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] **RCP** [redacted] **on behalf of:**

Name of your organisation

NCRI/RCP/RCR/ACP/JCCO

Coordinated by [redacted] **NCRI Haematological Clinical Studies Group**

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.)?

Chairman of the NCRI Haematology Oncology Clinical Studies Group

- 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.

Chronic lymphocytic leukaemia is the commonest leukaemia in the UK. The incidence of CLL is about 3/100,000. Roughly twice as many men have the disease as women. The median age of onset is 65-70 years. About 80 % of patients are diagnosed as a by chance finding when they have a blood count for another reason. The majority of these early stage patients will not require treatment at diagnosis and will undergo watchful waiting. About half will need treatment at a later date. Indications for treatment are the development of troublesome lymphadenopathy or splenomegaly, evidence of bone marrow failure, a rapid white cell doubling time or systemic symptoms (weight loss, night sweats, lassitude). The prevalence of patients requiring treatment is approximately 3.5/100,000 per annum; this figure represents a mixture of first line patients and those receiving treatment later in the course of their disease.

Chronic lymphocytic leukaemia is a very heterogeneous disease. Prognostic factors which can be used to predict outlook include measures of tumour bulk (clinical stage, LDH, β_2M) and tumour biology (cytogenetics, CD38 and ZAP 70 expression, unmutated VH genes) Patients with 17p deletion (mutated p53 genes) have an especially dismal outlook and respond poorly to conventional cytotoxic regimens. However these patients represent a small proportion of the total. There are no groups, which would be put at risk by the technology. However since the proposal is to consider rituximab in combination with fludarabine (and cyclophosphamide) caution will be needed in the elderly and in those with co-morbidities. FC is not well tolerated in those with poor performance status and should be avoided or used with care in the presence of renal impairment.

Current UK practice: For many years the oral alkylating agent chlorambucil (with or without prednisolone) was the mainstay of haematological practice in the UK for CLL. The advent of the purine analogues in the early 90's with high activity against lymphoproliferative disease resulted in a number of trials against chlorambucil. The UK LRF CLL 4 trial compared chlorambucil with fludarabine or fludarabine and

cyclophosphamide (Catovsky at el, 2007). The results showed a clear advantage for the FC combination over chorambucil or fludarabine monotherapy in progression free survival but no overall survival gain. Patients receiving FC had a greater incidence of infections and grade IV haematological toxicity but severe haemolytic anaemia was reduced. Quality of life data on the trial is awaited. Overall survival is, however, always difficult to use as an endpoint in CLL as many patients cross over to combination therapy after relapse. Following the publication of the LRF CLL4 trial, much of the practice in the UK has been to use FC chemotherapy for younger, fitter patients with CLL but many centres continue to use chlorambucil for older frailer patients and those with renal impairment. A Roche sponsored phase II trial of rituximab in combination with chlorambucil is currently underway in the UK.

Transplantation: Autologous (ABMT) transplantation may result in prolonged PFS but relapse is inevitable and in UK practice auto-transplantation was associated with a high incidence of myelodysplasia. The MRC and EBMT have recently completed a randomised trial of ABMT and the results are awaited. At the moment in the UK ABMT is not regarded as a standard of care.
Allogeneic transplantation may provide a curative modality for CLL but, even using reduced intensity techniques, is only applicable to a relatively small population of patients.

***Setting**: The technology is applicable to use in secondary care under the supervision of a haematologist or oncologist experienced in the management of chronic lymphocytic leukaemia and antibody-based therapy. It could be given in a community setting with appropriate safeguards. The reconstitution of rituximab by pharmacists and the long infusion times will place additional burdens on hard-pressed chemotherapy services.*

***Rituximab in Chronic Lymphocytic Leukaemia**:*
Rituximab is a chimeric anti-CD20 antibody with demonstrated activity against CLL cells. The strongest published data comes from the work in Houston where the combination of FC+rituximab has been studied for a number of years. (Keating 2005, Tam 2008). In the latest report in over 300 first-line patients with a six year follow-up, the FCR (fludarabine, cyclophosphamide +/- rituximab) (combination was associated with an 95% response rate and 72% complete remission. Forty-two per cent of patients became MRD negative by PCR. The median duration of response was 80 months and the toxicity was reported as low. One third of patients had one or more episodes of infection and half the patients experienced grade 3 or 4 neutropenia. 10% of patients suffered a late infection in the first year due to opportunistic infection. Myelodysplasia occurred in 3% of patients.

Tam et al, 2008

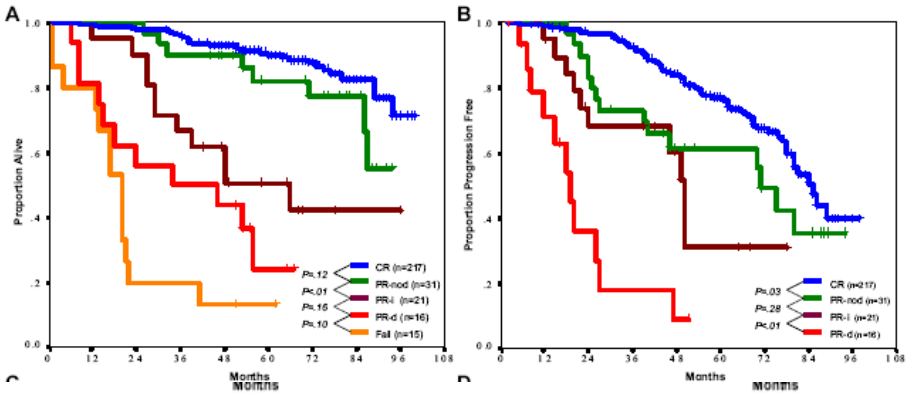

Figure 1. Overall survival (OS) and time to progression (TTP). (A) OS by treatment response. Patients in complete remission (CR) and nodular partial response (PR-nod) had similarly favorable survival (6-year OS 88% and 77% respectively, $P = .12$). Survival for other categories was as follows: partial response due to incomplete recovery (PR-i), 6-year OS 42%; partial remission due to residual disease (PR-d), 5-year OS 24%; and resistant disease, 5-year OS 15%. (B) TTP by treatment response. Median TTP was longest in CR patients (85 months), followed by PR-nod and PR-i (71 months and 50 months, respectively), and was only 19 months for patients in PR-d. (C) Impact of flow

The MD Anderson Group also examined historical controls receiving FC combinations without rituximab and demonstrated an apparent OS survival gain. Patients over 70 had less benefit than those under 70 and also those with p53 mutations and a high LDH but no risk group could be identified which defined the duration of response.

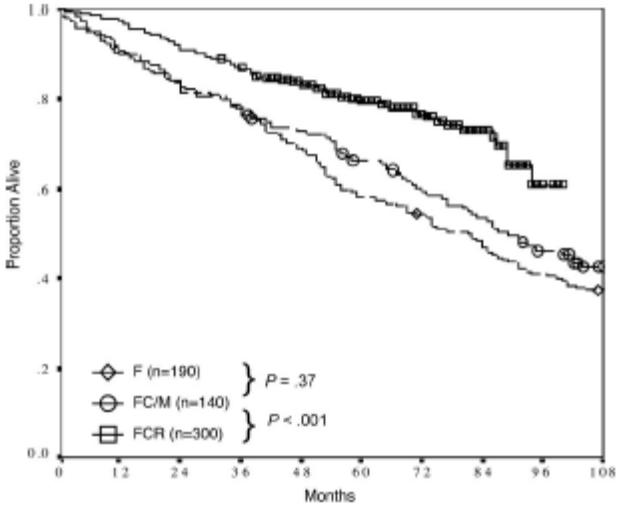

Figure 3. Survival of patients receiving fludarabine (F), fludarabine and cyclophosphamide or mitoxantrone (FC/M), and FCR as initial therapy of CLL at the M. D. Anderson Cancer Center. Six-year overall survivals were 54%, 59%, and 77%, respectively.

The achievement of absence of PCR detectable disease may be a worthwhile aim in CLL but in a non-randomised trial this may be a surrogate marker for a group of chemosensitive patients and the RCT data from the REACH and CLL8 trials will be valuable to disentangle this.

The Roche sponsored German CLL 8 trial compared FC with FCR in a RCT. The trial was stopped prematurely early in 2008 because it had reached its endpoint of demonstrating a 35% increase in PFS in the experimental arm. No further information is available but a report is expected at the American Society of Hematology Annual Meeting in December 2008. Finally Roche have also made a press release about the REACH trial. This compared FC v FCR in patients with CLL as second line or subsequent treatments and has also demonstrated a gain in PFS although full details are awaited.

***Rituximab and current UK practice**: There is patchy uptake of FCR in the UK. This is partly because of the lack of a UK licence but principally because of difficulties in accessing funding. Most Commissioners are reluctant to agree funding for high-cost drugs outside their NICE indications and the current exceptional funding processes are cumbersome and inconsistent. It is likely that a proportion of younger patients with CLL are receiving this therapy already but the exact numbers are difficult to estimate.*
Given the wide publicity of the ending of the German CLL8 trial and the recent publication from Tam et al, there is an expectation in both the haematology community and the CLL patient population that FCR is a new standard of care for

younger CLL patients requiring treatment, but evidence on cost effectiveness is awaited.

***References**.*

Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. Lancet. 2007;370:230–239

Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia [see comments]. Blood. 1999;94:1840–1847.

Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343:1910–1916

Ghia P, Guida G, Stella S, et al. The pattern of CD38 expression defines a distinct subset of chronic lymphocytic leukemia (CLL) patients at risk of disease progression. Blood. 2003;101:1262–1269

Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia Blood. 1999;94:1848–1854.

Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol. 2005;23:4079–4088

Orchard JA, Ibbotson RE, Davis Z, et al. ZAP-70 expression and prognosis in chronic lymphocytic leukaemia. Lancet. 2004;363:105–111

Constantine S. Tam, Susan O'Brien, William Wierda, Hagop Kantarjian, Sijin Wen, Kim-Anh Do, Deborah A. Thomas, Jorge Cortes, Susan Lerner, and Michael J. Keating Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia
*Blood, Aug **2008**; 112: 975 - 980.*

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?

Rituximab will require more pharmacy time for reconstitution and more day case attendance. Capacity in both these areas is currently limited as chemotherapy activity is currently rising at about 10% year on year. FCR is associated with a greater risk of serious infections and may result in more in-patient admissions. The technology should be used with caution in those aged greater than 70 and in those with reduced performance status. If combined with FC, dose adjustments to fludarabine are needed for modest renal impairment and fludarabine should be avoided if the GFR is low.

The results from MD Anderson are difficult to interpret with regards to applicability to the UK as MDACC attracts more affluent patients with lower co-morbidities compared with a population cross-section of UK patients with CLL. In addition the median age of 58 was significantly lower that the median age for patients with this disease. The German CL8 trial may be more applicable although frequently the populations of patients recruited to randomised trials do not always reflect the general population.

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.

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)?

Increased capacity will be needed in chemotherapy day units and pharmacy. The level of staff training is currently adequate to deal with the technology as most units have good familiarity with rituximab.