Clinical specialist 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.

Name: Paula HB Bolton-Maggs, Consultant Haematologist

I am a specialist in the treatment of people with the condition, and represent professional organisations (RCPath, BCSH, BSH)

About you

Your name:

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.

ITP may be treated in several ways:
1. If the count is more than 50x109/l most clinicians would watch and wait unless the patient was bleeding (unlikely without another reason) or needing urgent surgery. Some clinicians would watch and wait with counts lower than this, for example down to 30. Most clinicians are uncomfortable with counts less than 20, although the incidence of serious bleeding nevertheless is low.

2. Patients presenting with bruising and bleeding symptoms and a low count of <30 would receive oral steroids (usually prednisolone 1mg/dk/day) or IVIG to raise the count. The problem is that high dose steroids have signficant side effects and many responders will drop their count when the steroids are tailed down. IVIG produces a response lasting about 3-4 weeks.

3. There are therefore many (most adults) patients who require additional treatment to keep the count above 20-30. There is no predictable way of doing this, and treatment is tailored to the individual. Many drugs can work but the response is individual and unpredictable. It has been custom to advise splenectomy after relapse when steroids are withdrawn, but most patients do not want such drastic treatment, perceiving surgery to be invasive and potentially dangerous. While the operative risks of laparoscopic splenectomy for the patient in experienced hands are now low, the long term risk of overwhelming pneumococcal sepsis is not eradicated by vaccination or continuing antibiotic prophylaxis, and patients certainly worry about this. There is additional evidence emerging of an increased long term risk of thrombotic events (as well as short term risk of portal vein thrombosis in the

immediate post-operative phase) at least in people splenectomised for a different blood condition, hereditary spherocytosis.

The other treatment options have the major disadvantage of interfering with the immune system, putting the patients at increased risk of infections. In addition, all the treatments have very significant and potentially dangerous side effects.

Guidelines for the management of ITP have been published in 1996 by the American Society of Hematology (ASH), but these need updating. The authors noted the lack of evidence for treatment of ITP and considered all the publications in detail. The British Committee for Standards in Haematology published guidelines in 2003 which differed from the ASH conclusions, particularly in relation to management of children (who usually remit spontaneously within a few weeks and only require treatment for significant bleeding problems). New international guidelines are currently in preparation. These will probably continue to advocate steroids/IVIG/anti-D as first line treatment, but there is no ranking order for the several drugs available as second line therapy, and splenectomy is ranked with and not before all these reflecting the change in views

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 new TPO agents (Romiplostin and Eltrombopag) undoubtedly have a great advantage over the other medications available as

1. clinical trials demonstrate efficacy in about 60-70% patients in comparison to placebo and 2. There is much less toxicity. Romiplostin can be considered more physiological, enhancing normal 'hormone' activity.

Most haematologists have a few patients with ITP but are not very experienced with the people who have persistent severe thrombocytopenia (and who may or may not have bleeding symptoms). It is my view that Romiplostin should be restricted to specialist clinics and that there be a central registry to collect long term safety data (post-marketing surveillance).

Romiplostin will be easy to administer and the patients can be expected to learn to give their own. The evidence suggests that responders will be able to stop other potentially toxic medications.
Monitoring is by blood counts which are easy and routine.

The clinical trials selected uncomplicated patients with stringent exclusion criteria, but in general the results will extrapolate to the small group of people with refractory chronic ITP. The most important outcome is a rise in count to 'safe' levels (above 30-50x109/l).
Several quality of life benefits flow from this as indicated in the submission from the ITP support association.

Adverse events - the marrow fibrosis does not appear to be a problem but needs to be monitored, and post-marketing surveillance for other toxic events such as thrombosis is essential.

This agent should be reserved for people with counts <30 who have failed or cannot continue on steroids due to long term toxicity, and who have failed at least one other chronic therapy such as ciclosporin/dapsone/azathioprine.

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.

Additional source of evidence
A paper by Portielje (Blood 2001, 97, 2549) describes morbidity and mortality in 152 adults with chronic ITP (Leiden, Netherlands).

85% of 134 people with primary ITP obtained counts >30 and were off all therapy at 2 or more years of follow up. 12 patients (4%) had refractory disease and had an increased mortality risk of 4.2; interestingly the risk of infectious death was as great as bleeding and implies significant contribution from the immune suppressive therapy. In addition, those patients still requiring treatment had a significantly increased number of hospital admissions (5

times greater than those not on therapy) possibly related to side effects. This paper also comments on complications related to splenectomy (early 26%, late in 5%) and post-splenectomy deaths 2.

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)?

Delivery of the technology:
No extra resources would be required. Specialists are already familiar with the potential of this new agent, and education will be spread by the professional organisations (e.g. British Society of Haematology annual meeting) and guidelines.