# 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.

**Comments submitted by [redacted], [redacted] on behalf of:**

**NCRI/RCP/RCR/ACP/JCCO**

**Response coordinated by [redacted]**

**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.

There is no standard treatment for locally advanced or metastatic soft tissue sarcoma (STS) after prior treatment with an anthracycline (usually doxorubicin), with or without ifosfamide, these being the standard agents for palliative chemotherapy of STS worldwide. Trabectedin was licensed in September 2007 for precisely this situation and alternatives are few, and unlicensed.

The management of STS is becoming more complex, with a degree of treatment selection according to histological subtype. For example, angiosarcomas are often treated with taxanes, such as paclitaxel, or pegylated liposomal doxorubicin (Caelyx); leiomyosarcoma of the uterus may be treated with the combination of gemcitabine + docetaxel, which was first reported to be active against this disease (Hensley M, et al J Clin Oncol 2002;20:2824-2831). In a subsequent randomised study comparing gemcitabine with the gemcitabine + docetaxel combination, the latter was demonstrated to be superior in terms of progression-free (PFS) and overall survival (OS), and activity was seen both in leiomyosarcoma and other diseases, including MFH, pleomorphic liposarcoma and a variety of other histologies (Maki R, et al J Clin Oncol 2007;25:2755-2763). This combination is sometimes used as second line treatment after doxorubicin and ifosfamide, especially against leiomyosarcoma.

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

Trabectedin has not yet been included in any clinical guidelines, to our knowledge, owing to the very recent granting of a product licence.

**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?

The particular advantages of trabectedin for the patient are, firstly, that it is very well tolerated, with a low incidence of serious infection and no alopecia (hair loss). Secondly, although the reported objective remission rates (major tumour shrinkage) are low, i.e. in the region of 5-8%, it lacks the type of cumulative organ-specific toxicities that restrict prolonged therapy with doxorubicin and ifosfamide, treatment can be continued for long periods in responding patients and prolonged disease stabilisation has been reported in over a third of patients. It is now recognised that objective response rate is a poor indicator of effectiveness of new agents in STS, and current phase II studies in Europe now use progression free survival at 3 and 6 months as the primary endpoint. A retrospective analysis of the EORTC soft tissue sarcoma group (STBSG) database has defined an active agent as one with 3 and 6 month PFS rates superior to 39% and 14% respectively (van Glabbeke M, et al. Eur J Cancer 2002;38:543-9). By these criteria, trabectedin is clearly active with 3 and 6 month PFS rates of 52% and 35% (Morgan J, et al. J Clin Oncol 2007;25 (supplement 18S): abstract 10060).

There may be situations where trabectedin could be used when either doxorubicin or ifosfamide treatment is precluded by severely impaired cardiac or renal function, respectively.

Apart from the extremely rare incidence of rhabdomyolysis, the risk of which can be restricted by monitoring creatine kinase, serious toxicities are unusual. Disturbance of liver function is common but reversible and provided the guidelines on dose modification are followed the drug is remarkably safe. If administered using a portable pump (Baxter) it is an out-patient treatment, but a central venous catheter is required and arrangements have to be made to disconnect from the pump locally.

The randomised trial that led to the granting of the licence was conducted primarily in patients with leiomyosarcoma and liposarcoma (Morgan J, et al. J Clin Oncol 2007;25 (supplement 18S): abstract 10060). However, activity is also seen in other subtypes such as synovial sarcoma and there is some evidence in a retrospective study of particular efficacy against myxoid /round cell liposarcoma (Grosso F et al. Lancet Oncol. 2007;**8**(7):595-602).

In the randomised trial reported by Morgan et al, the activity in liposarcoma was not confined to the myxoid / round cell variant. This is important, since conventional agents such as doxorubicin are ineffective against de-differentiated liposarcoma, a relative common disease.

It is routine to assess response to sarcoma therapy using CT, performed after 2 cycles of therapy, i.e. at 6 weeks. It seems that around half to two thirds of potentially eligible patients would show evidence of progressive disease at this time-point and therefore would not be eligible for further therapy. Patients with stable disease would continue on therapy. A small proportion would only have undeniably progressed after 4 cycles, i.e. 12 weeks. The only other important issue, so far only defined in the context of myxoid liposarcoma but undoubtedly true for other sarcomas, is that if tumour deposits show a marked early reduction in contrast enhancement on CT, corresponding to tumour cell and blood vessel loss and reduced tumour density, this is a meaningful biological effect that is likely to translate into a conventional response, as measured by tumour shrinkage, at a later date.

Extensive experience with trabectedin outside the context of tightly defined clinical trials has confirmed its value in the palliation of advanced STS, especially in leiomyosarcoma, synovial sarcoma and myxoid liposarcoma. No additional safety concerns have come to light and extensive subsequent experience has confirmed the safety of the drug.

**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.

There are also data indicating that the DNA repair phenotype can predict the likelihood of clinical benefit, patients with a deficiency in homologous recombination repair, e.g. low expression of BRCA1, and proficiency in nucleotide excision repair, e.g. high expression of ERCC1 and XPG, have a higher chance of benefit (Schoffski P, et al. Proc Am Soc Clin Oncol 2006;24:abs 9522).

Further data on STS associated with specific chromosomal translocations have been collected by our colleagues in Milan. These concern 49 patients with diseases such as synovial sarcoma, alveolar soft part sarcoma, endometrial stromal sarcoma, treated in Spain, Italy, Germany, France and the UK. The objective response rate in this series was 16% and the progression-free rate at 6 months was 28%. These data were presented at the 2007 meeting of the Connective Tissue Oncology Society in Seattle. A prospective randomised controlled trial in translocation-driven sarcomas comparing trabectedin with doxorobicin is due to commence soon.

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**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)?

Implementation of a positive TCA would not require extensive additional resources since the number of patients with advanced STS who are fit and eligible for second / third line therapy is small. Provided care is taken to follow the prescribing guidelines this is not a difficult treatment to administer and assessment of clinical benefit does not demand sophisticated imaging facilities.