

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]

Name of your organisation:

1. UK CLL Forum [REDACTED]
2. Royal College of Pathologists [REDACTED]
3. British Committee for Standards in Haematology [REDACTED]

Are you (tick all that apply):

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

- other? (please specify)
[REDACTED]

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?

CLL is the commonest leukaemia in adults in the UK with an annual incidence of about 3-5 per 100,000 per year and typically presenting in the 7th decade. The disease runs a chronic relapsing course and results in significant morbidity and mortality. Treatment is indicated for symptoms or clear-cut disease progression.

Combination therapy with fludarabine plus cyclophosphamide (FC) has emerged as the first-line treatment of choice for fit patients. Less fit patients are treated with chlorambucil. The use of FC in fit patients is based on the clear progression-free survival advantage demonstrated in several large phase III clinical trials. Somewhere in the order of 50% of CLL patients in the UK are currently likely to receive FC as their initial therapy. This is in spite of NICE's decision not to consider fludarabine in the first-line treatment of CLL owing to its lack of explicit marketing authorisation for use in combination with other cytotoxics. To my knowledge, the use of FC in the UK is fairly uniform with no significant geographical variation.

Based on the failure of clinical trials to demonstrate that first-line FC confers an overall survival advantage, some CLL doctors argue that it is reasonable to give chlorambucil first line and move on to FC as second-line therapy. However, the body of opinion is that FC should be given as first-line therapy to those patients who are considered sufficiently fit.

The German CLL8 trial has recently compared FC with FC plus rituximab (FCR) in patients with CLL requiring first-line treatment. The trial closed ahead of schedule as it met its primary endpoint of demonstrating a progression-free survival advantage. The data, which strongly resonate with findings in non-Hodgkin's lymphoma, are to be presented at the December 2008 meeting of the American Society of Hematology. Assuming that the data hold up and toxicity is acceptable, it is likely that FCR will become the new standard of care for the first-line treatment of fit patients with CLL. Indeed, this is already the case in many countries. Other studies have examined or are examining rituximab in combination with other chemotherapy regimens, most notably chlorambucil, and a similar benefit is anticipated.

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?

Among the numerous prognostic factors in CLL, one stands out above all others as the most ominous predictor of short survival: deletion of the p53 tumour suppressor gene at chromosome 17p13 (or 17p- for short). Patients with 17p- CLL respond poorly to chemotherapy including FC. Many CLL experts think that these patients should be treated on separate treatment protocols, and this idea is embodied in guidelines recently published by the International Workshop in CLL (IWCLL). It is an open question whether adding R to FC will overcome the adverse prognostic effect of 17p- but I personally doubt it.

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)?

In the UK (but not the rest of Europe or the USA), both fludarabine and cyclophosphamide are available as an oral preparation, and FC is usually regarded as an oral regimen and prescribed in the out-patient setting. However, because rituximab is given by intravenous infusion, the FCR regimen would entail a visit to the day unit on day 1 of each cycle.

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?

Very few NHS centres in the UK are currently in a position to use FCR for CLL given the current lack of marketing authorisation for rituximab in CLL.

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.

The recently published IWCLL guidelines are mostly concerned with the conduct of clinical trials and do not cover specific treatment choices. The UK (BCSH) guidelines are out of date and will be re-written once the German CLL8 data are published.

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?

FCR will be slightly more difficult to administer than the FC owing to the fact the rituximab is given by intravenous infusion whereas the FC chemotherapy (at least in the UK) is given by mouth. For most patients this will entail several hours of time on the haematology day unit on day 1 of each cycle.

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.

The full data from the German CLL8 trial have yet to be published so it is difficult to say whether FCR will benefit all CLL sub-groups or whether there are particular issues relating to the administration of FCR that do not apply to FC. However, historical comparison of patient cohorts treated with FCR and FC provide no indication that special precautions will be required for FCR above and beyond those required for FC.

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?

The entry criteria for the German CLL8 trial were, to the best of my knowledge, fairly typical for a trial of first-line therapy in CLL. That said, it is clear that the age and fitness profile of patients who enter clinical trials involving FC is not representative, with over-representation of younger fitter patients who are considered by local PIs to be able to withstand the toxicity of the trial treatment. In my experience, about half of CLL patients fall into this category.

With regard to the trial end-points, a significant improvement in progression-free survival is generally accepted as being sufficient to alter routine the clinical management of CLL. This is because it is notoriously difficult in randomised trials of chronic relapsing disorders such as CLL to demonstrate overall survival advantage. The likely explanation for this is that many patients who are randomised not to receive the experimental treatment up front end up receiving it at a later stage during the course of the disease when it can still confer benefit. The notion that modern treatments prolong the natural history of CLL and extend life is supported by several studies showing a trend for longer overall survival in consecutive patient cohorts from the same institution/region/country.

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 a disease like CLL which runs a chronic relapsing course, it is important to consider treatment toxicity as well as efficacy, as quality of life depends on both of these things. The most important toxicity of chemotherapy is infection. In theory, adding R to chemotherapy might result in a higher risk of infection owing to depletion of normal B cells. This has not been borne out in trials of non-Hodgkin's lymphoma. Nevertheless it will be important to see whether FCR is associated with more infections than FC in this particular context and, if so, whether this is offset by its superior efficacy.

Another potential problem associated with the FCR regimen in CLL is tumour lysis syndrome (TLS) and cytokine release syndrome (CRS), both of which typically occur within the first few hours of therapy and result from the rapid breakdown of malignant cells. In theory, antibody therapy should increase the risk of developing these syndromes owing to the rapid lysis of circulating leukaemia cells. The risk should be particularly high in patients with a high CLL count, and some experts advise splitting the first dose of rituximab or even omitting it if the CLL count is over $30 \times 10^9/l$. However, others do not feel this is necessary. Interestingly, TLS/CRS has not been an issue for alemtuzumab, which is much more potent than rituximab when used as a single agent.

A controversial aspect of purine-alkylator combination therapy is its capacity to produce secondary myelodysplasia (MDS) and acute myeloid leukaemia (AML). Since these conditions may occur years after treatment, they may be under-reported in clinical trials. However, it should be borne in mind that by far the greatest threat posed to a patient with CLL is the CLL itself. Furthermore, the risk of secondary MDS/AML following FCR is unlikely to be any higher than after FC alone.

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 MD Anderson (Michael Keating) and Barcelona (Emili Montserrat) Groups have recently collated their long-term outcome data on CLL patients treated with FCR first-line. In both series, comparison with previous cohorts treated with fludarabine combinations not containing rituximab show that FCR-treated patients have a longer overall survival. Although this is a historical comparison and therefore intrinsically flawed, the results from the two groups are impressive and strikingly similar. The MD Anderson study was recently published in Blood but the Barcelona study has not yet been formally published.

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.

Replacing FCR with FC will impose more strain on haematology day units owing to the need for R to be administered by intravenous infusion, and this could exceed the capacity of some day units. However, this should not be used as a reason to defer the implementation of FCR as the new standard of care if it meets the criteria.

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 replacement of FC by FCR as the new standard of care would not pose too many challenges from a training/facilities/equipment point of view as all haematology day units will be very experienced at administering rituximab to patients with non-Hodgkin's lymphoma. The only potential problem will be one of capacity.