The British Uro-oncology Group (BUG) welcomes the opportunity to reply to this Appraisal consultation document (ACD) for bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma (RCC). The following comments are collated from the responses from individual members of BUG and do not necessarily reflect the opinions of all BUG members. We have retained the wording of responses from individual members, as this reflects in some instances very strong feelings about certain aspects of the document.

BUG would like to thank the NICE Panel for producing this document and inviting our response. The **Appraisal Committee's preliminary recommendations** as outlined in section **1** have caused concern and have been highlighted by our members. The refusal of sunitinib in particular, in treatment naïve patients has generated the most comment and this is detailed in our response.

Bevacizumab, sorafenib, sunitinib and temsirolimus are not recommended as treatment options for advanced and/or metastatic renal cell carcinoma.

People currently receiving bevacizumab, sorafenib, sunitinib and temsirolimus should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

These recommendations and our subsequent observations are discussed below in the relevant sections. We then specifically address the questions of consideration of the relevant evidence, summaries of clinical and cost effectiveness and whether or not the recommendations of the appraisal committee are sound or not in our concluding remarks.

Clinical need and practice

2.1-3

Renal cell carcinoma (RCC) is a type of kidney cancer that usually originates in the lining of the tubules of the kidney and contains many blood vessels. RCC accounts for 90% of kidney cancers and approximately 3% of all adult cancers. In England and Wales, kidney cancer is the 8th most common cancer in men and the 14th most common in women. In 2004, there were 5745 cases of newly diagnosed kidney cancer registered in England and Wales. The incidence of kidney cancer begins to rise after the age of 40 and

is highest in people older than 65. In England and Wales the estimated overall 5-year survival rate for RCC is 44%, but there are large differences according to the stage of disease at the time of diagnosis. The worldwide incidence of kidney cancer among both men and women has been rising steadily since the 1970s.

The American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system is used to grade RCC into stages I to IV. Advanced RCC, in which the tumour is either locally advanced and/or has spread to regional lymph nodes, is generally defined as stage III. Metastatic RCC, in which the tumour has spread beyond the lymph nodes to other parts of the body, is generally defined as stage IV.

In 2006, of people presenting with RCC in England and Wales for whom staging information was available, an estimated 26% and 17% had stage III and stage IV disease, respectively. About half of those who have curative resection for earlier stages of the disease also go on to develop advanced and/or metastatic disease. The prognosis following a diagnosis of advanced and/or metastatic RCC is poor. The 5-year survival rate for metastatic RCC is approximately 10%.

We agree it is imperative to emphasise the clinical setting of RCC in terms of its relative rarity, but rising incidence. It is seen that the majority of patients present with early disease (of whom around half are cured by surgery), so the actual numbers with advanced tumours in England and Wales, in particular metastatic disease is around only 1500 patients. Neither are all these suitable for further treatment so the actual numbers being considered for systemic therapy are going to be low indeed. This is truly a rare cancer, and needs to be considered as such.

2.4

There are currently no treatments that reliably cure advanced and/or metastatic RCC. The primary objectives of medical intervention are relief of physical symptoms and maintenance of function. Metastatic RCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy. People with advanced and/or metastatic RCC are usually treated with either interferon alfa-2a (IFN-α) or interleukin-2 immunotherapy or a combination of IFN-α and

interleukin-2. IFN-α (Roferon-A, Roche Products) is the most commonly used immunotherapy in England and Wales and has UK marketing authorisation for treatment for people with advanced RCC. For those people receiving immunotherapies for the treatment of advanced RCC it is suggested that, on average, median survival is increased by 3.8 months compared with those receiving control treatments. Commonly experienced adverse effects of IFN-α include flu-like symptoms, tiredness and depression. There is no standard treatment for people with advanced and/or metastatic RCC whose condition does not respond to first-line immunotherapy, or for people who are unsuitable for immunotherapy.

It is stated that there are currently no treatments that reliably cure advanced and/or metastatic RCC, and that metastatic RCC is largely resistant to chemotherapy, radiotherapy and hormone manipulation. Interferon has a response rate of 10-15%, significant toxicity with at best modest improvements in survival. There has therefore never been a clearer need demonstrated for alternative strategies to treat this disease.

The technologies
Sunitinib 3.3.3

Sunitinib is administered orally. The recommended dosage is 50 mg once daily for four consecutive weeks with a 2-week rest period (that is, a complete treatment cycle of 6 weeks). The price for a pack of 50-mg capsules (30 capsules per pack) is £3363.00 (excluding VAT; BNF edition 55). The average daily cost of sunitinib is £74.74, with an average 6-week cycle costing £3139. Costs may vary in different settings because of negotiated procurement discounts.

The pack is now a pack of 28 and the cost is correspondingly altered. There is, however, a nationally available scheme for making the first cycle available free of charge, and a 5% reduction in pack price (30 capsules) applied from 8th May 2007. This affects cost effectiveness and was fundamental in facilitating agreement of the PCTs in the north east of England to fund sunitinib, the first network to do so, prior to NICE.

Summary of clinical effectiveness 4.1.23

The Assessment Group concluded from a summary of the data on the clinical effectiveness of first-line treatments for people who are suitable for immunotherapy, that both bevacizumab plus IFN-α and sunitinib as monotherapy appear to have significant benefits compared with IFN-α alone in terms of progression-free survival and tumour response. Although promising, data on overall survival are in general immature. For people with poor prognosis, temsirolimus appears to have significant benefits compared with IFN-α in terms of overall survival, progression-free survival and tumour response rate. There is some evidence to suggest that temsirolimus may have a greater effect on people who have non-clear cell carcinoma and who have not undergone nephrectomy. The frequency of adverse events associated with the first-line treatments is comparable to that associated with IFN-α monotherapy, but the adverse event profiles differ between treatments.

There were data presented at ASCO (albeit a sub group analysis with crossover patients censored) which DID show a survival (OS) advantage for patients on sunitinib vs. interferon, which was statistically significant at 26 vs. 20 months. We express concern that given the timescale of the review that the group published their report before ASCO 2008, or at least undertook their literature search before this. We feel it is incorrect to describe these data as immature as the data is now relatively mature.

Evidence and interpretation
Cost effectiveness 4.2.1

No published studies of the cost effectiveness of bevacizumab, sorafenib, sunitinib or temsirolimus were identified. The manufacturers of each of the drugs submitted cost-effectiveness models and the Assessment Group developed a model for each treatment question.

There was a poster at ASCO 2007 (#6607) covering sunitinib vs. interferon which included utility values.

Updated data from Pfizer 4.3.2

The median overall survival in the final ITT population was no longer significantly different for those who received sunitinib (26.4 months) compared with those who received IFN-α (21.8 months, HR 0.821, 95% CI 0.673 to 1.001, p = 0.0510). The median overall survival in the final ITT population that was censored for crossover did show a statistically significant benefit for those who received sunitinib (26.4 months) compared with those who received IFN-α (20.0 months, HR 0.808, 95% CI 0.661 to 0.987, p = 0.0362). The median overall survival was statistically significantly higher in those who received sunitinib and did not receive any post-study treatment (28.1 months) than those who received IFN-α (14.1 months, HR 0.647, 95% CI 0.483 to 0.870, p = 0.0033).

Clearly all the relevant evidence has not been taken into account. In particular the insistence on overall survival as an end point despite the crossover design, and the then dismissal of the post hoc OS analysis showing 14 vs. 28 month survival in patients who received no further treatment. It should also be noted that progression free survival (11 vs. 5 months, p<0.000001) was the primary end point of this study, an appropriate end point in clinical trials evaluating the treatment of metastatic malignant disease where overall survival is ultimately affected by subsequent treatments. Indeed in this study patients crossed over in February 2006 when the primary end point had clearly been met. PFS as a relevant end point has been recognised previously by NICE.

Consideration of the evidence 4.4.6

The Committee then considered the estimates of cost effectiveness of sunitinib provided by the manufacturer and the Assessment Group. The Committee noted that the adjustments made to the survival curves by the Assessment Group and their different costing assumptions resulted in a larger ICER than that originally presented by the manufacturer (£71,500 per QALY gained compared with £28,500 per QALY gained, respectively). However, the Assessment Group's estimate was not larger than the updated baseline estimates of cost effectiveness provided by the manufacturer, despite the manufacturer's assumption of a free initial dose of sunitinib. The Committee

did not consider that the estimate of cost effectiveness derived from the post-hoc subgroup that received no post-study treatments in the sunitinib trial could be considered a robust basis for decision-making as the estimates had not been critiqued by the Assessment Group and no details about the post-hoc subgroup were provided. Therefore the Committee concluded that sunitinib as first-line treatment for people with advanced and/or metastatic RCC would not be a cost-effective use of NHS resources.

The Evidence review group criticised the immaturity of the data, but when more mature data is available the Evidence Review Group does not appear to have been asked to review it.

4.4.18

Having concluded that bevacizumab, sorafenib, sunitinib and temsirolimus were not cost effective, within their licensed indications for the treatment of RCC, the Committee considered the pricing strategies for bevacizumab and sunitinib proposed by the manufacturers, which include a 'dose cap' scheme and a free first cycle of drug treatment, respectively. The Committee was aware that these pricing strategies had not been considered by the Department of Health to establish whether the proposed discounts are nationally available and how long they will be in place.

It is our understanding is that the 1st cycle scheme is DH approved, available across the whole of the UK and has no end date. This clearly needs clarification as it is integral to the costs incurred.

Sensitivity analyses of the Assessment Group's model taking these pricing strategies into account reduced the ICERs for bevacizumab plus IFN-α to £91,000 per QALY gained and for sunitinib to £57,700 per QALY gained, the latter without taking into account the late data on survival from Pfizer. Therefore, the costs per QALY gained still remained above the levels considered compatible with the best use of NHS resources. The Committee concluded that the use of bevacizumab plus IFN-α and sunitinib as first-line treatments for advanced and/or metastatic RCC, irrespective of the proposed pricing strategies, would still not be a cost-effective use of NHS resources. The Committee suggested that any revised or new pricing strategies, put

forward to the Department of Health by the manufacturers, which could result in the use of these drugs being a cost-effective use of NHS resources, would be considered.

In this context it must be stated that this patient group included cross over - therefore the sub group analysis must be taken into account – or the costs of the sunitinib in the crossing over patients must be allowed for. The dose intensity and discontinuations after the first cycle must also be considered in this setting.

We at BUG understand that the Appraisal Committee is interested in receiving comments on the ACD under the following general headings:

Do you consider that all of the relevant evidence has been taken into account?

The ACD has discounted the sunitinib survival data presented at ASCO 2008 in which patients receiving 2nd line therapies were censored. We understand the committee's requirement for more detail on these data so that it can be accurately appraised, but we believe it would be against the interests of patients for a final recommendation to be published without these data being taken into account. A 14 month improvement on overall survival would have a major impact on the cost-effectiveness calculations. We would urge the Committee not to produce a final recommendation without these data being fully appraised. If an extra few weeks are required for the Committee to obtain the evidence it requires from the sponsoring company this would be time well spent.

We believe that the risk of not including these data when they are already in the public domain and for the data only to be appraised at the next planned assessment in 2011, would be for clinicians and patients to lose all confidence that NICE was performing assessments based upon the most relevant data. The ACD also appears to make no reference to the views of the clinical or patient experts that were submitted and this should be addressed.

We do not consider that the assessment took all relevant data into account, specifically the recently announced overall survival data in the sunitinib vs.interferon trial which was 26 vs. 22 months, 20 months if crossover excluded (p=0.0362 Log- rank, 0.0081 Wilcoxon). Median overall survival was 28.1 vs. 14.1 months p=0.033. (#5024 ASCO 2008) as indicated above in patients who did not receive any post study treatment.

We do not consider that the treatment of interferon as the comparator for all groups of patients with metastatic RCC was defensible since we know that it is not appropriate for most patients with the disease. Furthermore, the assessment of quality adjusted life was particularly inadequate in a disease like RCC with such variable outcomes. The ACD assumes that clinicians had no ability to select the appropriate treatment for individual patients.

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?

Clinical benefit rate (stable disease + partial response + complete response) and progression free survival (PFS) are regarded as the most relevant indicators of the clinical effectiveness of targeted agents. It is also crucial to state that reported response rates are always coloured by the inevitable mix of responders and non responders – those who benefit will have a greater duration of this than the reported mean. Similarly in the real world, patients are scanned after two cycles of treatment which would be stopped in those with documented radiological progression.

Clinical benefit rate (especially in these drugs where complete responses are not the norm) and PFS are particularly relevant in an environment where overall survival data has been confounded by cross-over after an interim analysis within a trial and 2nd line treatment outside a trial. Worldwide licensing authorities have accepted PFS as an appropriate surrogate endpoint for these reasons, as NICE has done previously. We emphasise again and emphatically that PFS and clinical benefit rate are clinically relevant endpoints; patients who experience disease control derive significant benefit in terms of palliation of tumour related symptoms and improvement in quality and length of life.

NICE's insistence on using measures of clinical benefit and therefore cost-effectiveness that do not take into account these issues results in an appraisal of the clinical effectiveness of drugs which is inherently flawed and which will inevitably under-estimate the benefit that patients will receive from these drugs. The summary of clinical effectiveness and therefore the summary of cost-effectiveness therefore do not reflect clinical reality and under-estimate the benefit these drugs provide. NICE therefore has a decision to make. NICE can continue using a methodology that is ill-equipped to reflect the clinical utility of these drugs by insisting on using a one size fits all technology that will inevitably deny cancer patients with incurable disease access to the drugs most likely to protect both their quality of life and life expectancy. Alternatively NICE could approve a technology that reflects what clinical experts, patients and licensing authorities have accepted. That PFS is an important indicator of the clinical utility of a therapeutic in this setting, and that assessments need to use a methodology that is sensitive to this.

Neither is the summary of cost effectiveness a fair assessment. There is no clear explanation of the variation in costs between £30,000 and £70,000 between models or the reasons for choice of particular models. The basis of the health state utility should be challenged. We would ask how these arbitrary numbers have been chosen.

The cost of sunitinib in particular is poorly described and this is fundamental to making the cost per QALY reasonable. We feel NICE needs to consider more fully the ASCO '08 sub-group analysis as it is the only representative data of the UK treatment pathway i.e. most patients will be treated with interferon only, with currently no access to future treatments as the situation currently stands. The clear survival benefit to sunitinib is dramatic.
It similarly must be considered with the free cycle which is a national initiative, freely available and any issues as to why that cannot be considered need to be addressed. Similarly, it is noted that around a third of patients dose reduce (or stop after 1 cycle). Data pertaining to the expanded access program presented at ASCO 2007 confirmed this as "real world" toxicity and this must be considered when costing. Ultimate costs may well be above the "QALY" limit that NICE sets itself, but that will not be any different for any drug used in the palliative setting for cancer care and must be seen in this context.

There are also real concerns that forthcoming trials will have sunitinib e.g. as control arm limiting any real participation by the UK in ongoing research. We would strongly encourage NICE to work with manufacturers to see if some form of acceptable pricing could be made, so at least there could be access in the first line setting e.g. risk shares schemes where the first two cycles could be refunded in non responders. The industry has already demonstrated a willingness to negotiate pricing strategies and these need to be more fully explored.

Are there any equality issues that may need special consideration?

We do not feel equality issues have been addressed. Many colleagues made the point that almost all other cancers are treated by many therapeutic modalities, often multiple lines of therapy, together costing far more than a single option available to renal cancer patients - with the availability of new agents in the rest of Europe and USA and the proposed veto of ANY effective agent in kidney in the UK. Perhaps it can be argued that the QALY calculation should not be about "one drug" but total costs for a cancer type (comparison could be made with the modest response of HERCEPTIN in metastatic breast cancer e.g.) vs. cost over the course of a disease, drawing out the "orphan" drug status of these compounds and the lack of expenditure on lines of chemo and radical treatment options for RCC in particular. The appraisal

states the drugs are better tolerated than IFN (except B+IFN obviously), work better than IFN and almost certainly have both a PFS and OS advantage, suggesting this is a purely financial decision and can only be contested on the basis of equality for patients in comparison with other cancers.
Other colleagues also voiced concerns about co payment, which is currently under review, with disquiet about the parallel time lines for these.

The provisional recommendations of the committee are inherently unsound. If issued as final guidance the result will be that patients are denied access to drugs which provide significant clinical benefit on the basis of an appraisal using incomplete data within an inappropriate technology.
We therefore do not consider that the provisional recommendations of the Appraisal Committee constitute a suitable basis for the preparation of guidance to the NHS. It is recognized that some PCTs already funding these drugs will continue to allow their use in these regions, but there is concern that if this assessment is confirmed the majority of PCTs will indeed deny treatment to patients with this disease. A number of colleagues believe interferon to be inappropriate for the majority of patients. There are serious concerns that NICE will mandate the use of ineffective, toxic, but cheaper interferon. It would be better if they said that most patients should be denied all treatment except palliative care.

Patients should expect that guidance to the NHS should be of the highest possible quality. Without such standards, NHS cancer care will inevitably be significantly worse than that provided by health systems in other countries with similar economies and the aspiration for cancer death rates in the UK not to be worse than that seen in other European countries will never be met.