness of Sorafenib	Comments noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Evidence on the clinical effectiveness of Temsirolimus	Comments noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.

Theme	Response
Personal experience of benefit from Sunitinib: *"I am a reasonably fit and healthy 56 year old, still working in the NHS as an Accident and emergency sister. I have just gone back to work as I am doing so well."* *"Over 12 months it shrank all 4 tumours to non-existence."* *"Sutent 50mg started 12/06, 75% shrinkage of lymph node within 6 months of treatment, continued stabilization to date."* *"I know one patient who has been taking Sutent for five years."*	Comments noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment report and the Appraisal Consultation Document. See the FAD sections 4.3.1, 4.3.2, 4.3.3 and 4.3.11
Personal experience of benefit from Bevacizumab: *"My sister was diagnosed with kidney cancer in October of 2002. One year later she developed metastases to her liver. She lives in the United Sates, California, and has been treated with a variety of drugs, including Nexavar, Sutent and Avastin. At the time of her diagnosis, statistically, she had a 5% chance of being alive 5 years later. It is now almost 6 years, and thanks to the drugs, she is still here. She is on a holiday right now and doing well."*	Comments noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Personal experience of benefit from Sorafenib: *"This drug has totally stabilised my condition. In fact my secondary tumours have all decreased and significantly shrunk within this period. This treatment has so far prolonged my life by some THREE AND HALF YEARS."*	Comments noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.

Theme	Response
Personal experience of benefit from Temsirolimus: *"My father has kidney cancer and was lucky enough to get funding for Sutent.It worked for 11 months.He his now taking Torisel. If it were not for these drugs he would be dead. "*	Comments noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Treatment extends survival: *"even just a few months extended to someones life could give more beautiful moments more precious than any sum of money could buy."* *"We all hope that the drugs will keep us all alive long enough to see a cure for kidney cancer."* *"It may be "just six months" to a complete stranger to you, but these drugs mean a return to better health for six months and an expansion of the patients' lives of far longer than the actual six months."*	Comments noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Treatment improves/ promotes quality of life: *"Since my nephrectomy in Feb of 2006 I watched my son marry a beautiful young lady, I walked my daughter down the aisle to wed a great young man, I celebrated my 60th birthday, I celebrated my 37th and 38th wedding anniversary with the greatest lady in the world."* *"These new technologies offer the only real hope of clinical stability, improved quality of life and an extension of life."*	Comments noted. See above.

Theme	Response
Treatment should be provided regardless of cost: *"There is NOTHING more precious than a human life, and anything that can be done to extend it is more than worth the time and money."* *"There's nothing I wouldn't pay--nor nothing I wouldn't expect that state-sponsored health programs pay--to extend the comfortable life of my father, who is a victim of this miserable disease."* *"As a hospital governor I am aware of the need for cost effectiveness – cost savings can be found in numerous other ways without the unwarranted removal of life saving drugs which will directly cause premature death of numerous individuals"* *"You say it is apparently not 'cost effective' to prolong mRCC patients lives. Yet they are given interferon – which is recognized not to be clinically effective in this type of cancer (15%)…. A complete waste of money but also total madness."*	Comments noted. See above
Total financial burden to NHS is small	Comments noted. The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3).
Future research will be hindered as the public will no longer want to fund it.	Comment noted. The FAD recommended sunitinib as a first-line treatment. See FAD section 1.1, 1.2 and 1.3.

Theme	Response
Decision will stop drug companies funding research – immunotherapy will not be the standard of care in future trials	Comment noted. The FAD recommended sunitinib as a first-line treatment. See FAD section 1.1, 1.2 and 1.3.
The pharmaceutical companies should reduce the price: *"We do need to push for reduced prices from the drug manufacturers, I agree with that. But, under no circumstances should people be cut off from the drugs they need to keep them alive."*	Comments noted. The Committee is not able to make recommendations on the pricing of technologies to the NHS. See Guides to the methods of technology appraisal section 6.1.8.
NICE has underestimated survival benefit: *"the recent statement made by NICE on the Today Programme on radio 4 that these drugs only extend life by a few weeks is a blatant lie! I know of patients who are now in their 3rd year on the drug."*	Comments noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment report and the Appraisal Consultation Document. See the FAD sections 4.3.1, 4.3.2, 4.3.3 and 4.3.11
NICE process discriminates against rare conditions: *"Kidney cancer is a relatively rare cancer and affects only 2-3% of all cancer diagnoses in the UK, Of this number only 25% wil present with advanced disease. Therefore your decision places all RCC patients at an immediate disadvantage by suffering from a less common cancer with limited treatment options ..you are therefore discriminating against them."*	Comments noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.

Theme	Response
NICE decision made by uninformed decision makers: *"Why don't you listen to what the Dr's who are working with kidney cancer patients every day have to say, these are the people with the expertise."* *"You do not do your own research, and you allow the drug companies to supply dodgy research information or refuse to give you any data at all, which few of your reviewers have the knowledge tor experience to assess. That is not to say they are ignorant, just that their specialisms are not engaged in the assessment of drugs for other specialisms."*	Comments noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the assessment report and the Appraisal Consultation Document. The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the Assessment Group.
NICE has over-estimated cost of the drugs: *"I am puzzled by the costs you quote as Pfizer, the manufacturer of Sutent quote £28,000 for a years treatment."*	Comment noted. This is the annual cost of sunitinib treatment which was used in the assessment of the cost effectiveness of sunitinib. The methods of cost effectiveness are explained in the Guide to the Methods of Technology Appraisal section 6.2.6.

Theme	Response
Inhumane/ immoral decision: *"I expect you are all well meaning people, but this recommendation, and the reasons given for it, appear quite wicked."* *"it is morally wrong to withhold treatments that can make a difference on the grounds of cost alone."* *"To leave [my husband] in a position with no hope to get the treatment he needs, as your decision will have for all mRCC patients, 6000 in the UK, is cruel and in human."* *"I was always taught that God was to make that decision.....not the government or any other person."*	Comments noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Drugs are funded in other countries: *"If Sutent, together with Avastin, Nexavar and Torisel are cost effective to, and presently available in Europe why should they not be available in England and Wales?"* *"it would appear that by denying effective therapies to NHS patients that are available to citizens of other countries, the British government places less value on the lives of its citizens than other governments do on theirs"*	Comment noted. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions.

Theme	Response
Human rights legislation: *"It is against a person's human rights to refuse them life saving or life preserving treatment/drugs – no matter what the cost."*	Comments noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD section 4.3.4. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.3.11, 4.3.12 and 4.3.13. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
Disability or other equality discrimination: *"Although renal cancer affects only 2-3% of all cancer diagnoses in the UK and only 25% of these patients will present with the advanced disease, this should not place this minority group of people at a disadvantage. Indeed, to do so could be construed as actively discriminating against them."*	Comments noted. See above
Some people can afford private treatment while others can't	Comment noted. The Institute only issues advice to the NHS and cannot take private payments into account.
Unfair when treatments are funded for less deserving causes: *"How much does it cost a year for 1 asylum seeker, How much does it cost a drug addict on methadone. How much does it cost to give n alcoholic a liver transplant. How much does it/will it cost to fight this very hard to treat cancer? You people have very tough decision to make. But to give kidney cancer sufferers no hope at all is inhumane"*	Comments noted. The Committee does not consider the affordability that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3).

Theme	Response
NICE has not given sufficient consideration to subgroups	Comment noted. The Committee carefully considered all subgroup analyses where the evidence allowed. For sunitinib there was insufficient data to allow separate exploration of these subgroups. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus' for further details of the Committee's considerations of subgroups
National Insurance/tax payer/NHS, public sector worker/war veteran: *"Now you are refusing treatment to decent people like a London Fire Officer who became ill in the course of duty and the toxicity gave him terminal cancer"*	Comments noted. In developing clinical guidance for the NHS, no priority should be given based on individuals' income, social class or position in life and individuals' social roles, at different ages, when considering cost effectiveness (SVJ principle 8).
There should be an earlier review date for the appraisal	Comment noted. The guidance will be considered for review within two years of the publication date of the guidance. See FAD section 8.2.
There should be an 'only in research' recommendation (particularly for second line and those unsuitable for IFN)	Comment noted. See the ACD 'bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma' for details of the Committee's considerations about bevacizumab, sunitinib (second-line), sorafenib and temsirolimus.
The implementation section appears redundant and a waste of resources if none of the technologies are recommended for use	Comment noted. This comment is being considered within the Institute.

Theme	Response
I believe this judgement to be heavily flawed due to the underestimation of the benefit of these agents. As acknowledged in your report, all major trials in this area are contaminated by crossover to active therapy. We have audited our survival with renal cancer by postcode - we have around 40 pts who received sorafenib or sunitinib and compared them with survival in pts from areas not funding the drugs who had funding declined in the same time period. Pts were well matched for prognostic factors. Median survival was 7 months for those with no drug access versus >22 months for those receiving treatment giving a hazard ratio of 0.46. Resource use, captured from PBR data, was similar for the two groups but spread over a much longer time period in those on active treatment as opposed to best supportive care. We have posted our audit on the BMJ website: http://www.bmj.com/cgi/eletters/337/aug14_1/a1262#200895 I am happy to provide the Committee with a detailed rundown of our data, which we are currently preparing for publication.	Comments noted. The Committee understood that there had been both crossover after disease progression, but also participants had had second-line treatment after the study had ended. This could be expected to exaggerate overall survival estimates for people in the UK receiving IFN-α in the future, as the Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate. Updated evidence was submitted by the manufacturer of sunitinib which was incorporated into the analyses and considered fully by the Committee. See FAD sections 4.1.3, 4.2.4, 4.2.5, 4.2.10, 4.2.11, 4.2.12, 4.2.13, 4.3.7, 4.3.8, 4.3.9, 4.3.10 and 4.3.13.