NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Sunitinib for the treatment of gastrointestinal stromal tumours

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
Pfizer	Sunitinib is both clinically and cost-effective, compared to best supportive care, when used to treat patients with gastrointestinal stromal tumours. It is understood why the Committee is minded not to recommend sunitinib and trust that the provision of the requested analyses will provide sufficient reassurance that sunitinib is affordable to the NHS.	Comment noted. See detailed responses below.
Pfizer	Pfizer's response to the Appraisal Consultation Document is focused upon providing the following additional information: 1. Detailed explanation of the application of the rank preserving structural failure time (RPSFT) model and justification for its use within the base case of our economic analysis 2. An assessment of the impact upon cost effectiveness of including within the sunitinib costs, additional costs associated with continued use of sunitinib after disease progression 3. An analysis of sunitinib costs that is based upon the sunitinib treatment duration in the expanded access protocol A6181036 4. An analysis that censors patients assigned to best supportive care at the point they crossed over to receive sunitinib. 5. Complete updated probabilistic sensitivity analyses for each of the above analyses	Comment noted. See detailed responses below.
Pfizer	For comparison with the base case analysis, Table 1 presents each additional analysis and their associated PSA estimates (Weibull parameters for each analysis can be found in Appendix 1). While we recognise these are important analyses for testing the variability of the ICER for sunitinib vs. BSC; we are concerned that these analyses each have their own limitations and biases and consequently we maintain that the base case we originally submitted reflects appropriately the benefit of using sunitinib to treat patients with GIST. These additional analyses were performed in response to NICE's request. *Table 1 and Appendix 1 provided, but not reproduced here.*	Comment noted. The additional analyses were submitted in time for the second meeting and were appraised by the Evidence Review Group and considered fully by the Committee. See FAD sections 3.17, 3.18, 3.19, 3.20, 3.21, 4.5, 4.6 and 4.7.

Consultee	Comment	Response
Pfizer	In addition, sunitinib for the treatment of GIST should be considered adopting the supplementary criteria for evaluating end of life medicines. The reasons for this are provided below related to the criteria established by NICE: The treatment is indicated for patients with a short life expectancy, normally less than 24 months; - Whilst there is little published data examining life expectancy for patients with advanced /metastatic GIST who have failed imatinib therapy, UK clinical expert opinion suggests that this patient group will live for circa 9 months if they do not have access to sunitinib. Of note, the RPSFT analysis estimated survival in the BSC group to be approximately 39 weeks which is similar to clinical expectation. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, - The RPSFT analysis of the A6181004 trial suggests that sunitinib offers patients on average an additional 9 months of life compared to BSC, which is the current standard NHS treatment for this patient group. No alternative treatment with comparable benefits is available through the NHS, - Sunitinib is the only drug licensed for use post-imatinib failure in advanced/ metastatic GIST. The treatment is licensed or otherwise indicated, for small patient populations. - Estimates vary widely on the incidence of new cases of GIST in the UK, with figures between 200 and 2,000 quoted (NICE, 2004), with an apparent acceptance of an upper limit of 240 (NICE, 2004). Approximately half of new cases of GIST are likely to be metastatic and/or unresectable on first presentation. (NICE 2004)	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 4.8. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.9, 4.10 and 4.11.

Consultee	Comment	Response
Pfizer	1) **Detailed explanation of the application of the rank preserving structural failure time model and justification for its use within our economic analysis** As discussed within our submission, the results of the ITT overall survival analysis within our clinical trial are confounded by treatment crossover to sunitinib in the placebo arm. Although a common approach to this problem is to censor placebo arm patients at the point of crossover, we maintain that in this instance, this would be invalid as a) crossover is informative and patients who crossover are unlikely to be comparable to those who do not; b) crossover occurred very early in the time span of the clinical trial; c) a large proportion (84%) of patients crossed over.	Comment noted. The additional clarification of the RPSFT method was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee acknowledged that the RPSFT was an appropriate method to account for crossover in this situation. See FAD sections 3.19, 3.21 and 4.4.
Pfizer	Based on these factors, Pfizer identified the RPSFT analysis as the most appropriate statistical analysis for these data. This methodology can correct for time-dependent treatment changes in survival data whilst respecting the randomisation. (Robins et al 2004). The results from applying this methodology to the sunitinib A6181004 trial were presented at ASCO 2008. In preparing for the NICE submission Pfizer sought independent validation concerning the applicability of this method in this setting. Mr Ian White, a biostatistician at the Institute of Public Health, confirmed the appropriateness of RPSFT and provided additional confirmation that Pfizer had carried out the methodology correctly. Mr White provided further guidance concerning the use of the original ITT p value as it was considered scientifically inappropriate to revise the p value based on the data estimated with RPSFT. In addition, Mr White suggested re-censoring of the data which Pfizer also undertook and used within our base case analysis. Contrary to the suggestion we had carried out the methodology incorrectly, Mr White agreed with the methodology performed and Pfizer applied his advice to the analysis to ensure we were consistent with the current thinking. Consequently, as agreed by both independent statistical expert advice and the Evidence Review Group (ERG), in this situation the correct analytical approach is to use the rank preserving structural failure time (RPSFT) model.	Comment noted. See detailed response above.

Consultee	Comment	Response
Pfizer	The purpose of this post-hoc analysis was to estimate the 'true' treatment difference in overall survival between sunitinib and placebo, as if the placebo patients had not crossed over on to sunitinib. Unlike simply censoring overall survival at the time of crossover from placebo to sunitinib treatment, the RPSFT analysis relates a patient's observed event time in the placebo arm to an event time that would have been observed if crossover to sunitinib treatment had not occurred, assuming treatment has a multiplicative effect on a patient's lifetime. This approach produces a randomisation-based effect estimator; that is, the treatment estimate is based on the treatment arms as randomised, thus avoiding many of the potential pitfalls and biases introduced with subgroup analyses. Appendix 2 provides further details upon the methods used. *Appendix 2 provided, but not reproduced here.*	Comment noted. See detailed response above.
Pfizer	RPSFT methodology is based upon randomisation, and therefore does not change the level of evidence against the null hypothesis. It does change the estimated hazard ratio, bringing it further from the null, consequently the 95% confidence intervals of the revised hazard ratio are wide. When the placebo data is adjusted for crossover using the RPSFT method, this produced a hazard ratio of 0.505 (95% CI: 0.26 to 1.13).	Comment noted. See detailed response above.
Pfizer	In our base case economic analysis Weibull curves were fitted by linear regression to the observed overall survival curve for sunitinib and independently for the estimated RPSFT curve for BSC. This provided the best fit to both the sunitinib and BSC data, hence we maintain this is the most appropriate base case. In sensitivity analysis we explored fitting Weibull curves to the RPSFT curve for BSC and applying the hazard ratio to this curve to estimate the sunitinib curve. Using the hazard ratio to predict the sunitinib curve, however, gives a poor visual fit between the modelled and empirical sunitinib curve. As an alternative, the ERG fitted Weibull curves to the sunitinib empirical evidence and applied the reciprocal of the hazard ratio to estimate the BSC curve (Figure 1). With this approach the curve for the BSC data could be considered a poor fit. Using this alternative approach results in a cost per QALY estimate of £25,783 and is 58% cost effective assuming a willingness to pay of £30,000 per QALY (see Table 2). *Figure 1 and table 2 provided, but not reproduced here.*	Comment noted. See detailed response above.

Consultee	Comment	Response
Pfizer	**2) An assessment of the impact upon cost effectiveness of including within the sunitinib costs, additional costs associated with continued use of sunitinib after disease progression** In our base case economic analysis, patients stop sunitinib treatment at disease progression and therefore, sunitinib costs are only incurred for the progression-free phase of the model. Although 22% of sunitinib patients within the clinical trial remained on treatment beyond disease progression, there is insufficient evidence to understand whether this would happen within clinical practice. However, for the purpose of informing NICE decision making, we present estimations for the impact of including additional costs with the continued use of sunitinib after disease progression. In assessing the cost of using sunitinib beyond disease progression, we have used the formula as suggested by the ERG (page 87 of the ERG report); however when recreating this formula within our model, we noted the cost per patient of sunitinib in PD differed from that reported by ERG (£2,229 calculated by Pfizer, £2,237 calculated by ERG). As we wanted to test individual parameters within this formula, we have used the value we calculated.	Comment noted. The additional analysis including the sunitinib costs given after disease progression was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee concluded that the sources of sunitinib effectiveness data and cost data should be consistent and that costs of sunitinib given after disease progression should be included. See FAD sections 3.17, 3.20, 4.6 and 4.7.
Pfizer	Within sensitivity analysis we altered the following parameters within the ERG formula: • Proportion of patients continuing to receive sunitinib in PD • Mean duration of patients who took sunitinib in PD • Dose intensity of sunitinib while taken in PD The cost effectiveness results generated by including the additional costs associated with sunitinib after disease progression are detailed in Table 1, and the sensitivity analysis results are shown in Table 3. *Table 3 provided, but not reproduced here.*	Comment noted. See detailed response above.

Consultee	Comment	Response
Pfizer	3) **An analysis of sunitinib costs based upon sunitinib treatment duration in the expanded access protocol A6181036** Pfizer recognises the concern raised by NICE with regards to a difference in the median TTP in the sunitinib arm derived from RCT and EAP. The rationale for these differences is unclear and may be a consequence of a number of factors as listed in Table 4. *Table 4 provided, but not reproduced here.* We understand the Committee's rationale for exploring this data, as observational studies such as the EAP can reflect "real-world" effectiveness of the intervention. However, the results should be considered with caution as they are susceptible to bias due to internal and external validity issues such as the lack of control of confounding factors. Hence, it could be argued that the phase III RCT A6181004 study is the best evidence to support the use of sunitinib in patients with advanced GIST. The EAP results support the pivotal RCT and provide more insight into the efficacy and safety of sunitinib. The use of this data within the economic analysis is problematic and leads to a bias against sunitinib for the following reasons: • There is no control arm in the EAP hence the relative benefit of sunitinib versus BSC is unknown for the EAP and may differ to that from the RCT • At the time of enrolment the positive results from the A6181004 study had been publicly presented. Therefore sunitinib may have been chosen by patients or physicians with this knowledge, coupled with a more 'relaxed' inclusion criteria, potentially leading to a different patient population At the time of data cut-off 50% of patients were still alive in the EAP compared to 30% in the RCT. Thus, although the overall survival results appear comparable between the RCT and the EAP, the EAP results could be an underestimate of overall survival	Comment noted. The additional analysis including the sunitinib costs based on the treatment duration in the EAP was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee concluded that the sources of sunitinib effectiveness data should be consistent with those for best supportive care and that the EAP was subject to bias. See FAD sections 3.18 and 4.5.

Consultee	Comment	Response
Pfizer	In order to incorporate the EAP data into our economic analysis it is believed greater uncertainty has been introduced into the cost-effectiveness results. Within this analysis (presented in Table 1), we have used the EAP data to model sunitinib time to tumour progression and overall survival (see Figure 2) and the PFS data and RPSFT analysed data to model the BSC comparator. In the sensitivity analysis presented in Table 5, we have used alternative methods for fitting the four sets of curves to explore the sensitivity of the methods. *Figure 2 and table 5 provided, but not reproduced here.*	Comment noted. See detailed response above.
Pfizer	4) **An analysis that censors patients assigned to best supportive care at the point they crossed over to receive sunitinib** As the ERG has indicated, patient cross over is a recurring problem in cost-effectiveness assessments of cancer drugs and that analysis based on the unadjusted ITT data would underestimate the true relative effect of sunitinib. Traditional approaches to correct for crossover involve censoring placebo patients at the point of crossover so that the overall survival is based on only placebo data. However, as previously discussed, this method has a number of issues associated with it, namely, a) crossover is informative and patients who crossover are unlikely to be comparable to those that do not; b) crossover occurred very early in the time span of the clinical trial and c) a large proportion (84%) of patients crossed over from placebo to sunitinib treatment.	Comment noted. The additional clarification of the RPSFT method was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee acknowledged that the RPSFT was an appropriate method to account for crossover in this situation and that censoring produced implausible results. See FAD sections 3.19, 3.21 and 4.4.

Consultee	Comment	Response
Pfizer	Following the recommendation of the independent DMC after the interim analysis of trial A6181004, Pfizer decided that the trial be completely unblinded and patients who were randomised to placebo, who had not already crossed over to sunitinib at tumour progression prior to interim analysis, were able to crossover to sunitinib treatment even in the absence of tumour progression; this crossover was not mandated but left to the discretion of the investigator. Hence, the decision to cross a patient over to sunitinib treatment was an informed decision. Patients who were not crossed over to sunitinib treatment may have been too ill to benefit from crossing over or they may have had indolent disease and may not have needed to crossover. Either way, data from patients who crossed over and patients who did not crossover cannot be considered representative of the entire placebo randomised population with both subgroups being a biased sample. Any estimation based on censoring the data of patients who crossed over (at the time of crossover) and relying solely on the longer-term follow-up of patients who did not crossover is fraught with bias.	Comment noted. See detailed response above.
Pfizer	For exploratory purposes we have summarised time to death and produced Kaplan-Meier curves for both an analysis that censors patients at crossover and for the subgroup of 15 of patients who did not crossover from placebo to sunitinib treatment. Median overall survival for BSC when patients are censored for crossover is 156 weeks vs. 72.7 weeks for sunitinib (hazard ratio 0.824, 95% CI: 0.454, 1.499). Median overall survival for the BSC patients who did not crossover is 9.7 weeks.	Comment noted. See detailed response above.
Pfizer	Figure 3 presents these Kaplan-Meier overall survival curves for comparison with the placebo overall survival ITT curve and the placebo curve generated using the RPSFT methodology. The Kaplan-Meier plot for patients censored at crossover results in a vast overestimation of BSC benefit as the majority of patients crossed over and, as crossover occurred early, only 13 patients had died before censoring. Conversely, the Kaplan-Meier plot for the few patients who did not crossover shows a rapid decline in survival and may provide a worse case scenario for patients with GIST treated with placebo (see Appendix 3 for a comparison of the Kaplan-Meier estimates used in these two analyses). Given the relative small numbers contributing to these two subgroups we urge caution when interpreting this data and are not confident that these present a valid assessment of placebo survival that can be used within economic modelling for decision making. *Figure 3 provided, but not reproduced here.*	Comment noted. See detailed response above.

Consultee	Comment	Response
Pfizer	While these analyses present a very biased estimate of survival for BSC, we have used these values in sensitivity analysis to test our base case results. Using the overall survival data from the analysis in which BSC patients were censored at crossover results in BSC dominating sunitinib that is sunitinib costs more but produces less benefit (see Table 1). When the overall survival data for the patients who did not cross over is used instead of the RPSFT derived overall survival data the cost per QALY for sunitinib compared to BSC is £20,618 (see Table 6) *Table 6 provided, but not reproduced here.*	Comment noted. See detailed response above.
Pfizer	**5) Complete updated probabilistic sensitivity analyses for each of the above analyses** For ease of reference, complete probabilistic sensitivity analyses (PSAs) have been presented when describing the results for each requested analysis. The probabilistic variables have been corrected for errors and omissions identified by the ERG. Where applicable, probabilistic analyses have been conducted using two alternative ways of estimating efficacy; a) Weibull parameters for BSC are calculated and HR applied to estimate sunitinib survival curves and b) Weibull parameters for sunitinib are calculated and the HR is applied to estimate BSC survival curves. We have used both approaches as in some instances the Weibull parameters for BSC remain unchanged even though sunitinib survival has changed. Therefore, to run the PSA using Weibull parameters would not investigate the sensitivity within the parameter changes.	Comment noted. The updated probabilistic sensitivity analyses were submitted in time for the second meeting and were appraised by the Evidence Review Group and considered fully by the Committee. See FAD sections 3.20, 3.21 and 4.7.

Consultee	Comment	Response
Pfizer	**Conclusion** In conclusion, although it is understood why the Committee were minded not to recommend sunitinib we trust that in providing the requested analyses the Committee has sufficient reassurance to recommend sunitinib for the treatment of GIST. While the additional analyses demonstrate the variability of the ICER, the RPSFT methodology is the correct analytical approach to use in interpreting the clinical evidence for sunitinib. Pfizer's use of this methodology has been guided by independent statistical expert advice and the additional detail presented within this document should reassure the Committee that the methods have been used correctly. The extra analyses presented within this ACD response support the conclusions of Pfizer's original submission that sunitinib is both clinically effective and cost-effective for the NHS compared to best supportive care, when used to treat patients with gastrointestinal stromal tumours.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and detailed responses above.
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	**Do you consider that all of the relevant evidence has been taken into account?** We believe that all the available data have been made available and have been reviewed. However we do not believe that all relevant evidence, in the form of expert clinical interpretation from specialists treating GIST, and from patient submitted information, has been taken fully into account.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the professional and patient groups' submissions, the Assessment Group's economic analysis and the manufacturer's submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment report and the Appraisal Consultation Document.

Consultee	Comment	Response
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	**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 summary of clinical efficacy concludes that sunitinib is an effective treatment for this group of patients. We welcome this conclusion.	Comment noted. No actions required.
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	We do however wish to clarify and comment on points made in the Evaluation Report. In the additional notes on page 2, the first assumption, that treatment has the same effect on everyone, is untrue. We know that a proportion of patients get no benefit from sunitinib, but since this can be determined during the first cycle, funded by Pfizer under current arrangements, there is no risk to the NHS.	Comment noted. The economic analysis provided by the manufacturer assumed that 20% of all patients who start taking sunitinib do not complete the first cycle of treatment and this was derived from the trial.
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	We also know that about the same proportion of patients gain between 5 and 15 months of PFS. A small but very important group of patients gains long-term PFS. We do not know yet how long this can be: the longest we know of has now passed the 4-year mark. We also do not know in detail how to predict which patients will fall into which of these groups. We do know that the mutation type is a valuable predictor: patients with exon 9 mutations or those with wild type GIST, including the very rare but very important paediatric GIST patients, generally respond less well than other patients to imatinib, but better to sunitinib.	Comment noted. The economic analysis provided by the manufacturer was carried out according to the scope agreed at the scoping workshop. The analysis did not include mutation testing, as this does not routinely happen in the NHS. The economic analysis is based on mean time to progression and mean overall survival.

Consultee	Comment	Response
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	In the same paragraph it is stated that, "This is not necessarily true, but minor departures probably won't matter much." It may not matter very much to the analyst, but it matters a great deal to patients, especially if they belong to one of the groups of patients who stand to benefit most from sunitinib, or are parents of a child or teenager with GIST.	Comment noted. The Summary of Product Characteristics states that sunitinib use in paediatrics has not been established and sunitinib should not be used in a paediatric population until further data become available. The Appraisal Committee does not make recommendations regarding the use of a technology outside the terms of its marketing authorisation, as set out in the summary of product characteristics. See guide to the methods of technology appraisals, section 6.1.8.
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	On page 2 of the pre-meeting briefing, third bullet point, the issue of the 54 patients who continued to take sunitinib after progression is discussed. Today these patients would most probably be entered into a Phase I/II clinical trial, and not continue on sunitinib. We know that there is often clinical benefit in staying on sunitinib after progression, because some of the tumour(s) are still responding. However new treatments and combinations of drug treatments are being studied. We suspect that the proportion of patients who stay on sunitinib after progression has already decreased markedly, and will continue to do so. The issue in the paragraph is now of less significance.	Comment noted. Additional analysis including the sunitinib costs based on the treatment duration in the EAP was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee concluded that the sources of sunitinib effectiveness data should be consistent with those for best supportive care and that the EAP was subject to bias. See FAD sections 3.18 and 4.5.

Consultee	Comment	Response
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	The question is raised about whether patients take more than the NICE approved 400mg dose of imatinib. We know that in the UK, there are a number of patients who are taking escalated doses under a compassionate support programme funded by Novartis. Many of these have the rare exon 9 mutation, wild type GIST or paediatric GIST. Some of these are still receiving the 800mg dose to which they were randomized on the trial starting in 2001. Most receive it because of disease progression. We believe that most oncologists will increase the dose of imatinib after progression on 400mg, before moving the patient onto sunitinib. A Phase 3 randomized trial is now underway to examine this choice.	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 in whom their condition is resistant or intolerant to imatinib.
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	The summary of cost effectiveness gives us cause for great concern. We applaud the committee's request for further information from Pfizer, the manufacturer.	Comment noted. No actions required.

Consultee	Comment	Response
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	It is clear from the ACD, and from the public session of the Committee's meeting, that the Evidence Review Group (from Peninsula) was unable to address the Committee's questions about how Pfizer applied its choice of the Rank Preserved Structural Failure Time (RPSFT) model in analyzing comparators for cost effectiveness. This raises questions about the procedures employed by NICE in this Appraisal. If the ERG is to act as expert adviser to the Committee they should be in the position of addressing the committee's concerns to the manufacturer prior to the meeting, not afterwards. It is worth noting that Pfizer's health economist working on this Appraisal was in the room, albeit as a member of the public. Her presence would have been known about by NICE personnel in the room as all public attendance is pre-registered. She was not called upon to respond to questions which could have been addressed, and possible resolved, quickly. While such a step may be unusual, we believe the Committee faced an unusual problem – lack of competence by the ERG. The failure to adapt to this unusual situation reflects badly on NICE. Although we cannot know what took place during the Techonology Appraisal committee's secret session it was quite apparent in the public session that the malfunctioning of procedure was creating a blockage for the Committee. This is reflected by the extensive discussion of this issue in the ACD.	Comment noted. In the combined 10 year experience of NICE and its academic advisors the RPSFT method had never been submitted before. The ERG attempted to seek further clarification from the manufacturer and independent statistical advisors about the RPSFT method prior to the first Committee meeting. Public consultation has now resulted in more clarity from the manufacturer on the RPSFT method. The Committee meetings are held in public but do not allow for engagement with the public and/or only one stakeholder.

Consultee	Comment	Response
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	We have availed ourselves of NICE's offer to inspect the Pfizer economic model. This model comprises 17 interconnected Excel spreadsheets. It is complex and difficult to penetrate, especially considering the absence of adequate internal commenting. It is a case of trying to deduce what the question was by examining the answer. However we did detect one glaring error in cell K64 of the Budget Impact sheet, where the total has omitted the BSC cost of £334,771. This in turn results in an overstated Budget Impact of £334,771 for year 2011. In other words the Sutent route is made to appear more expensive than it should be for 2011.	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. See section 6.2.14 of the guide to the methods of technology appraisal (http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

Consultee	Comment	Response
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	It is easy to understand how errors of this kind can be made by the original builders of the model, but what really concerns us is that the error was not spotted in the course of all the subsequent analysis, and that the error has been carried forward verbatim on to page 87 of the Pfizer submission in the Evaluation Report. If errors of this kind can slip through, it can only sap our confidence in the ERG as independent experts in examining the more complex aspects of the model.	Comment noted. The ERG is not commissioned to review the budget impact of a technology. In addition, 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. See section 6.2.14 of the Guide to the methods of technology appraisal (http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf). A costing template outlining the budget impact of sunitinib for the treatment of GIST will be produced by NICE in consultation with the manufacturer.

Consultee	Comment	Response
A Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	The number of patients in the RCT was small (235 on treatment, 115 on placebo – numbers vary according to the point reported). The comparison of TTP was so significant that the trial was stopped and remaining placebo patients crossed over to active treatment. Of the 99 patients who had crossed over prior to the trial being stopped 13 achieved an objective partial response. Overall survival (OS) is the most robust measure for assessing cost effectiveness and median OS for patients who received sunitinib through randomsation or cross-over was similar. Eliminating the effect of cross-over is the purpose of analysis using the Rank Preserved Structural Failure Time (RPSFT) model.	Comment noted. Additional clarification of the RPSFT method was submitted by the manufacturer in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee acknowledged that the RPSFT was an appropriate method to account for crossover in this situation and that censoring produced implausible results. See FAD sections 3.19, 3.21 and 4.4.
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	The analysis of RPSFT on overall survival data was presented at ASCO in 2008[1]. It demonstrated correlation with the interim analysis of the trial using Kaplan-Meier methods, suggesting a valid approach to estimating OS for the placebo group should the trial have remained blinded. The critical group of patients in this analysis is therefore the group of 13 who extended the overall survival of the placebo group by responding to sunitinib following cross-over. We do not believe it is valid, in any scientific or moral sense, to determine the future of this treatment in the NHS on suppositions about statistical models, however academically robust they may be, based on a group of 13 patients.	Comment noted. See detailed response above.

[1] Novel statistical analysis of long-term survival to account for crossover in a phase III trial of sunitinib (SU) vs. placebo (PL) in advanced GIST after imatinib (IM) failure. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 10524). Authors: G. D. Demetri, X. Huang, C. R. Garrett, P. Schöffski, M. E. Blackstein, M. H. Shah, J. Verweij, V. Tassell, C. M. Baum, P. G. Casali

Consultee	Comment	Response
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	One further consideration which needs to be taken into account, when considering the availability or non-availability of Sutent, is the psychological well-being of the patient. How a patient feels about his future, and whether he can see some sort of hope for his condition, is a very important part of how he will assess his quality of life when he is asked to do so. In the A6181004 trial all the patients, whichever arm they were in, would have known that they were participating in a trial aimed at improving their outcome. This knowledge in itself would have put a positive bias on how they reported their EQ-5D status. If patients in the UK, who have failed on Imatinib, know that there is a drug which might help them, but which is not available, this fact in itself will adversely impact their quality of life, because of the negative emotions engendered. No account of this appears to have been taken in the course of NICE's deliberations so far.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	**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 - for the following reasons: Sunitinib is an effective and generally well tolerated medication that usefully extends survival and maintains quality of life in patients with GIST after failing imatinib. The ACD recognises this clinical benefit.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Consultee	Comment	Response
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	The magnitude of benefit seen in the registration trial has been exceeded in clinical practice. Owing to the rarity of this disease gathering retrospective data and publishing case series is problematical. To support this assertion we note that an increase in overall survival was observed at the time of the interim analysis of the registration study, including data on patients allowed to cross-over to active treatment following progression on placebo. The ERG/PENTAG group acknowledged that Pfizer's method for calculating cost-effectiveness (RPSFT) was superior to using the data from the whole trial, even though it failed to defend this expert opinion to the Appraisal Committee.	Comment noted. Additional clarification of the RPSFT method was submitted by the manufacturer in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee acknowledged that the RPSFT was an appropriate method to account for crossover in this situation and that censoring produced implausible results. See FAD sections 3.19, 3.21 and 4.4.

Consultee	Comment	Response
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	NICE now accepts the principle that a medicine can be approved for use if certain rarity criteria apply and the medicine can be seen to be applicable to 'end-of-life'. This was applied in the recent FAD for sunitinib for renal cell cancer. The technology is used for treating a population of less than 7000 new patients a year (we estimate the relevant GIST population here to be 120-150) It is indicated for patients with a terminal illness and a life expectancy of less than 24 months (untreated median survival with GIST is <40 weeks) There are no alternative treatments available with comparable benefit via the NHS (this is the situation for patients with GIST resistant to imatinib) Assessment of cost-effectiveness places it above the range normally considered to be cost effective. We conclude that it is appropriate to consider sunitinib for GIST as an 'end-of-life' exception to the £30,000 cost per QALY gained benchmark.	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 4.8. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.9, 4.10 and 4.11
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	Failure to approve sunitinib for GIST patients who have relapsed on imatinib will effectively bring to an end all treatment options in the NHS for this small group of patients. Clinical trials (currently running and planned) of new technologies have entry criteria which require failure on sunitinib, a fully authorized standard treatment in 84 countries. Patients who have not received sunitinib are ineligible for these trials. Future marketing authorisation of such new technologies will reflect these criteria if current authorization practice is applied. Failure to approve sunitinib will therefore close future treatment options to GIST patients within the NHS.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Consultee	Comment	Response
Joint response from: Sarcoma UK, GIST Support UK and the Rarer Cancers Forum	**Are there any equality related issues that need special consideration that are not covered in the ACD ?** Equality is not often discussed in the context of rarity of disease. The cohort of patients with relapsed GIST treated by imatinib is approximately 250 per annum in the whole UK. Accurate data is not available, despite NICE TAG86 (2004) recommending to the NHS that data are gathered. Of those resistant to imatinib at 400mg/d some are prescribed sunitinib. An estimate indicates that this is about 120 patients in England/Wales. Again, no data are available. At every turn the GIST community encounters the problem of numbers, an inescapable result of rarity. We can accept that NICE makes no allowance for rarity when developing its procedures. However we believe that Technology Appraisals must acknowledge extreme rarity (ultra-orphan conditions), and make allowances for the problems it presents to clinicians, patients and manufacturers in making a case for approval. Demonstration of that understanding would be appreciated, and matters just as much as any demonstrations of the understanding of issues concerning the ethnic, religious, cultural or sexual realities of life.	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 4.8. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.9, 4.10 and 4.11.
Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) of the technology appraisal of Sunitinib for the treatment of gastrointestinal stromal tumours. Nurses working in this area of health have reviewed the ACD for this appraisal on behalf of the RCN. The RCN notes that the Appraisal Committee has recommended that NICE request further clarification from the manufacturer of sunitinib to inform the use of this technology. We look forward to reviewing the report following the second Appraisal Committee.	Comment noted. No actions requested.
Expert 1	Thank you for giving me the opportunity to respond to the ACD. I appreciate that additional information has been requested from the manufacturer and that this is a provisional decision that might be altered in response to new information.	Comment noted. No actions requested.

Consultee	Comment	Response
Expert 1	**Do you consider that all of the relevant evidence has been taken into account?** Yes, I believe that all the available data have been made available and have been reviewed.	Comment noted. No actions requested.
Expert 1	**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, I have serious concerns about the interpretation of the evidence, as discussed below:	Comment noted. See detailed responses below.
Expert 1	<u>1. Clinical benefit</u> 1.1 I am pleased to see that the Appraisal Committee concluded that sunitinib was an effective treatment with a likely survival benefit for patients with GIST progressing on or intolerant of imatinib (4.2, page 13). This is certainly consistent with my own experience as a treating physician with a large population of patients with GIST, many of whom appear to have benefited greatly from this agent. Similarly, although serious side effects can occur, the fact that in the randomised clinical trial (RCT) the quality of life (QoL) as measured by the EQ-5D tool did not differ between the treatment and placebo groups (section 3.6, page 8 of the ACD) is consistent with the fact that most side effects are mild and can be managed with symptomatic treatment or by modifying the dose of the drug. Any drug-related detriment to QoL is compensated for by a decrease in disease-related symptoms. This is a point to which I will return when considering the definition of QUALY in relation to this agent.	Comment noted. See detailed responses below.

Consultee	Comment	Response
Expert 1	1.2 What is clear from the ACD and the discussion I took part in at the STA meeting on February 5, is that owing to the design of the RCT used to support the licence application there are some uncertainties regarding the magnitude of the benefit of sunitinib owing to the study being unblinded at the time of the interim analysis and the subsequent cross-over to active treatment of the majority of patients who were taking placebo at that time. The additional data considered concern an expanded access programme (EAP), termed the cohort study by the company, which was designed to make the drug available for patients who were ineligible for the RCT or without access to it. I think the key value of the EAP is that it confirms that sunitinib is safe and effective in this setting in a much larger group of patients. The differences in eligibility criteria and response assessment between the RCT and the cohort study may explain some of the differences observed in progression-free and overall survival between the two.	Comment noted. Additional analysis including the sunitinib costs based on the treatment duration in the EAP was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee concluded that the sources of sunitinib effectiveness data should be consistent with those for best supportive care and that the EAP was subject to bias. See FAD sections 3.18 and 4.5.
Expert 1	1.3 Median survival in the cohort study was 75 weeks, similar to the 73 weeks for the RCT (summarised in Table 16 on page 63 of the Expert Review Group (ERG) report) but that median time to progression (TTP) was 41 weeks rather than 29 weeks for the overall RCT and 27 weeks for the interim analysis. This seems a little surprising, since median performance status (PS) was slightly worse in the cohort study owing to less strict entry criteria. However, the figure of 29 weeks PFS for the entire study includes those patients allocated to placebo who crossed over to active treatment after unblinding but may have begun to progress prior to cross-over. By the time the study was reported in full the ITT analysis was effectively a comparison of early versus delayed sunitinib therapy.	Comment noted. Additional analysis including the sunitinib costs based on the treatment duration in the EAP was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee concluded that the sources of sunitinib effectiveness data should be consistent with those for best supportive care and that the EAP was subject to bias. See FAD sections 3.18 and 4.5.

Consultee	Comment	Response
Expert 1	1.4 A sub-analysis, as described in the ERG report in section 4.2.3 on page 61, in which patients with similar PS, i.e. 0-1, treated in the cohort study and the RCT were compared, gave figures of 88 weeks for OS in the expanded access study (EAP), otherwise known as the cohort study, versus 73 weeks for the RCT and for PFS 41 weeks versus 29 weeks respectively. This again suggests that there is a systematic bias based on disease burden in favour of the EAP. The discrepancy cannot be explained by the cross-over since the ITT interim analysis, which is not confounded by cross-over gives a figure of 27 weeks PFS on sunitinib.	Comment noted. Additional analysis including the sunitinib costs based on the treatment duration in the EAP was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee concluded that the sources of sunitinib effectiveness data should be consistent with those for best supportive care and that the EAP was subject to bias. See FAD sections 3.18 and 4.5.
Expert 1	1.5 An additional confounding factor when comparing these studies is that to be eligible for the RCT patients had to have demonstrated disease progression using the strict size criteria of RECIST, whereas one of the eligibility criteria for the cohort study was not being eligible for the RCT, which could have been on the basis of disease measurability. This means that different criteria for assessment of progression might apply between the two studies. Perhaps in spite of the strict PS entry criteria the requirement for proof of disease progression by RECIST may have selected patients with bulkier, more rapidly progressive disease for the RCT.	Comment noted. Additional analysis including the sunitinib costs based on the treatment duration in the EAP was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee concluded that the sources of sunitinib effectiveness data should be consistent with those for best supportive care and that the EAP was subject to bias. See FAD sections 3.18 and 4.5.

Consultee	Comment	Response
Expert 1	2. Cost-effectiveness 2.1 When considering benefit, not in terms of disease control, or survival, which does not appear to be in doubt, but in terms of cost-effectiveness, what I think clinicians and patients find hard to accept is the apparent implication from some of the discussion in the ACD that the better a drug works, the worse its cost-effectiveness would be. This appears to be contrary to the normal rules by which we estimate the value of anything, especially a new drug. In particular, emphasis was placed on the fact that 22% of patients continued on sunitinib in the RCT after they had "progressive disease" according to RECIST as they were still experiencing clinical benefit (e.g. section 4.5, page 14 of the ACD). If the cost of treating these patients is taken into account the cost per QUALY increases, albeit only by £2,237 (section 5.4.1.2 page 87 of ERG report). I think it is reasonable to take this into account, since, as I explained on February 5, disease progression may occur according to RECIST owing to the development of a single new lesion, even when the overall disease burden is reasonably stable and under control of a drug such as imatinib or sunitinib. Thus treatment may continue while a patient is "benefiting clinically", in other words, while their disease-related symptoms are being controlled and areas of non-progressive disease are still responding to treatment. What patients sometimes describe when treatment is stopped in this situation is a rapid escalation in symptoms with deterioration in appetite, an increase in pain and abdominal distension, fatigue and weight loss. This "tumour flare" phenomenon may occur when all treatment is withdrawn, hence the entire tumour burden progressive, rather than simply the component that has become resistant to the tyrosine kinase inhibitor being administered.	Comment noted. Additional analysis including the sunitinib costs based on the treatment duration in the EAP was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee concluded that the sources of sunitinib effectiveness data should be consistent with those for best supportive care and that the EAP was subject to bias. See FAD sections 3.17, 3.18, 4.5 and 4.6.

Consultee	Comment	Response
Expert 1	2.2 Although the ERG accepted that it was an appropriate thing to do, I realise that there are difficulties in understanding how the rank preserved structural failure time (RPSFT) model was applied by the manufacturer. Whatever the drawbacks of the RPSFT it seems clear that it is more appropriate than using the ITT analysis of the entire study including the subsequent open label treatment with sunitinib in the absence of censoring. This is acknowledged in the submission by PenTAG on page 61. They actually state that the RPSFT is more appropriate than censoring the data at the primary endpoint yet this is specifically recommended as something to be explored in section 4.9, page 19 of the ACD.	Comment noted. Additional clarification of the RPSFT method was submitted by the manufacturer in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee acknowledged that the RPSFT was an appropriate method to account for crossover in this situation and that censoring produced implausible results. See FAD sections 3.19, 3.21 and 4.4.
Expert 1	2.3 At the time of the interim analysis, when the trial was unblinded on the advice of the IDMC, there was a highly statistically significant difference in survival. This occurred in spite of the fact that patients were allowed to cross-over to sunitinib on progression if they were found to be on placebo and were still fit enough to receive the drug. The criteria for allowing cross-over did, however, include RECIST assessable progression and maintenance of performance status 0-2 (not 0-1, I apologise if I misled the committee on this point). In other words their performance status was permitted to have deteriorated somewhat, since study entry demanded a PS of 0-1. The difference in survival must indicate either that a significant percentage of patients on placebo died before their disease status could be determined objectively or that they were no longer fit enough to receive sunitinib by the time it was proven that they had progressed. This latter problem could in part be due to the use of RECIST which is now acknowledged to be suboptimal in assessing response status in patients with GIST. The fact that the difference between the 2 arms dissipated over a further year of follow-up (Fig 4, page 45 or ERG report) is hardly surprising, given that the majority of patients who had been assigned to placebo and were still alive and well were given the active drug. As acknowledged, an intention to treat analysis of the entire study period up to the time that median survival had been reached in both arms merely compares immediate with delayed sunitinib therapy.	Comment noted. See detailed responses above.

Consultee	Comment	Response
Expert 1	2.4 I was present in the open part of the STA meeting when the RPSFT model was discussed and strongly criticised. It seemed surprising to me as an observer was that the representatives from PenTAG did not seem to be expressing such negative views. A lot of the discussion had been prompted by the fact that an independent expert on the model had challenged certain assumptions and in particular the narrow confidence intervals for the hazard ratio proposed by Pfizer. A comment was made that these confidence intervals were impossibly narrow. Again from the naïve perspective of a treating physician I find this puzzling. It can be seen that according to intention to treat at the time of the interim analysis, the sunitinib and placebo arms were diverging, both for PFS and OS. This occurred in spite of the fact that patients were allowed to cross-over to sunitinib on progression within the RCT. What the RPSFT does is assume that patients remained on the allocated treatment and then looks to see what would have happened to them. This does not really mimic what would have happened if the trial had not been unblinded in January 2005. What if we examine another hypothesis? Whatever determined the death of the patients in the placebo arm, as discussed above in 2.3, it would have continued to happen if the trial had continued to accrue patients in a blinded fashion for, let us say, another year. In this situation it is surely not unreasonable to assume that the curves would have continued to separate because a proportion of placebo patients would have failed to cross-over on progression or would not have been salvaged owing to the extent of disease progression and would have died earlier than if they had been on active treatment from the time of randomisation. In this case while the hazard ratio may have been the same, the confidence interval (CI) would surely have been narrower and the HR even more significant than it was at the time of the interim analysis, when it was 0.491 (CI 0.29 – 0.833) P = 0.007 (Fig 2, page 43 of the ERG report). It seems very unlikely that the survival benefit observed was due to chance when the PFS curves are considered (Fig 1, page 42 of the ERG report). It is unfortunate if it is deemed that the RPSFT is not able to produce a more reliable figure for the survival benefit of sunitinib than that seen at the time of the interim analysis which is only perhaps thought to be suspect because median survival had not yet been reached. To me, this seems arbitrary and unnecessary.	Comment noted. Additional clarification of the RPSFT method was submitted by the manufacturer in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee acknowledged that the RPSFT was an appropriate method to account for crossover in this situation and that censoring produced implausible results. See FAD sections 3.19, 3.21 and 4.4.

Consultee	Comment	Response
Expert 1	2.5 This brings me to the application of this discussion to the economic model. Section 3.12 it states that if instead of using the base-case ICER supplied by the manufacturer, which gave a figure of £27,365 per QUALY gained, if one uses the unadjusted ITT data the figure was £77,107. I presume, on the basis of the previous discussion, that this means the ITT analysis of the whole study. It then discussed using these data to model the placebo plus best supportive care overall survival curve. However, we know that the only data that can reasonably be used to model that curve are the data up to the time of the interim analysis. What I find the most disturbing statement of all is at the end of section 3.12. It is stated that on the basis of comparing the most favourable with the least favourable cost-effectiveness calculations there is a 50% chance of sunitinib being cost-effective. Is this a basis for not approving its use? Patients would willingly accept a 50% chance of a treatment being successful!	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
Expert 1	**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, I do not for the following reasons: Sunitinib is an effective and reasonably well tolerated medication that usefully extends survival and maintains quality of life in patients with GIST after imatinib failure.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
	The magnitude of benefit is under-estimated by the registration trial. A significant increase in overall survival was observed at the time of the interim analysis in spite of patients being allowed to cross-over to active treatment on progression.	Comment noted. The Committee agreed that the ITT analyses of the trial were confounded by crossover. See FAD section 4.4.

Consultee	Comment	Response
Expert 1	Whatever the strengths or weakness of the method proposed by Pfizer for calculating cost-effectiveness (RPSFT), it appears superior to using the data from the whole trial and was acknowledged by the ERG to be appropriate if used correctly.	Comment noted. Additional clarification of the RPSFT method was submitted by the manufacturer in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee acknowledged that the RPSFT was an appropriate method to account for crossover in this situation. See FAD sections 3.19, 3.21 and 4.4.

Consultee	Comment	Response
Expert 1	According to recent supplementary advice, within the scope of which sunitinib was approved for the treatment of renal cancer, a medicine could be approved for use if the following conditions apply 1. It be used for treating a population of less than 7000 new patients a year 2. It would be indicated for patients with a terminal illness and a life expectancy of less than 24 months 3. There are no alternative treatments available with comparable benefit via the NHS 4. Assessment of cost-effectiveness places it above the upper end of the range normally considered to be cost effective, i.e. £30,000 per QUALY gained. It would seem that sunitinib fits these criteria very well.	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 4.8. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.9, 4.10 and 4.11.
Expert 1	It is clear that if sunitinib is not approved for use in imatinib-refractory GIST this will be a step backwards in the management of this rare disease. Access to the drug via the exceptional use prescribing route would become even more difficult, if not impossible, and access to other new drugs would also become very difficult. This is because the standard treatments for GIST worldwide following progression on imatinib 400 mg daily are imatinib 800 mg daily and sunitinib. Certain clinical trials now about to start in the UK are restricted to patients who have received these interventions.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Comments received from commentators

Commentator	Comment	Response
Department of Health	Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted. No actions required.

Comments received from the public

Role	Comment	Response
Patient 1	these recommendations are very wrong and will take away a patients right to life. side effects are a lot less with sunitinib than with conventional chemo which does not work with GIST. SUTENT works and has been proved, particularly in other european countries and USA.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Role	Comment	Response
Patient 1	Evidence should only be accepted from experts in the field of GIST	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the professional and patient groups' submissions, the Assessment Group's economic analysis and the manufacturer's submissions. It also carefully considered the comments received from all consultees and commentators in response to the Assessment report and the Appraisal Consultation Document.
Patient 1	Most people we know of are not on the full dose of sutent so your cost effectiveness of the drug is impracticable	Comment noted. The cost effectiveness analysis provided by the manufacturer uses the dose intensity of sunitinib given in the trial.
Patient 1	research is very much needed, particularly as in other countries trials are pointing to the fact that Sutent is successfull for people who have different mutations of GIST. How many people are going to die in the meantime, we are supposed to be living in a civilised society.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Role	Comment	Response
Patient 2	I oppose the preliminary recommendation, for reasons given below. From my own point of view as a patient suffering from GISTs, I can add that my own case supports the argument for clinical effectiveness. Following surgery, which successfully removed a huge GIST, GISTs recurred, and at that point I was put on Glivec at the usual dosage of 400mg. This failed to work within a year, and the dosage was doubled. That too failed to work, I could feel another tumour growing inside me, and I was becoming more and more tired. My consultant asked my PCT (Oxfordshire) to permit the use of Sutent. Luckily, the PCT agreed, and I have now been on Sutent for three months. A scan has just shown that the tumour that was growing is shrinking and that the others are stable. I have much more energy than I did before starting Sutent. I can now go for runs again, and have just finished writing a book. Without Sutent, I would be looking to the end of things.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
Patient 2	NICE accepts the clinical effectiveness of Sutent (section 4.2). This is on the basis of statistical arguments relating to the first part of the trial, which seems to have demonstrated a very strong effect of the drug in slowing tumour progression Â (a very unusually significant effect statistically), and a somewhat weaker but still strong effect on survival time (Sections 3.2 and 3.3 respectively). The Pfizer statisticians then performed some unusual analyses to try and correct for the fact that since the drug showed such a strong effect early on, it would have been unethical to leave the control patients on the control alone, and thus they did some sort of imputation of what might have happened if those patients had continued on the control. I know that the Pfizer statisticians are offering a reanalysis of this data (at the request of NICE), but to my mind the crucial point is that the outstanding success of the drug in the first phase comprised the trial. This has resulted in a loss of power to detect differences in survival times, but in any case NICE accepts that they are probably lengthened (4.2).	Comment noted. Additional clarification of the RPSFT method was submitted by the manufacturer in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee acknowledged that the RPSFT was an appropriate method to account for crossover in this situation. See FAD sections 3.19, 3.21 and 4.4.

Role	Comment	Response
Patient 2	NICE should not rule out Sutent on cost grounds. Sutent does not work for everyone with GISTs, but as Pfizer will pay for the first cycle, the cost of non-effectiveness is very small. Of course, the cost of successful treatment is high, but this country should meet that cost: 1. The quality of life which Sutent gives is very high (to judge not only from myself, but also other GIST patients on Sutent). We can live near-normal lives. 2. NICE has agreed to fund Sutent for those with terminal kidney cancer, because the benefit of a little extra time for those with only a few months left to live is overwhelming. But it would be inconsistent and immoral not to extend this argument to GIST patients (who also suffer from an incurable disease). If every day matters for terminal kidney cancer patients, every day matters equally for us GIST patients, who will have quite a bit longer to live if we get Sutent. 3. The NICE Citizens Council has published a report with a number of strong arguments in support of the public funding of drugs like Sutent for GISTs. 4. Every other country in Europe, the States and Canada already prescribes Sutent for GIST patients.	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 4.8. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.9, 4.10 and 4.11..
Patient 3	I am very disappointed about the Committees "not minded" stance. Â This section seems to imply that the Committees only interest is cost and nothing else.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the professional and patient groups' submissions, the Assessment Group's economic analysis and the manufacturer's submissions. It also carefully considered the comments received from all consultees and commentators in response to the Assessment report and the Appraisal Consultation Document.

Role	Comment	Response
Patient 3	It would have been helpful if this statistical analysis could have been displayed in a modified version, easier to understand for people who are non-statisticians. Â However, there is no doubt that Sunitinib has a strong effect on survival time and is working well for patients receiving it.	Comment noted. Additional clarification of the RPSFT method was submitted by the manufacturer in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee acknowledged that the RPSFT was an appropriate method to account for crossover in this situation. See FAD sections 3.19, 3.21 and 4.4.
Patient 3	As NICE accepts that Sunitinib is clinically effective in treating GIST how can they have any doubt remaining that this drug should be made available to patients as needed. Â Because GIST has only been treatable with a drug, i.e. imatinib, for approx 8 years any additional drug shown to be clinically effective must surely be welcome. Â Imatinib and Sunitinib as a new generation of targetted cancer drugs represent hope for the future in that they may consign chemotherapy and radiotherapy to the medical dustbin. Â The doubts NICE has about the statistical analysis should not deter them from recommending a drug which is clearly very effective.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
Patient 3	Because GIST is such a rare cancer I imagine that there will always be some difficulty in recruiting numbers for trials and this should be taken into account.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Role	Comment	Response
Patient 3	If GIST ptients who will need Sunitinib are denied it then in all probability they wont be alive in 2012.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence. The guidance will be considered for review by two years after the publication date. See FAD section 8.2.
Patient 4	The language used in the consultation document is extremely technical and full of unnecessary jargon. Plain English is always preferable! Overall the negative terminology used by the committee is insensitive and unacceptable to patients who have GIST, and who may well not survive if sunitinib is not approved. Â Sunitinib has already been proven to be clinically effective within the global GIST community over many years of use. Â It is only in the UK that NICE is insisting upon more statistical trials, which can only confirm what is known to the rest of the world. Sunitinib works! Â The Committee's arguments on cost effectiveness are also unacceptable, since the UK comparisons and costs are not in line with studies carried out elsewhere in the world where sunitinib is already accepted for GIST. The Committee must be the only Quango or Government department not accepting European rulings. Â I ask the Committee to explain how Spain can not only accept sunitinib as cost effective for GIST, but also publish their detailed calculations in the public domain. Is the Committee now minded to publish its calculations with a comparison against the Spanish figures?	NICE is a corporate member of the Plain English Campaign and we do try wherever possible to use plain English in all of our consultation and guidance documents. However there are circumstances where the technical language associated with a particular treatment means that it would not be appropriate to reword the text used. NICE has produced a glossary to help people understand the technical terms in our documents (see: http://www.nice.org.uk/website/glossary/) because there are terms that can't be simplified. We are exploring whether in future a reference to the glossary can be added to the ACD consultation pages.

Role	Comment	Response
Patient 4	If the cost effectiveness of sunitinib has only been calculated using 50mg once daily, then the figures are almost certainly flawed and inaccurate. It is necessary to factor into the calculations, the lower dosages being taken by many GIST patients who are being successfully treated with dosages of 25mg or 37.5mg once daily. In other words the cost in their cases is 50% or 75% of the calculated figure.	Comment noted. The cost effectiveness analysis provided by the manufacturer uses the dose intensity of sunitinib given in the trial.
Patient 4	This section of the appraisal consultation document clearly indicates that the Committee is allowing its cost effectiveness remit to take precedence over its remit from the Department of Health to ensure the best care for all cancer patients. The manufacturer of sunitinib is under attack from the Committee for allowing the crossover of the placebo group once it was apparent that the trial group taking sunitinib were achieving better survival outcomes. Whilst there may be a case for requesting further details of the method used for the Committee's future information, it is also true that the ERG appointed by the Committee has admitted that, "they are not experts in the method, and do not have the required IPD to re-run the analysis." The ERG also accepted that an independent researcher working for the MRC, has published on the method used and endorsed the use of the method for crossover data. Â The Committee should be applauding the commonsense, and humanity of manufacturers who allow crossover in the interests of the patient, and use new methodology, rather than criticise them because they use statistical methods which are simply not known to the ERG which they appointed.	Comment noted. Additional clarification of the RPSFT method was submitted by the manufacturer in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee acknowledged that the RPSFT was an appropriate method to account for crossover in this situation. See FAD sections 3.19, 3.21 and 4.4.

Role	Comment	Response
Patient 4	The Committee states that,"it was also mindful of the need to take account of the effective use of NHS resources". It also concluded, "that sunitinib is a clinically effective treatment for unresectable and/or metastatic malignant GIST which is resistant or intolerant to imatinib." It is thus important for the Committee to clearly define the NHS resources to which it refers, and in particular the components of supportive care which it has taken into account. The cost of sunitinib as an effective and on-going treatment for GIST, which allows patients to function normally in society, without financial benefit claims, or treatment other than regular oncology consultations must be compared against the support required for a terminally ill patient, with all of the attendant financial and other benefits, and additional palliative treatment costs. GIST patients should at the present time be recognised as having an incurable illness which is treatable, but who may become terminally ill if denied the best drugs available in their particular case. NICE and its committees could of course sponsor research into a cure for GIST, when cost effectiveness exercises such as this will become academic.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
Patient 4	The outcome of the trial of sunitinib compared with 800mg of imatinib will clearly affect cost effectiveness calculations. It must also be recognised by the Committee that that many of the GIST patients currently being treated with sunitinib only transferred to it once 800mg imatinib ceased to be clinically effective. The full NICE appraisal of 800mg imatinib is still, I believe, awaited by GIST patients, and is long overdue considering the large number of GIST patients who have been, or are being treated with it. It is also a fact that many of the patients who have switched from imatinib to sunitinib are on lower sunitinib doses than 50mg once daily, and I believe that the cost of the lower dosage is in fact cheaper than the higher imatinib dose. Future research may also be necessary to ascertain whether a combination of both imatinib and sunitinib is a more effective treatment in some cases. NICE should sponsor routine mutation testing of all GISTs. This would be as a basis for research into the most effective use of all future GIST treatments determined by the GIST mutation type. It is probable that some mutations are resistant to imatinib but not to sunitinib and vice versa.	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 in whom their condition is resistant or intolerant to imatinib.

Role	Comment	Response
Patient 4	I repeat my earlier comment that that the full appraisal and approval for 800mg imatinib is still awaited, and is long overdue. Â I question the wisdom of having an overlap in appraisals for two treatments which are interrelated. Â It may be that some GIST mutations react favourably to 800mg imatinib, whilst others react better to sunitinib. It must be better to approve both treatments to allow maximum flexibility in treatment regime.	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 in whom their condition is resistant or intolerant to imatinib. The review of imatinib for GIST (TA 86) is to be undertaken, date is yet to be confirmed.
Patient 4	The proposed review date of March 2012 will be far too late for some GIST patients who will have succumbed to their illness by that time, and particularly if sunitinib is withheld. The very latest date should be March 2011, by which time more evidence of clinical effectiveness and cost effectiveness will be available. Â For sunitinib, its use for other forms of cancer is highly probable, which should have a significant effect on the manufacturer's cost structures. I also feel that the Committee should place less reliance on statistical models, and more on clinical outcomes and cost. This should speed up NICE appraisals and allow more flexibility in the review processes. In conclusion I recommend that the Committee heed the quotation used by Professor Sir Michael Rawlins in his speech to the Royal College of Physicians, "'God forbid that truth should be confined to mathematical demonstration'.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence. The guidance will be considered for review by two years after the publication date. See FAD section 8.2.

Role	Comment	Response
Patient 5	I am a GIST patient with secondary GIST in my liver, I am taking Glivec at the moment, but after 3-5 years on this drug I WILL become Glivec resistant, what will I be offered then... palliative care? What is the point of all this money being spent on research/trials etc if the drug is not utilised for the patients it has been proven to help, Â the NHS is funded by the public for the public and should therefore be for the benfit of the same. Thank you for taking the time to read this appraisal.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
Patient 6	It is not easy for a lay patient to get to grips with evidence which has been compiled by a group of professionals working, I am aware that you are working with a set of criteria which you have created for yourselves which you may say is not open to challenge. Nevertheless let me create my own criteria for challenging your apparent of the use of Sutent within the NHS, It is a drug which may be effective in a few very rare cases of GIST sufferers where Glivec is not effective. At this stage it means Sutent or death. Do not misunderstand the effect of your decision- what you are prescribing is death. You may claim to have economic justification to make such a decision but where is your ethical and moral justification for such inhumanity. If we were the only country in the world making such decisions then we should have no basis for judging whether you are acting reasonably but we are not alone. I do not know the world wide situation accurately but I feel fairly confident in saying that Eire, Spain, Mexico, Australia, most of EU, Canada and the USA are all countries which do approve the use of taxpayers money for the prescription of Sutent to GIST sufferers. Why not the UK?	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Role	Comment	Response
Carer 1	NICE have said they welcome responses from patients and carers. The report is, however, written in such unfathomable English that one might be forgiven for imagining that we are being deliberately deterred from responding.	NICE is a corporate member of the Plain English Campaign and we do try wherever possible to use plain English in all of our consultation and guidance documents. However there are circumstances where the technical language associated with a particular treatment means that it would not be appropriate to reword the text used. NICE has produced a glossary to help people understand the technical terms in our documents (see: http://www.nice.org.uk/website/glossary/) because there are terms that can't be simplified. We are exploring whether in future a reference to the glossary can be added to the ACD consultation pages.
Carer 1	In assessing side-effects from drugs it is important to allow for the fact that many patients will be content to tolerate these on a daily basis if they know the overall effect is beneficial.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Role	Comment	Response
Carer 1	The report highlights an extra cost arising from prescribing Sunitinib even after recommencement of disease progression. This cost could be offset if NICE continued to license new drugs which are already in the pipeline and known to work in reducing GIST tumours, for example, Nilotinib. I am concerned that a QALY is cited as though it were a scientific given, but it is, in fact, a subjective statistical model whose basis is not explained to us. The arbtrary figure of Â£30,000 as the annual ceiling for quality of life valuations has not been revised for many years. Does this include the health costs from carers fatigue and bereavement care to the family of the patient?	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the methods of technology appraisal, section 5.4.1. (http://www.nice.org.uk/media/B52/A7/TAMethods Guide UpdatedJune2008.pdf)
Carer 1	The committees conclusion flies in the face of the evidence cited in the report that Sunitinib works. It is also the opposite to the conclusion of the health insurance committee in Mexico - a much poorer country than England - which found in favour of using Sunitinib for GIST. It takes no account of recent government assurances to offer better support for rare tumours. There are very few GIST patients so overall costs will not be great. Sunitinib has been recommended for some renal cancers where it can offer a few months extra before death. This seems a cynical application of the argument in favour of saving on cost and penalises GIST sufferers because their tumours respond better to the drug.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
Carer 1	Advice on the recommended use of Imatinib is out of date and has not been reviewed in light of the changing experience of researchers and oncologists treating GIST.	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 in whom their condition is resistant or intolerant to imatinib. The review of imatinib for GIST (TA 86) is to be undertaken, date is yet to be confirmed.

Role	Comment	Response
Carer 1	All delays in review and committee discussions means that real human beings are running out of time. There is a tone in the report which suggests that the committee chooses not to view patients as people. Participants in trials are described as participants that..... Correct grammar would suggest that they are participants who.....	NICE is a corporate member of the Plain English Campaign and we do try wherever possible to use plain English in all of our consultation and guidance documents. However there are circumstances where the technical language associated with a particular treatment means that it would not be appropriate to reword the text used. NICE has produced a glossary to help people understand the technical terms in our documents (see: http://www.nice.org.uk/website/glossary/) because there are terms that can't be simplified. We are exploring whether in future a reference to the glossary can be added to the ACD consultation pages.
Public 1	As you are conducting a consultation on an issue that affects the lives of other human beings, I think it is important that the consultation document is written in accessible language. This is unnecessarily complex. What you appear to be exploring is whether it is cost effective to keep people alive with this drug, but you start from the statement that you are "minded" not to. I disagree with this recommendation as I feel that decisions about treatment should be made by clinicians involved with the patient.	NICE is a corporate member of the Plain English Campaign and we do try wherever possible to use plain English in all of our consultation and guidance documents. However there are circumstances where the technical language associated with a particular treatment means that it would not be appropriate to reword the text used. NICE has produced a glossary to help people understand the technical terms in our documents (see: http://www.nice.org.uk/website/glossary/) because there are terms that can't be simplified. We are exploring whether in future a reference to the glossary can be added to the ACD consultation pages.

Role	Comment	Response
Public 1	Presumably the patient access scheme is to assess whether the patient responds to the drug or not. This seems to be sensible and means that if NICE is "minded" not to approve the drug it will be withdrawn from people who might have benefitted from it on the basis of cost alone.	Comments noted. The patient access scheme has been agreed by the Department of Health and considered by the Committee, see FAD section 2.3. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
Public 1	The drug seems to work!	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Role	Comment	Response
Public 1	This should be clearly written - do you all speak in this sort of language? A debate of this kind is important and should not be restricted to the chosen few who chose to write mind boggling sentences.	NICE is a corporate member of the Plain English Campaign and we do try wherever possible to use plain English in all of our consultation and guidance documents. However there are circumstances where the technical language associated with a particular treatment means that it would not be appropriate to reword the text used. NICE has produced a glossary to help people understand the technical terms in our documents (see: http://www.nice.org.uk/website/glossary/) because there are terms that can't be simplified. We are exploring whether in future a reference to the glossary can be added to the ACD consultation pages.
Public 1	If you do not approve this drug, what will you do about people who are already taking it?	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Role	Comment	Response
Public 1	The people taking this drug are really part of a human trial - whats the point of further research if your decisions are based on cost alone?	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
NHS Professional 1	As one of the few medical oncologists in the country with experience using this agent I am very concerned to hear the committees initial response which appears to ignore substantial evidence that this is an active drug with life extending value to a small number of patients with a rare disease for whom there is no other treatment available. Â Failure to approve this drug would place the UK well below the benchmark of Europe, creating a worrying differential in the standard of care within the EU.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
NHS Professional 1	Some mention has been made of continuation on therapy after progression. Â The committee should understand two aspects of this. Â First there is continuing on therapy after "pseudo-progression" i.e. when the patient is judged to be progressing according to the rules of RECIST or WHO but the experienced clinical team judge that this is spurious and the patient is responding. Â In this case continuation is entirely appropriate and I have had patients on therapy with this drug and with imatinib which is very similar, long after a CT scan was erroneously reported as progression. The second situation is continuation on therapy in the face of definite progression. Â I accept this is sometimes done where patients experience tumour flare when the tyrosine kinase inhibition is stopped completely. Â In my experience this is rare - probably 15% of patients and usually does not last more than about 3 months because these patients are deteriorating and unfortunately, succumb to the disease.	Comment noted. Additional analysis including the sunitinib costs based on the treatment duration in the EAP was submitted in time for the second meeting and was appraised by the Evidence Review Group and considered fully by the Committee. The Committee concluded that the sources of sunitinib effectiveness data should be consistent with those for best supportive care and that the EAP was subject to bias. See FAD sections 3.17, 3.18, 4.5 and 4.6.

Role	Comment	Response
NHS Professional 1	The committee should understand that in practice this drug either works or it doesn't and this is usually readily apparent at the first CT scan. Â It is true that assessment of response requires experience because the pattern is not the same as for other cancers and their response to chemotherapy. Â However, while we may be arguing over objective tools to use in clinical trials, in practice, those teams with experience have little difficulty in identifying which patients are responding to treatment. The drug works in a good proportion of patients bearing out the trial data. Â The detailed analysis of the phase III trial is difficult but the basic message is very clear: a dramatic difference in relapse free survival compared to placebo and even, despite cross-over, a detectable difference in overall survival. Â This drug extends life.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.
NHS Professional 1	In my opinion the model of cost-effectiveness is flawed because in contrast to population based treatments where it is reasonable to calculate the number needed to treat, with drugs like this, only those patients responding to drug continue on therapy. Â Therefore the proportion of patients responding only applies to the first 2 or 3 months of therapy and after that all patients effectively are gaining benefit until the drug stops working and then the treatment is discontinued.	Comment noted. The economic analysis provided by the manufacturer assumed that 20% of all patients who start taking sunitinib do not complete the first cycle of treatment, as they receive no benefit from the treatment, and this was derived from the trial. The cost effectiveness analysis provided by the manufacturer uses the dose intensity of sunitinib given in the trial.
NHS Professional 1	The committee should understand that, due to national referral patterns and recent IOG, if this drug is approved, its use will largely be restricted to highly specialised sarcoma teams probably numbering no more than a dozen in the whole country: London (UCH and Marsden), Birmingham, Manchester, Leeds, Sheffield, Cambridge, Bristol, Liverpool, Preston, Newcastle, Hull. Â One team in each of the above. Â This will account for probably 90% of usage in England. Â These teams already have experience with the drug through participation in the trial discussed above. Â It would be appropriate to restrict access to this drug through these teams because of the expertise required and because this is clearly a fast moving area of practice in a rare tumour group and there would be concern that clinicians with very limited case numbers would rapidly become out of date regarding best practice.	Comment noted. Section 1.2 of the FAD states that "The use of sunitinib should be supervised by cancer specialists with experience in treating people with unresectable and/or metastatic malignant gastrointestinal stromal tumours after failure of imatinib treatment because of resistance or intolerance."

Role	Comment	Response
NHS Professional 1	This area remains of high interest for future research and participation in clinical trials with this drug and related agents in the same setting (i.e. after failure of initial imatinib therapy) should be encouraged. Â This would be another strong reason to recommend restricting access through designated sarcoma teams (as per IOG).	Comment noted. Section 1.2 of the FAD states that "The use of sunitinib should be supervised by cancer specialists with experience in treating people with unresectable and/or metastatic malignant gastrointestinal stromal tumours after failure of imatinib treatment because of resistance or intolerance."
NHS Professional 1	I am the local PI for one international study (EORTC 6202) which is supported by Novartis and for which I recieve no personal funding but free drug is available to the trial participants and a small amount of per patient fees are paid to support my research team.	Comment noted.
Email 1	Before I respond to the comments in your email, I want you to hold a person in your mind. My father had a gastrointestinal stromal tumour (GIST) removed 7 years ago. It weighed 5kgs. He was given a 25% chance of surviving the operation. For the past few years he has taken Imatinib, but is now showing signs of resistance to it. He started taking Sunitinib a couple of weeks ago. It may not work for him, but if it does he may have a number more years of meaningful life ahead of him. Who knows how long any of us will live for? If is does not work he will die. He will also die if NICE removes the chance of life from him. My father is an active and intelligent person. On Friday 19th March he was at the Northern College doing academic work; the day before he was playing tennis with his friends. He is 79 years old. I am not contacting NICE because I can not cope with the idea of my father dying. I accept death as a part of life. What I cannot accept is that treatments that might prolong life are denied to people who might need them. Accepting the death of my father from old age or cancer will be very different from accepting his death at the hands of NICE.	Comment noted. Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance. See section 1 of the FAD and section 4 for the consideration of the evidence.

Role	Comment	Response
Email 1	I would like to make the following points in response to your email to me: You describe NICE as an “independent” organisation. I am not sure what independent means in this case. NICE is closely associated with the NHS; the NHS is legally obliged to provide funding for the medicines and treatments it recommends and, as you say, it has to respond to demands from the NHS to issue guidance as quickly as possible. Your definition of the purpose of NICE does not mention rationing, which is one of its primary roles. Incidentally, NICE is an unfortunate acronym for an organisation that may remove life prolonging treatment from my father. I am reminded of the “Ministry of Love” in George Orwell’s book, “Nineteen Eighty-Four”, which is where the torment of prisoners takes place.	Comment noted.
Email 1	You say that three weeks consultation is “in line with our standard process timeline” and that NICE does not have to stick to the government’s consultation guidelines. If the needs of bureaucracy have overtaken the needs of patients to this extent then the NHS is in a sorry state indeed. I can appreciate that asking patients to comment on the continuation of their own treatment is a bit like asking turkeys to vote for Christmas. One of your colleagues, Professor Mike Campbell, put this a bit more bluntly in a reply to my father, when he wrote, “All patients think that their area should be a priority”. However, we live in a democracy and we have not yet arrived at a stage where we kill off the old and the disabled in our society. The least that NICE can do is to listen to the views of **all** the stakeholders and this means that people must have time to comment. Three months seems to me to be a much fairer time to allow for consultation; three weeks suggests that the decision is already made and that NICE is just going through the motions.	Comment noted. The consultation period of three weeks for commenting on this type of draft guidance is in line with our standard process timeline. See Guide to the single technology appraisal (STA) process, appendix B for diagrammatic timeline.

Role	Comment	Response
Email 1	I do not accept that the consultation document on Sunitinib has to be presented in its current technical language. It may require some technical language, but this can be explained in the text. The point of plain English is that the text becomes accessible to everyone; it is not a requirement to write “Noddy” language. It should be accessible to healthcare professionals and lay people alike.	NICE is a corporate member of the Plain English Campaign and we do try wherever possible to use plain English in all of our consultation and guidance documents. However there are circumstances where the technical language associated with a particular treatment means that it would not be appropriate to reword the text used. NICE has produced a glossary to help people understand the technical terms in our documents (see: http://www.nice.org.uk/website/glossary/) because there are terms that can’t be simplified. We are exploring whether in future a reference to the glossary can be added to the ACD consultation pages.
Email 1	Finally you have invited me to comment on how much I think society should be prepared to pay for life-extending treatments. My response is this: All treatments are life-extending, not life-saving. I have insulin dependent diabetes and my life has been extended by nearly 40 years so far because of treatment with insulin. Hopefully, insulin will not be removed from me if I reach 79! As we are all going to die, the debate is really about how much we want to spend on treatment from the NHS to keep ourselves alive for a few more years if we get ill. We can’t single out a few people for a different debate. The doctors who discovered insulin would not have known how long the first patients who were treated with it would live for or what the quality of their lives would be like.	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 4.2. The Committee concluded that sunitinib fulfilled the end-of-life criteria and considered it as such. See FAD sections 4.9, 4.10 and 4.11.

Role	Comment	Response
Email 1	I accept that the NHS has finite resources and that the money has to be spent wisely. However, there are examples where money has not been spent wisely. I work in public services (not the NHS) and when I started my present job I liaised with two health authorities; there were two Chief Executives and two sets of premises to maintain. A few years ago the two health authorities were reorganised into seven Primary Care Trusts; seven Chief Executives and seven sets of premises to maintain. Liaison became difficult as seven people had to attend a meeting instead of two. The cost of the reorganisation and subsequent duplication of work must have been enormous. A couple of years ago the Primary Care Trusts were reorganised again and we are now back to two. In his book, “Thatcher & Sons”, Simon Jenkins refers to the NHS as, “stumbling under the weight of its own overheads, dazed by constant change”.	Comment noted.
Email 1	I know that issues of funding in the rest of the NHS do not come within the remit of NICE but, I believe, because of imprudence, treatments are being assessed for their “cost effectiveness” in a way that reorganisations, targets and posts are not. This has to provide the context for any debate about the resources available for patient care in the NHS.	Comment noted.