Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Pharmacist PCT/CCG
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Axitinib for this population group is not a cost effective use of NHS resources. The ICER of £65,000 per QALY (in the subgroup who had received prior cytokine therapy) is likely to have been an over-estimate. However, other uncertainties in the economic models mean that the most plausible ICER (for both prior-cytokine and prior-sunitinib populations) is still likely to exceed £50,000 per QALY gained and could not be considered a good use of NHS resources for this population. agree with NICE
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	There are no second-line drugs currently approved for people who have become resistant to first-line treatment and no trials have directly compared axitinib with best supportive care. Sorafenib is not approved by NICE as cost-effective for use in the NHS. The well conducted AXIS trial found that, compared to sorafenib, axitinib improved progression-free survival in people who had received prior cytokine treatment. However, there were serious limitations with the simulated treatment comparisons performed for the prior-sunitinib population; and also no comparison of axitinib with pazopanib or sunitinib for the prior-cytokine population.
Section 4 (Consideration of the evidence)	Due to value of the ICERs and the uncertainty around the ICERs cannot be considered good use of NHS resources - even with PAS.
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	1/10/2013 4:51:00 PM

Name	[redacted]
Role	Pharmaceutical Industry
Other role	
Location	England
Conflict	no
Notes	

Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	The manufacturer's submission presents a simulated treatment comparison (STC) between axitinib and best supportive care based on the RECORD-1 (everolimus vs. best supportive care) and AXIS (axitinib vs. sorafenib) trials. While network indirect comparisons have been recommended by NICE in the absence of head-to-head trials, these methods could not be applied for the sunitinib refractory population treated with axitinib due to lack of a suitable network of trials. Though STC attempts to address this data limitation, the STC approach lacks precedent and has significant limitations, some of which have been noted in the NICE draft response and some additional limitations that we describe below. It is stated in the MS that similar methodologies have been accepted in recent HTA appraisals to overcome gaps in the evidence network which rule out a standard indirect comparison approach, including NICE TA171 (Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy) and the SMC approval of everolimus in pancreatic neuroendocrine tumour. However, upon closer inspection, neither of these examples provides a precedent for acceptance of the STC methodology applied in the axitinib manufacturer's submission. Firstly, both examples were based on connected networks of trials that included a common comparator, unlike the axitinib MS. Secondly, the indirect comparison considered by the SMC evaluation of everolimus for pancreatic neuroendocrine tumors included confidence intervals for the estimated treatment differences, which are lacking from the axitinib MS. Finally, though analyses similar to STC were considered in NICE TA171 with a common comparator, the Evidence Review Group repeated the indirect comparisons using methods it considered to be more appropriate. For these reasons, we do not believe that either of these examples can be considered a precedent for acceptance of the STC methodology applied in the axitinib manufacturer's submission. The lack of confidence intervals for the STC, and inability to assess uncertainty in the results, has already been raised as a significant limitation by the ERG and in NICE's draft appraisal. We believe there are additional significant limitations with the STC analysis that would persist even if confidence intervals were derived. STC attempts to account for cross-trial differences in patient characteristics by fitting a model. It is therefore appropriate to evaluate the STC approach similarly to a multivariable regression model in an observational study. From this perspective, the STC applied in the axitinib submission has significant shortcomings. Firstly, in selecting which baseline characteristics to use for adjustment, the STC approach only considers their effect on axitinib outcomes. This is insufficient for detecting important confounders, by the usual

	standards of epidemiological studies, because it excludes confounders that impact outcomes on everolimus and BSC but not axitinib. Furthermore, the STC analysis used p-values as the criterion to select variables for adjustment in the final model. This approach is widely-viewed as inadequate for identifying confounders in a regression model (e.g., Epidemiology: an Introduction by K. Rothmann). The MS states that the final equations were checked for their ability to replicate the source data. However, replication of source data in no way validates the selection of confounders or the ability of the model to generalize to other patient populations such as RECORD-1. For these reasons, the STC analyses do not follow generally accepted practices to adjust for confounding.
Section 4 (Consideration of the evidence)	Given the STC's heavy reliance on MSKCC to account for cross-trial differences, it is worth noting that the MSKCC scores are defined differently in the two trials. The MSKCC score calculated in the AXIS trial substituted ECOG in place of KPS (see page 51 of the MS), which differs from direct use of KPS in the validated MSKCC score for previously treated patients (Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol. 2004;22:454-463) used in RECORD-1. Though this substitution may seem like a small and reasonable change, it is likely to have a substantial and biased impact on the MSKCC risk stratification. This can be seen via a simple re-analysis of the RECORD-1 data (data on file). In the original RECORD-1 trial, using the standard definition of MSKCC that includes KPS < 80% as a risk factor, the proportion of patients classified as poor prognosis was 18%. However, if the KPS threshold is changed to <= 80% the proportion with poor prognosis jumps to 39% (most KPS scores are reported as multiples of 10%), which is greater than the proportion with poor prognosis in AXIS. This change makes the KPS score threshold more comparable to the ECOG >= 1 threshold used for the non-standard MSKCC score in AXIS. This can be verified by noting that the description of KPS=80% (normal activity with some difficulty, some symptoms or signs) is much more similar to ECOG=1 (Symptomatic but completely ambulatory, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work) than it is to ECOG=0 (Asymptomatic, fully active, able to carry on all pre-disease activities without restriction). Given the substantial impact of this difference in MSKCC definition, the ability of the differently defined MSKCC scores to adjust for or interpret cross trial differences between AXIS and RECORD-1 is limited. Furthermore, given the comparison of the KPS and ECOG scales, the non-standard MSKCC score used in AXIS is likely to over-estimate severity relative to the standard MSKCC score used in RECORD-1. Therefore, the adjustments for MSKCC in the STC would introduce substantial bias against everolimus. Besides the cross trial differences within the STC, the analysis incorporate selective use of external evidence. In particular, PFS data for everolimus from one source and OS data from a

	different source are used, rather than using both PFS and OS data from the same source. The study selected OS data from a paper by Di Lorenzo. However, it doesn't use the PFS data from either Di Lorenzo (24.1 weeks or 5.6 weeks) which is the same source as the OS data or Calvo 2012 which has PFS of the same population of sunitinib as the only prior anti-neoplastic agent as AXIS population (PFS 4.6 months). Instead it uses the PFS from Motzer 2010 which has the shortest PFS among the three (3.9 months). No justification is given for use of the different sources of evidence. In addition, while no data are available from RECORD-1 to estimate the mean, and only the median is available for everolimus, the STC extrapolates a mean PFS and OS for everolimus based on assumptions; and reports mean differences in PFS and OS that are larger than the medians, and that favor axitinib. These selective modeling decisions compound the uncertainty in the comparative clinical and cost-effectiveness derived from the STC. It is also noteworthy that the OS results in the STC were not adjusted for post progression treatment differences. On the basis of the STC, it has been projected that patients receiving treatment with axitinib would achieve (better) PFS benefit (8.3 months) than those receiving everolimus (4.6 months). The cost effectiveness results presented to NICE are based on this inference. However, the analysis does not account for substantial differences in the availability and use of other therapies post progression with everolimus vs. axitinib. As the data from two trials show, patients in the AXIS trial had access to more treatments post progression and almost half of the patients used them. In the RECORD-1 trial, about one third used any treatments post progression. It would be misleading to conclude that any overall survival difference between axitinib and everolimus is solely attributable to the efficacy of axitinib
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	1/10/2013 3:15:00 PM

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Location	England
Conflict	yes
Notes	Honoraria for advisory boards and lectures and research funding received both by me and my institution from Pfizer.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's	This is a regrettable decision on a number of counts. First, axitinib is a well-tolerated and effective TKI. Second, most

preliminary recommendations)	patient in England at least receive everolimus second line through the CDF. For many patients, this is a more toxic and less effective agent than axitinib. The key point is that we will effectively be directed to using an equally expensive but more toxic and less effective agent for the majority of 2nd line RCC patients. I am sure this is not what the committee intends to achieve.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	12/24/2012 1:06:00 PM