Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Submitted by [redacted] on behalf of:

Name of your organisation

NCRI/RCP/RCR/JCCO/ACP

Comments coordinated by Professor Ian Judson (clinical expert nominee)

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Although imatinib has revolutionised the care of patients with unresectable or metastatic gastrointestinal stromal tumour (GIST), resistance will develop in a significant percentage of patients, with a median time of onset of about two years. The currently licensed treatments for this situation are increasing the dose of imatinib, which will result in disease stabilisation or response in about a third of patients, and sunitinib, the subject of the current STA. Apart from the small subgroup (10%) of patients with exon 9 mutations in the *KIT* gene, who clearly benefit from imatinib 800 mg (further discussed below), sunitinib may be more likely to result in an objective response in patients progressing on imatinib, although a formal comparison of these 2 interventions is only now underway. Sunitinib is undoubtedly an effective agent. It is not without significant toxicities, but these are manageable, as discussed below.

Regional variations in the use of sunitinib do exist, to a worrying degree, since access to the drug is currently on the basis of the exceptional use prescribing route hence decisions made by individual PCTs vary enormously.

Patient fitness for treatment is important, but only those patients who are severely cachectic, or whose performance status was severely compromised would be regarded as ineligible for treatment with sunitinib.

The drug should only be used in special centres, experienced in the management of GIST and in the use of the drug. The only variation from the precise licensed indication concerns the choice of dose and schedule, which often involves the use of a lower dose, sometimes given continuously, rather than on the 4 weeks on 2 weeks off regimen used in the Phase III trial that led to registration.

Guidelines that pertain to the treatment of patients with gastrointestinal stromal tumour, including the use of sunitinib for those patients whose tumours are resistant to imatinib, or who are intolerant of imatinib were published by the NCCN in 2007 (NCCN Task Force Report: Optimal Management of Patients with Gastrointestinal Stromal Tumor (GIST) – Update of the NCCN Clinical Practice Guidelines. Journal of the National Comprehensive

Cancer Network 2007;5:Supplement 2. http://www.nccn.org/JNCCN/PDF/GIST2007.pdf). The NCCN guidelines are evidence-based where possible, otherwise advice is based on consensus. The level of evidence is provided in the guidelines.

A recent update to existing guidelines on the management of GIST from the European Society of Clinical Oncology (ESMO) was also recently published which states that sunitinib is regarded as standard second line therapy once problems with compliance (adherence) have been ruled out, usually after progression on the higher dose of imatinib, i.e. 800 mg daily, which is regarded as the first routine intervention following progression on 400 mg daily (Casali PG, Jost L, Reichardt P et al. Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:ii35-8). These were evidence-based guidelines produced at a consensus meeting of clinical experts.

The key evidence underpinning the recommendation to use sunitinib was provided by a Phase III randomised, placebo controlled trial, which demonstrated a highly significant progression-free survival advantage (Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-38). On the advice of the IDMC the study was closed early, unblended and patients on placebo crossed over to active drug. An early survival advantage became statistically insignificant after 12 months of further follow-up. A recent re-analysis of these data to take account of the cross-over did demonstrate a significant survival benefit for sunitinib in this situation (Demetri GD, Huang X, Garrett CR et al. Novel statistical analysis of long-term survival to account for cross-over in a Phase III trial of sunitinib versus placebo in advanced GIST after imatinib failure. J Clin Oncol 2008;26 May 20 suppl:abstr 10524)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

In my view sunitinib is an extremely valuable agent that is capable of re-establishing disease control in a significant proportion of patients with imatinib-resistant GIST. Its toxicities are generally manageable by symptomatic measures, use of antihypertensive medication if required, or dose modification. In some cases further responses, i.e. significant tumour shrinkage, occur, in others the benefit consists of disease stabilisation and an improvement in disease-related symptoms. Our longest responder to sunitinib has been on treatment for over 3 years following progression on imatinib. The patients who took part in the Phase I/II and Phase III clinical trials were representative of the patients routinely seen with this condition in the UK and the trial results are undoubtedly applicable to UK practice. The fact that the key endpoint for the Phase III trial was progression-free survival is addressed above. There is no doubt that for some patients treatment with sunitinib offers a significant survival advantage, was could be seen in the study, since without treatment the rate of death from disease in the placebo arm was high.

It was demonstrated in early trials with sunitinib that patients with the less common exon 9 mutation in the *KIT* gene and those patients without detectable mutations in *KIT* or *PDGFRA* fared best on imatinib (Heinrich MC, Maki R.G., Corless C.L., Antonescu C.R., Fletcher J.A., Fletcher C.D., Huang X., Baum C.M., Demetri G.D.: Sunitinib (SU) response in imatinib-resistant (IM-R) GIST correlates with *KIT* and *PDGFRA* mutation status. J Clin Oncol 24:abstract 9502, 2006 and Heinrich et al J Clin Oncol, in press). The question that is as yet unanswered is whether patients with exon 9 mutations should be treated with imatinib 800 mg daily, which has been shown to produce superior progression-free survival in a meta-analysis of 1640 patients from both the European-Australasian and North American trials (Van Glabbeke MM, Owzar K, Rankin C et al. Meta-analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors (GIST): A meta-analysis based on 1640 patients. J Clin Oncol 2007;25 June 20 Suppl:abstr 10004), or with sunitinib. A clinical trial that compares sunitinib with imatinib 800 mg in patients progressing on imatinib 400 mg daily is currently underway, although it is not specifically designed to address the issue of the exon 9 mutant disease patients. There is clearly a role for routine mutational analysis early after diagnosis and for the relatively small subgroup of patients with exon 9 mutations in *KIT*, or no mutations (wild-type disease), alternative treatment approaches are likely to be required early on in the course of treatment.

Returning to the question of adverse events, the only side effect not reported initially is that of hypothyroidism. It is now routine to monitor thyroid function tests and a significant proportion of patients require thyroxine replacement. This is not a problem clinically, being easily managed and well tolerated. Other side effects, such as sore mouth, diarrhoea, hypertension, fatigue, etc, are all manageable in the majority of patients who enjoy a good quality of life.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The accumulated experience of patients with imatinib-resistant GIST treated with sunitinib in extended access studies and studies using alternative schedules to the licensed one, i.e. continuous dosing at 37.5 mg daily , as opposed to 50 mg daily for 4 weeks on a 4 weeks on, 2 weeks off schedule, provides further evidence in a large number of patients that the results reported in the Phase III study are representative, since the proportion of patients experiencing clinical benefit (response + prolonged stable disease) and the incidence of type of side effects reported are very similar across all of these studies (George S, Blay JY, Casali PG et al. Sunitinib (SU) on a continuous daily dosing (CDD) schedule in pts with advanced GIST. Proceedings GI ASCO 2008; abstr 39.). In addition, data from UK centres treating GIST patients with sunitinib might be available on request, although it would not have been collected in a consistent fashion.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No additional resources, training or equipment are required, since sunitinib is in use and centres treating significant numbers of patients with GIST are familiar with the drug. One could make a case for adequate access to positron emission tomography (FDG-PET), since this technology can sometimes assist in deciding whether or not a patient is benefiting from sunitinib. In addition, as mentioned above, the available of mutational analysis can be important in determining whether or not a patient is particularly likely to benefit. Unfortunately, early hopes that mutational analysis of progressing tumours would be helpful has been tempered by reports that secondary resistance mutations can be extremely variable, even in the same patient (Heinrich MC, Corless CL, Blanke CD, et al: Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 24:4764-74, 2006