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:

[redacted] **submitting comments on behalf of:**

NCRI/RCP/RCR/ACP/JCCO

Comment 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?

- 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)
  [redacted] sits on the Clinical Trials Committee of the UK CLL Forum who run the NCRN trials in CLL in the UK. Also sits on the Clinical Guidelines Committee of the UK CLL Forum who are presently updating our treatment guidelines (last published 2004) for the UK.

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

How is the condition currently treated in the NHS? 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?

The present recommendations by NICE is that frontline therapy for patients with Chronic Lymphocytic Leukaemia who require treatment is a combination of fludarabine, cyclophosphamide and rituximab (FCR) for patients with an adequate performance status and renal function and Chlorambucil (dose unspecified) for all others. This advice will be re-iterated in the soon to be submitted BCSH/UK CLL Forum Guidelines. Estimates vary into what proportion of UK patients receive each of the two options but I understand that up to 70-80% of patients still receive Chlorambucil as their first line therapy. This probably reflects long-standing UK practice, the relatively good results achieved with Chlorambucil in the UK CLL 4 trial and suspicions amongst some clinicians that FCR is a toxic regimen and that relatively few patients are suitable for it. If you take the German CLL Study Group data however it appears that up to 70% (of Germans!!) are suitable for FCR therapy. There is also a wide variation in the UK with regards to the dose and particular regimen of Chlorambucil in use although the UK CLL 4 study did highlight the $10mg/m^2$ for 7 days regimen which has to a certain extent helped standardise the dose. However continuous low dose and intermittent lower dose Chlorambucil use is widespread in the UK.

A relatively small proportion of patients (~10%) who have p53 deletions/mutations will receive a steroid and/or Alemtuzumab based regimen as frontline therapy.

Bendamustine use as a single agent is supported by a peer reviewed and published randomised clinical trial comparing it with Chlorambucil. There is also a German CLL Study Group comparing FCR with Bendamustine/Rituximab combination therapy but results from this study are not anticipated for several years. One of the potential advantages of Bendamustine is that it can be used in patients with poor renal function in whom Fludarabine is contraindicated and it may be more tolerable compared to FCR therapy. It will almost certainly be cheaper that FCR therapy but probably not Chlorambucil.

Is there significant geographical variation in current practice?

We are unaware of any geographical differences in the use of the two presently recommended frontline therapies with the exception that we understand the SMC allow Rituximab to be used in conjunction with Chlorambucil.

There is certainly a wide difference in individual clinicians practice with on the one side thosewho feel every effort should be made to give a patient FCR (given the significantly improved progression free survival compared to FC therapy – and on previous study evidence Fludarabine monotherapy and Chlorambucil monotherapy) and those who feel Chlorambucil is “safe” and Fludarabine regimens can be tried later on at first or subsequent relapse.

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)?

This is probably a secondary care technology as Bendamustine is administered as an infusion over 30-60 minutes. In theory it could be administered in the community assuming adequate nursing experience and access to a physician with experience of Bendamustine use is immediately available. The main problem is not so much related to possible infusional reactions to Bendamustine but more the decision of whether the blood counts and patient performance status are satisfactory for Bendamustine therapy.

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?

Bendamustine has been available for about 3 years initially as a free drug on a named patient basis but since its Licensing became imminent one has had to pay for the last 6 months or so. The License for Bendamustine has just been granted for its use as first line therapy in CLL and Multiple Myeloma and relapsed indolent Non-Hodgkin's lymphoma. Thus many UK clinicians already have experience of using Bendamustine at varying doses.

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?

CLL patients with p53 deletions or mutations do not do well with alkylator agent or fludarabine based regimens either as monotherapy or in combination. We have to date seen no convincing data to suggest that Bendamustine will have a particular role in this subgroup of patients.

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.

As indicated above Dr Fegan is a member of the UKCLL Forum/BCSH CLL Guidelines writing committee. Although these (as of now) have not been finalised it is highly likely that Bendamustine:

1) Will be one of the frontline therapeutic options recommended to clinicians.
2) Will be recommended for patients who relapse post Chlorambucil therapy who are deemed unfit for a Fludarabine based regimen.
3) Will be recommended for CLL patients with severe renal impairment

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?

Bendamustine being an infusional product will not be as easy to use as oral Chlorambucil but will be much easier than FCR which requires a much longer infusion and is much more likely to lead to immediate infusional reactions . We suspect it will be more expensive than Chlorambucil but significantly cheaper than FCR. Thus in the UK where a clinician is of the "Chlorambucil first" persuasion then adopting Bendamustine will increase the requirement for Day Unit resources. However if like myself you are of the "FCR first" persuasion then it is conceivable that there will be a reduction in the both upfront drug costs and also Day Unit resource requirement.

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.

We cannot think of any real issues in this regard for this particular technology.

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?

As you are no doubt aware Bendamustine has been used for over 30 years for the treatment of various haematological and non-haematological cancers initially in the old "Eastern Europe" and has only relatively recently following the unification of Germany come under closer scrutiny. Thus small cohort studies of its potential activities in the various tumours has been accumulating during this time period (see JCO 2009; 27: 1492-1501 for Review). The "Licensing" study was that of Knauf et al (JCO 2009; 27: 4378-4384) in which Bendamustine was compared with Chlorambucil in a randomised phase III study. It was shown to be superior with regards to Overall Response (68% versus 31%), Complete Response (31% versus 2%) and Progression Free Survival (21.6 months versus 8.3 months). This study has been the subject of ongoing discussion within the UK as the dose of Chlorambucil was less than that used in the UK CLL 4 trial and the Overall Response rate was lower (72% in the UK CLL 4 Study) and the duration of response was shorter in the Knauf study (UK study Chlorambucil - PFS 10% at 5 years which "must" be superior to Knauf as median follow up 35 months in Knauf study).

However such a comparison, in the view of our experts, is really meaningless as:

1) The UK CLL 4 study was comparing Chlorambucil with Fludarabine monotherapy and a combination of Fludarabine and Cyclophosphamide. Thus the UK study was clearly aimed as patients whose performance status was adequate for FC therapy if by chance that was the arm the patient was randomised to. We are not completely clear why the patients in the Knauf study were not receiving an frontline Fludarabine based regimen. Although I know at the time that there was a competing German study (CLL5) comparing Chlorambucil with Fludarabine monotherapy. The CLL 5 study in fact showed that Chlorambucil therapy was equal to Fludarabine monotherapy – similar to the UK CLL 4 data.
2) The Knauf study response rate was confirmed by an Independent Committee for Response Assessment whereas the UK CLL 4 study was not.
3) The dose of Chlorambucil used in the Knauf study was in fact the second highest ever used in a randomised CLL study with only the UK CLL 4 study using a higher dose. Thus many other therapies have been compared with lower doses of Chlorambucil and still Licensed. Further more the new German CLL 11 study uses exactly the same dose of Chlorambucil as used in the Knauf study as this was the median tolerated dose in the German CLL 5 Study. Also as I mentioned above there is no agreed "standard" dose or dosing regimen for Chlorambucil in the UK.
4) One really should not be comparing one arm of a randomised study with that of another. For example the severe infection rate was 8% for Bendamustine in the Knauf study and 20% for Chlorambucil in the UK CLL 4 study,

What is the relative significance of any side effects or adverse reactions?

Bendamustine both in Clinical Trial data and my own personal experience has a very satisfactory safety profile with neutropenia (+/- admission for neutropenic sepsis) being the main one – only 23% grade 3/4 neutropenia in the Knauf study.

In what ways do these affect the management of the condition and the patient's quality of life?

No real impact and certainly less of a toxicity problem than FCR.

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Bendamustine has been used for so long that we very much doubt such a problem will occur.

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.

Many studies underway both as monotherapy and in combination with other agents but full reports awaited.

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)?

The staff expertise is already in place but there may just be some capacity issues for the smaller Day Unit services.