NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Rituximab for the first-line treatment of stage III–IV follicular lymphoma (review of NICE technology appraisal guidance 110)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Roche	**I. Has all of the relevant evidence been taken into account?** Yes. Roche broadly supports the committee's recommendations, as detailed in the ACD, and will present no further data. Roche shares the committee's concerns, as discussed in the previous committee meeting, about the inequality of access to rituximab for older or less-fit patients who would be suitable for R-chlorambucil and who will now receive chlorambucil alone. Roche is firmly convinced that the addition of rituximab to chlorambucil would be of significant benefit to a subset of older, less-fit patients, and would be a cost-effective use of NHS resources. This is a view shared by clinical experts. Unfortunately, there are no randomized controlled trials to support this treatment combination, and despite the overwhelming evidence for the value of rituximab in combination with other chemotherapy agents, we must acknowledge that NICE's evidence requirement cannot be met. Roche would like to emphasise to the committee that in the treatment of follicular lymphoma, expert opinion and all available trial data indicates that the chemotherapy regime chosen is of less importance than ensuring that rituximab is given with that chemotherapy. This explains the heterogeneity observed in the choice of chemotherapy: the combination of rituximab and chemotherapy is widely held to be of value for all patients (with the possible exception of patients too frail or unwell to visit the hospital for infusions) while there is less certainty about the best chemotherapy agent.	Comment noted. The Committee recognised that treatment with CVP or CHOP may not be suitable for all patients and that for these patients chlorambucil may have a role in treatment (see FAD section 4.3.3). The Committee was persuaded that on the basis of the evidence submitted and comments provided that rituximab would provide an additional clinical benefit when added to chemotherapy (see FAD section 4.3.8). The Committee was mindful of the limited clinical data and the absence of a formal cost effectiveness analysis, but for the group of patients likely to receive rituximab plus chlorambucil in the NHS, the Committee concluded that rituximab plus chlorambucil was an appropriate use of NHS resources (see FAD section 4.3.14).
Roche	**II. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Roche continues to have concerns, as previously discussed in our response to the AG report, around the AG's approach to the issue of a potential reduction in efficacy of rituximab when used second-line, following first-line R-chemo and R-maintenance. In the ACD (sections 4.2.20 and 4.3.8) it is highlighted that the AG conducted a sensitivity analysis exploring a 25% reduction in efficacy of second-line rituximab treatment. Roche believes that there is no basis for the arbitrary assumption of a 25% reduction in efficacy. Inasmuch as there is uncertainty around this question (as noted in section 4.3.8) and given the possibility that an increase in efficacy is theoretically plausible, it would have been equally reasonable to explore an arbitrary assumption of a 25% increase in efficacy – or maybe to explore and	Comment noted. NICE do not respond to comments in the Assessment Report because this is an independent academic report. The Committee considered that the efficacy of rituximab when used as a re-treatment is uncertain. However, the Committee agreed that this uncertainty was not such that rituximab in combination with CVP, CHOP, MCP, CHVPi or chlorambucil should not be considered a cost effective treatment option (see FAD section 4.3.13).

Consultee	Comment	Response
	present both.	
Roche	**III. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Yes, with reference to the comments made above.	Comment noted. See response above.
Roche	**IV. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** As discussed previously, Roche is concerned that the current recommendation will deny a subset of older patients access to rituximab therapy on the basis of their age. While a patient's level of biological fitness and comorbidity is of importance when determining fitness for a given therapy, age is also a consideration for many clinicians. While not all older patients who would receive chlorambucil would be suitable for treatment with R-chlorambucil, a proportion may be. Roche is concerned that as these patients may be deemed unfit for more aggressive therapies partly due to their age, they will therefore also be denied access to treatment with rituximab—from which they could otherwise derive benefit— due to their age, with the recommendations as they stand in the ACD.	Comment noted. The Committee recognised that treatment with CVP or CHOP may not be suitable for all patients and that for these patients chlorambucil may have a role in treatment (see FAD section 4.3.3). In addition, the Committee was persuaded that on the basis of the evidence submitted and comments provided that rituximab would provide an additional clinical benefit when added to chemotherapy (see FAD section 4.3.8). The Committee was mindful of the limited clinical data and the absence of a formal cost effectiveness analysis, but for the group of patients likely to receive rituximab plus chlorambucil in the NHS, the Committee concluded that rituximab plus chlorambucil was an appropriate use of NHS resources (see FAD section 4.3.14).
Leukaemia CARE and Lymphoma Association	Thank you for the opportunity to comment on the Appraisal Consultation Document for stage lll-IV follicular lymphoma. Both the Lymphoma Association and Leukaemia CARE are pleased that you intend to recommend the use of rituximab in combination with CVP, CHOP, MCP and CHVPi as an option for the treatment of symptomatic stage III and IV follicular lymphoma. This decision is very welcome and will improve the range of treatment options for the patients we represent, as well as improving their quality of life. However there is a group of patients who we feel will not benefit from these very welcome changes - older patients. This exclusion may fall foul of your equalities policy. While we are aware that there is a lack of clinical evidence to support the use of rituximab with other chemotherapy regimens, we are disappointed that the recommendation does not extend the use to rituximab with any chemotherapy,	Comment noted. The Committee discussed the addition of rituximab to other chemotherapy regimens and was persuaded that it would provide an additional clinical benefit (see FAD section 4.3.8). It noted that the addition of rituximab to other chemotherapy regimens had not been modelled and it agreed that recommending rituximab with any chemotherapy regimen was not appropriate (see FAD section 4.3. 14). However, the Committee specifically discussed the addition of rituximab to chlorambucil and consultation comments that this combination would be useful for older patients or patients with a lower performance

Consultee	Comment	Response
	which would be in line with the UK marketing authorisation. It was clear from the appraisal committee meeting that clinicians may on occasions wish to have a wider range of options, such as rituximab with chlorambucil, depending on the clinical circumstances. As patient organisations, we would support giving clinicians the wider freedom to use their clinical judgement which approval of the licensed indication would provide. This may be of particular benefit to older patients for whom the recommended chemotherapy regimens may be unsuitable. As follicular lymphoma is a disease of the elderly, there is a not infrequent problem of coincident diabetes which makes steroids problematic and also may prevent the use of vincristine if there is diabetic neuropathy. This is a particular problem with the increasing Asian population too. In these circumstances, chlorambucil is probably the chemotherapy of choice and it would be illogical to deprive such patients of rituximab as the benefit of rituximab has been seen with every regimen where it has been tested and it is highly improbable that the situation would be different with the chlorambucil regimen. We therefore ask the committee to reconsider the conclusion stated in 4.3.6 in favour of recognising that "the consistency in effect seen in clinical trials for the use of rituximab with CVP, CHOP, MCP and CHVPi **is** sufficient to generalise the outcomes to all other chemotherapy regimens used in clinical practice".	status. The Committee was mindful of the limited clinical data and absence of a formal cost-effectiveness analysis for the group of patients likely to receive rituximab plus chlorambucil, but it concluded that rituximab plus chlorambucil was an appropriate use of NHS resources (see FAD section 4.3.14).
Royal college of Physicians on behalf of NCRI/RCP/RCR/ACP/JCCO	I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with regard to the above ACD consultation. We are grateful for the opportunity to respond and would like to make the following comments with regard to the consultation questions. We believe that rituximab in combination with chemotherapy is now the undisputed standard of care worldwide for the first line treatment of patients with follicular lymphoma who need a treatment intervention (because of symptoms, bulky disease or peripheral blood cytopenias due to bone marrow involvement). The real issue is which chemotherapy and our experts favour an extension of the recommendation to include rituximab-bendamustine. In a pivotal study presented at ASH 2009 (abstract 405), Rummel and colleagues showed that R-bendamustine was superior and less toxic than R-CHOP; in particular there was no alopecia and less neutropenic sepsis and unlike CHOP, bendamustine is not known to be cardiotoxic. On the basis of these data many new phase III trials are using R-bendamustine as the standard arm and it is therefore entirely appropriate that non-trial entrants should be allowed access to this combination which produces more benefit for patients with less immediate and later (cardiac) toxicity. This reduction in toxicity is likely to have cost benefits to the healthcare	Comment noted. A NICE technology appraisal of bendamustine plus rituximab as first-line treatment of indolent non-Hodgkin's lymphoma is planned to start in 2012 The use of rituximab plus bendamustine as a first-line treatment of follicular lymphoma will be considered in this planned appraisal (see FAD section 4.3.5).

Consultee	Comment	Response
	system. We would point out that R-bandamustine is available through the interim cancer drugs fund for patients with recurrent disease. We can see no discrimination issues around availability of R-chemo to NHS patients. A final point is that in considering induction therapy for first line therapy of follicular lymphoma the PRIMA trial data (Salles at al) shows clear benefits associated with R-maintenance for patients achieving complete or partial remission and it may be worth alluding to this in the recommendations.	Comment noted. No action required Comment noted. The recommendations in this current appraisal consider induction therapy for first-line therapy only and do not consider rituximab maintenance therapy which is considered in a separate guidance document (TA226).
Department of Health	No comments	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Patient expert	1. Do you consider that all the relevant evidence has been taken into account? *If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?* **All the available published info has been taken into account. I am disappointed that they have restricted the use to certain chemotherapy regimens as I believe that this disadvantages the elderly where few clinical trials are carried out. I think rituximab should be available with first line chlorambucil**	Comment noted. The Committee recognised that treatment with CVP or CHOP may not be suitable for all patients and that for these patients chlorambucil may have a role in treatment (see FAD section 4.3.3). The Committee was persuaded that on the basis of the evidence submitted and comments provided that rituximab would provide an additional clinical benefit when added to chemotherapy (see FAD section 4.3.8). The Committee concluded that rituximab plus chlorambucil was an appropriate use of NHS resources despite the limited clinical data and absence of a formal cost-effectiveness analysis for the group of patients likely to receive rituximab plus chlorambucil (see FAD section 4.3.14).
Patient expert	2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations? **Yes**	Comment noted. No action required.

Nominating organisation	Comment	Response
Patient expert	3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound? **They are reasonable**	Comment noted. No action required.
Patient expert	4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland? **Yes**	Comment noted. No action required.
Patient expert	5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. **Probably no major impact as I believe that most centres are using Rituximab with regimens other than RCVP**	Comment noted. No action required.
Patient expert	6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. **No**	Comment noted. No action required.

Comments received from commentators

Commentator	Comment	Response
Commissioning Support Appraisal Service (CSAS)	On behalf of Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for ***Rituximab in combination with chemotherapy for treatment of symptomatic stage III and IV follicular lymphoma***. In general, CSAS supports NICE's provisional recommendation that "Rituximab, in combination with cyclophosphamide, vincristine and prednisolone (CVP), cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), mitoxantrone, chlorambucil and prednisolone (MCP), or cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α (CHVPi), is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people".	Comment noted. No action required.
Commissioning Support	**Rituximab in combination with chemotherapy is more clinically effective than chemotherapy alone.** There is evidence to demonstrate that Rituximab plus	Comment noted. The Committee was

Commentator	Comment	Response
Appraisal Service (CSAS)	CVP, CHOP, MCP and CHVPi is more effective than CVP, CHOP, MCP and CHVPi alone for the treatment of advanced follicular lymphoma. The addition of rituximab to CVP, CHO and MCP produced statistically significantly improved rates of overall survival at 4 or 5 years. The addition of rituximab to CVP, CHOP, MCP and CHVPi improved progression-free survival and duration of response.	persuaded that on the basis of the evidence submitted and comments provided that rituximab would provide an additional clinical benefit when added to chemotherapy (see FAD section 4.3.8)
Commissioning Support Appraisal Service (CSAS)	**Rituximab in combination with specified combination chemotherapy regimens does appear to be a cost effective use of NHS resources.** NICE considered cost-effectiveness analyses, with or without the addition of rituximab, for the chemotherapy regimens CVP, CHOP and MCP and considered the manufacturer's submission for CHVPi. The addition of rituximab to CVP, CHOP, MCP and CHVPi gave incremental cost-effectiveness ratios (ICERs) of: £7720, £10,800, £9320 and £9251 respectively per QALY gained, and these are well below NICE's usual ceiling of £20,000-£30,000/QALY.	Comment noted. No action required
Commissioning Support Appraisal Service (CSAS)	**No issues with safety were raised.** The addition of rituximab to CVP, CHOP, MCP and CHVPi did not significantly increase adverse event rates.	Comment noted. No action required.
Commissioning Support Appraisal Service (CSAS)	**The quality of available research was good**. The assessment of efficacy was based on four good quality trials, which included chemotherapy regimens used in the NHS (CVP, CHOP, MCP and CHVPi). It would not be appropriate to generalise these results to other chemotherapy regimens, for example, those containing chlorambucil, fludarabine or bendamustine.	Comment noted. The Committee noted that there are randomised studies comparing different rituximab chemotherapy regimens that have been published as abstracts. The Committee was persuaded that on the basis of the evidence submitted and comments provided that rituximab would provide an additional clinical benefit when added to chemotherapy (see FAD section 4.3.8).
Commissioning Support Appraisal Service (CSAS)	**There were, however, limitations to the inputs in the economic model.** Neither the manufacturer nor the Assessment Group models included the use of rituximab as maintenance treatment after induction therapy, or modelled the re-use of rituximab as second-line treatment where it may be less effective. It was probably reasonable for the Appraisal Committee to consider that there was insufficient uncertainty to increase the ICER above £20,000-30,000/QALY. It should be noted that the ICER estimates for R-CHVPi were taken solely from the manufacturer's submission, but the Assessment Group was probably reasonable in not including this chemotherapy combination in its model due to design issues with the trial and because the combination is infrequently used in clinical practice.	Comment noted. The Assessment Group model included maintenance treatment in a scenario analysis and the ICERs for this analysis were considered by the Committee (see FAD section 4.3.11).

Commentator	Comment	Response
	Crude cost estimates suggest that the addition of rituximab to CVP, CHOP, MCP and CHVPi would cost an additional £20,000 per 100,000 population per year (i.e. to treat two patients per 100,000 population per year) in drug costs alone. The impact of VAT and locally negotiated prices could make an important difference to the true cost to commissioners.	
ScHARR	**1) p.10: Section 4.1.10: Although an increased statistically significant incidence of leukocytopenia, neutropenia and granulocytopenia was observed in the trials in the rituximab plus chemotherapy arms, this was not associated with an increase in the rate of infection (infection is associated with leukocytopenia, neutropenia and granulocytopenia).** This is incorrect. Most trials did not report if leucocytopenia, neutropenia and granulocytopenia were of a statistically significant difference between R-chemo and chemo arms. The exceptions were: • A statistically significant difference in granulocytopenia between the R-CHOP and CHOP arms in the GLSG-2000 trial • A Statistically significant difference in neutropenia for the FL2000 trial. • Leukocytopenia was not significantly different between R/CHOP and CHOP in the GLSG-2000 trial.	Comment noted. The FAD as been amended (see FAD section 4.1.12).
ScHARR	2) **p 12: Section 4.2.2: Three of the trials (Dunbar et al, 2006, 2009 and Homberger) only considered rituximab plus CVP** This is incorrect. These are not trials but economic evaluations. Furthermore, the names should be corrected from *Dunbar* to *Dundar* and *Homberger* to *Hornberger*.	Comment noted. The FAD has been amended (see FAD section 4.2.2).
Health Improvement Scotland	1. Do you consider that all the relevant evidence has been taken into account? *If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?* I agree that the key randomised data comparing R-chemotherapy with the corresponding chemotherapy alone has been taken into account. There are key studies comparing different types of R-chemotherapy with one another. Two of these are large randomised studies (R-bendamustine v R-CHOP, and	Comment noted. The Committee considered the studies of rituximab plus other chemotherapy which had been published as abstracts. It considered that these data include rituximab in all treatment groups and therefore do not provide direct evidence of the benefit of adding rituximab to

Commentator	Comment	Response
	R-CVP v R-CHOP v R-FM). Both of these studies have appeared in abstract form and when fully published might suggest one form of R-chemotherapy is more clinically and/or cost effective than another. For example R-bendamustine seems non-inferior to R-CHOP but with less side effects.	chemotherapy. The Committee considered that there was uncertainty as to the relative effect and absolute response rates of the addition of rituximab to chemotherapy regimens other than those studied in the clinical trials. However, the Committee was persuaded that on the basis of the evidence submitted and comments provided that rituximab would provide an additional clinical benefit when added to chemotherapy (see FAD section 4.3.8).
Health Improvement Scotland	2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations? I fully support the interpretation of the clinical and cost effectiveness summaries. It is clearly acknowledged that subsequent therapy decisions are important in this area but are not easily predicted for the whole cohort of patients. Clinicians will choose relapsed regimens based on the initial treatment used and the initial length of the first response. It is of course assumed in the model that first line R-maintenance will have the same benefit independent of the initial R-chemotherapy. This might not be the case, with R-maintenance having more benefit following less intense regimens, such as R-CVP, than in more intense regimens such as R-CHOP.	Comment noted. The recommendations in this current appraisal consider rituximab induction therapy only and do not consider rituximab maintenance therapy which is considered in a separate guidance document (TA226).
Health Improvement Scotland	3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound? Yes, I think the decisions are sound and a very appropriate basis for guidance to the NHS.	Comment noted. No action required.
Health Improvement Scotland	4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland? The same as for Scotland	Comment noted. No action required.
Health Improvement Scotland	5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? Current SMC guidance is for Rituximab in combination with chemotherapy (not specified)(SMC 493/08). Whilst the same trials were compared in the SMC	Comment noted. The Committee discussed the addition of rituximab to other chemotherapy regimens and was persuaded that it would provide an additional clinical benefit (see FAD section 4.3.8) but it noted

Commentator	Comment	Response
	appraisal, the final guidance used the general term 'chemotherapy' and did not specify limits on which regimens could be used. The only change to Scotland would be if the NICE guidance was considered to be a multi-technology appraisal relating to the 4 named immunochemotherapy regimens and as such superseded the general term 'chemotherapy' in the SMC guidance. This would disallow useful combinations such as R-chlorambucil in older/frail patients which can currently be interpreted by clinicians and Health Boards as useable under the SMC guidance.	that the addition of rituximab to other chemotherapy regimens had not been modelled. It agreed that recommending rituximab with any chemotherapy regimen was not appropriate. However, the Committee specifically discussed the addition of rituximab to chlorambucil and consultation comments that this combination would be useful for older patients or patients with a lower performance status. The Committee was mindful of the limited clinical data and absence of a formal cost-effectiveness analysis for the group of patients likely to receive rituximab plus chlorambucil, but it concluded that rituximab plus chlorambucil was an appropriate use of NHS resources (see FAD section 4.3.14).
Health Improvement Scotland	6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? No	Comment noted. No action required.
Health Improvement Scotland	7. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment Nothing, other than to re-iterate the difference between this guidance, which specifies 4 named chemotherapy regimens and the current SMC guidance which recommends R-Chemotherapy (not specified), as discussed in 6 above.	Comment noted. No action required.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	The technologies	We have reviewed the appraisal consultation document alongside the related NICE TAs 226, 110 & 137. The PCT can confirm that the treatment is not currently listed as one of those approved by the North	Comment noted. The ACD section 4.1.10 incorrectly stated that there was a significant incidence of leukocytopenia, neutropenia and

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		West Cancer Drugs Fund. From the evidence reviewed, the PCT is satisfied that whilst there was a significant incidence of leukocytopenia, neutropenia and granulocytopenia in those treated with rituximab and chemotherapy, this was not associated with an increase in the rate of infection. Furthermore, from a patient safety perspective, the addition of rituximab to the four chemotherapy regimes did not appear to increase adverse event rates.	granulocyctopenia in all the clinical trials. This has been corrected in the FAD (see FAD section 4.1.12).
NHS Professional 1	Evidence and interpretation	The PCT acknowledge the 4 good quality RCTs that have been included in the review by NICE. The evidence supports the preliminary recommendation for the use of rituximab as an option in the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people. From a cost effectiveness point of view, the PCT acknowledge the three economic models for rituximab combined with CVP, CHOP and MCP. However, the PCT would like to seek further clarification on whether or not the economic model for the combination of rituximab with CHVPi will be reconsidered before the final TA. Furthermore, clarification on whether or not the economic model will be reviewed to take further account of the use of rituximab as first-line maintenance treatment, and, the assumption that the efficacy of rituximab will be maintained when used second line. The prevalence indicates that the additional cost to Trafford would be in the region of £40k. This is based on Trafford's population. At this stage, it is not possible to predict which service would need to be reviewed in order to fund this additional cost. This would need to be considered by the PCT's Prioritisation Panel.	Comment noted. The Committee recognised that the Assessment Group had not included the combination of rituximab plus CHVPi in its model. The Committee accepted that using the manufacturer's estimates, and taking into account the Assessment Group's concerns, the ICER was still likely to be within acceptable levels (see FAD section 4.3.13). The Committee noted that the ICERs increase when it is assumed that rituximab first-line maintenance treatment is provided. It considered that the efficacy of rituximab when used as a re-treatment is also uncertain, and if there is a loss of efficacy then this would further increase the ICER. However, the Committee was persuaded that this uncertainty was not such that it increased the ICERs to above the threshold range (£20,000–30,000) that would normally be considered cost effective (see FAD section 4.3.13).
NHS Professional 2	Appraisal Committee's preliminary recommendations	I support the preliminary recommendation as described above.	Comment noted. No action required
NHS	Evidence and	I agree with the committees interpretation and application of the	Comment noted. No action required

Role*	Section	Comment	Response
Professional 2	interpretation	evidence.	
NHS Professional 2	Implementation	I note that the gains in overall survival are modest with certain regimens but are well within the range usually considered cost-effective. However, this will still require funding and will add to the financial pressures. It highlights the issue of needing robust processes in place to enable effective prioritisation particularly in the near future and changes in the NHS.	Comment noted. No action required