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: Andrew R Pettitt

Name of your organisation

1. **UK CLL Forum (Chair)**
2. **Royal College of Pathologists (representative)**

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES (Clinical lead for CLL for the Royal Liverpool University Hospital and Merseyside & Cheshire Cancer Network)**

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES (Member of the NCRI Haematological Oncology Clinical Studies Group and CLL Subgroup)**

- 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.)? **NO**

- other? (please specify)
  Medical advisor to 4 national/international patient groups dealing with CLL (CLL Support Association, CLL Topics, Leukaemia Care and the Lymphoma Association)

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 usually requires multiple treatment episodes. Treatment is indicated for symptoms or clear-cut disease progression. This strategy is based on the fact that pre-emptive treatment with chlorambucil is of no benefit in patients with asymptomatic early-stage disease.

Combination therapy with rituximab, fludarabine and cyclophosphamide (R-FC) has recently emerged as the internationally accepted first-line treatment of choice for fit patients. This consensus is based on the clear superiority demonstrated in several large phase III clinical trials of FC over either fludarabine monotherapy or chlorambucil, and more recently the clear superiority of R-FC over FC demonstrated in the German CLL8 trial. Somewhere in the order of 50% of CLL patients in the UK are currently likely to be candidates for R-FC as their initial therapy. For less fit patients chlorambucil remains the standard of care, although this could change depending on the results of the current UK trial of chlorambucil in combination with rituximab.

With regard to subsequent therapy, things get rather more complicated owing to variation between patients in terms of how many and which treatments have previously been administered and how well each treatment has worked. As a general rule of thumb, if patients obtain more than 2 years of remission with a given treatment before requiring further therapy then it is reasonable to give the same treatment again. If, on the other hand, patients require further therapy sooner than this, then it is reasonable to try a different treatment regimen. Furthermore, because early progression indicates aggressive disease, this can justify the use of more intensive and potentially more toxic regimens than would be considered appropriate as first-line therapy. For example, patients who receive chlorambucil as first-line therapy owing to fitness considerations may nevertheless go on to receive fludarabine combination regimens if they do not respond or undergo early progression.

The REACH trial (on which the present NICE submission is based) essentially replicates the results of the first-line German CLL8 trial in previously treated patients. Thus, compared to FC, R-FC was associated with twice as many complete responses, significantly longer progression-free survival, increased neutropenia but no increase in infection.

Based on the results of the REACH trial, it would be reasonable to propose that R-FC should replace FC in current treatment algorithms applicable to previously treated patients. In practice, this refers to the following groups of patients:-

(1) relatively fit patients who progress at any time following prior treatment with chlorambucil or fludarabine monotherapy.
(2) relatively fit patients who progress more than 2 years after receiving fludarabine combination therapy (usually FC).
(3) less fit patients who progress within 2 years of receiving chlorambucil or fludarabine monotherapy – careful risk/benefit analysis needs to be applied to patients falling into this category and dose attenuation may be indicated.

All trials of second-line therapy suffer from the problem that by the time mature data are available first-line treatments will have changed and one is then faced with the difficulty of interpreting the trial results in the context of modern first-line treatments. The REACH trial is no exception to this rule. Most notably, patients recruited into the REACH trial were not previously treated with rituximab. It is therefore difficult to be certain that that second-line R-FC would be superior to FC in patients who received rituximab as part of their first-line therapy. This is an important consideration now that R-FC looks likely to become the first-line treatment of choice for fit patients. However, absence of proof is not the same as proof of absence, and it is noteworthy that NICE approved rituximab as an adjunct to second-line chemotherapy for follicular lymphoma irrespective of prior rituximab exposure, despite the lack of proven benefit in patients who previously received rituximab as part of their first-line treatment.

Another difficulty intrinsic to disorders such as CLL that require more than one treatment episode is that it is extremely difficult to show that new treatments prolong life within the framework of randomised trials, even if they show considerable benefit in terms of progression-free survival. This is probably because patients who are allocated not to receive the new treatment as first-line therapy go on to receive it later during the course of their disease when it can still make a significant impact. In keeping with this theory, historical comparisons of successive cohorts of patients treated within the same institution have shown that patients diagnosed more recently (who have had access to the latest treatments) have a longer survival. Following on from these considerations, the international CLL community now accepts progression-free survival as a more meaningful endpoint than overall survival as a way of assessing the effectiveness of new treatment regimens.

Alternative treatment options to (R)-FC in previously treated patients include glucocorticoids or alemtuzumab, either alone or in combination. Although these treatments have their particular strengths – notably activity in patients with mutation/deletion of TP53 at chromosome 17p13 who respond poorly to chemotherapy – they also have limitations and disadvantages. For example, glucocorticoids rarely produce complete and durable responses whereas alemtuzumab is relatively ineffective in patients with bulky lymphadenopathy. In addition, both agents have significant toxicity and are probably best confined to patients who do not respond well to FC or who have a TP53 deletion/mutation.

To my knowledge, the use of FC in the UK is fairly uniform with no significant geographical variation.

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?

A range of biological variables can predict outcome in CLL. These range from basic clinical features such as age, fitness and clinical stage (a measure of tumour burden) to sophisticated molecular tests such as immunoglobulin gene mutation status. Apart from predicting survival, some of these variables can also predict tolerance to and sensitivity to specific treatments.

Fitness and co-morbidity (not necessarily age per se) are good predictors of tolerance of stronger chemotherapy regimens such as FC. However, in routine clinical practice assessment of patients for their suitability for FC is very much based on clinical judgement rather than formal scoring systems such as WHO performance status or critical illness rating score (CIRS). One aspect of patient assessment that is essential when considering fludarabine is to assess the creatinine clearance and attenuate the dose if there is significant impairment of renal function. Somewhere between half and two thirds of previously treated patients are likely to be candidates for (R)-FC based on fitness and co-morbidity considerations.

With regard to predicting response to chemotherapy, the one biomarker that stands out above all others is deletion of TP53 at chromosome 17p13, which is readily detectable by interphase fluorescence in-situ hybridisation (FISH). Most cases with TP53 deletion also harbour a TP53 mutation on the remaining allele resulting in biallelic inactivation. In addition, some patients have a TP53 mutation only which may affect both alleles through the acquisition of uniparental disomy. Available evidence suggests that the latter patients are clinically indistinguishable from those with a deletion of TP53. However, mutation analysis is more difficult to perform than FISH analysis and has not yet become part of routine clinical practice. TP53 abnormalities are present in about 5-10% of patients requiring first-line therapy and in up to 30% of patients who are refractory to fludarabine.

The predictive value of biomarkers, including TP53 deletion/mutation, depends on the clinical and therapeutic context. For example, the German CLL2H trial has shown that TP53 deletion loses is prognostic value in fludarabine-refractory patients who receive alemtuzumab. It is unclear whether this is because it is "trumped" by fludarabine resistance as a predictor of adverse outcome, or whether alemtuzumab overcomes its adverse prognostic effect. Similarly, in previously untreated patients the negative prognostic effect of deletion of ATM at chromosome 11q23 is partially overcome by using FC instead of chlorambucil or fludarabine monotherapy, and almost completely overcome by adding rituximab to FC.

One further point of note in relation to predictive biomarkers is that, although patients can be identified that do badly with a new treatment, this does not necessarily mean that such patients do not benefit from the new treatment relative to the old one. For example, although TP53 deletion was strongly predictive of poor outcome in the German CLL8 trial of first-line R-FC, outcome for these patients was even worse if they were treated with FC alone.

Therefore, simply demonstrating that a particular group of patients does relatively badly with non-first-line R-FC is not in itself a reason to withold it, especially in the absence of proof that alternative treatments are any better. That said, however, alternative treatments based on alemtuzumab and glucocorticoids appear to be more effective than R-FC in patients with TP53 defects, although formal proof of their superiority is lacking.

In short, there is no good reason for excluding specific sub-groups of patients from receiving R-FC based on predictive biomarkers, although the regimen may be too toxic for some patients with poor performance status and/or significant co-morbidity.

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 R-FC regimen would entail a visit to the day unit on day 1 of each cycle (2 visits for the first cycle as it is recommended that the first rituximab dose is split over 2 days)

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?

Hitherto, very few UK centres have been in a position to use rituximab as part of the first-line or subsequent treatment of CLL. However, now that R-FC looks likely to be approved by NICE for first-line treatment, it is likely that some centres will start to use R-FC in previously treated patients who are currently candidates for FC.

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 in the process of being re-written to take into account the results of the German CLL8 and REACH trials. It is highly likely that they will endorse the use of R-FC as both first-line and subsequent therapy.

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?

R-FC 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, with an additional visit for cycle 1 owing to the need to split the first dose of rituximab over 2 days. This could have manpower and/or service capacity implications for some units.

With the exception of a single dose of antihistamine and paracetamol to offset rituximab infusion reactions, concomitant medication for R-FC should be no different to that used for FC alone, namely anti-emetics, allopurinol, co-trimoxazole (controversial but adopted by most UK centres) and aciclovir (if there is a prior history of herpes simplex or herpes zoster reactivation). R-FC might be associated with an increased use of G-CSF owing to its greater propensity to induce neutropenia.

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 REACH trial have yet to be published so it is difficult to know whether there are particular issues relating to the administration of R-FC that do not apply to FC in the relapsed/refactory setting (although none have emerged from the German CLL8 trial in relation to first-line R-FC). As with FC, it is customary to assess response midway through the planned 6 cycles to confirm that the treatment is working and change to alternative treatment if this is not the case.

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?

There is no reason to suspect that the results of the REACH trial should not apply to UK practice. 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.

As explained above, a significant improvement in progression-free survival is generally accepted as being sufficient to alter routine the clinical management of CLL.

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 such as 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 rituximab to chemotherapy might result in a higher risk of infection owing to depletion of normal B cells. Furthermore, both the German CLL8 trial and the REACH trial have shown that R-FC is associated with more neutropenia than FC alone. Despite these considerations, however, R-FC does was not associated with an increased risk of infection in either the CLL8 trial or the REACH trial.

Another potential problem associated with the use of rituximab 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. This seems to be a much more significant problem in CLL than in "solid" lymphomas. There is general consensus that first dose of rituximab should be split over two days in CLL, especially in the presence of a high white-cell count.

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 R-FC 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.

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)?

Replacing R-FC with FC will impose more strain on haematology day units, and this could exceed the capacity of some day units in terms of nursing manpower, space and clerical infrastructure. Further, although all haematology day-units will be very experienced in using rituximab in "solid" lymphoma, its use in CLL is associated with more severe infusion reactions and day-ward staff will need to be educated about this and be in a position to deal with it effectively.