Non-Hodgkin's lymphoma

Consultation on draft guideline
Stakeholder comments table

29/01/16 to 11/03/16

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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83	Addenbrookes Hospital	General	General	General	**Comments from East of England lymphoma clinicians re: Draft NICE Guideline for the Diagnosis and Management of Non-Hodgkin's Lymphoma** This guideline has been reviewed and discussed extensively by clinicians managing lymphoma in all 15 NHS acute trusts from across the East of England. The list of hospitals represented and named signatories to these comments are listed at the end of the document. We applaud NICE for their attempt to construct a guideline for the management of a disease as complex and diverse as Non-Hodgkin's Lymphoma. However, as the Guidelines Committee (GC) have not been able to comment on areas of NHL management covered by pre-existing NICE technology appraisals (TAs), we believe this has fundamentally flawed the guideline process. The result is a document that in critical areas is a guide to NICE TAs, rather than a guide to managing NHL. A number of TAs are now over 10 years old and simply not reflective of current international NHL practice. It is our opinion that by preventing the GC from reviewing these areas of NHL management, the NICE 'rules' have delivered a guideline with major flaws that need to be rectified before it can be a usable document.	Thank you for your comments.

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					Without covering these areas, the statement in the first paragraph is simply wrong: 'NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness,…..' We have summarised our major and more minor concerns below: **<u>MAJOR CONCERNS – highly likely to be detrimental to patient care and survival</u>** 1. Removal of rituximab for DLBL patients treated with anything other than CHOP and for patients with stage I disease. This is the most concerning part of this guideline and goes completely against UK and international practice. We believe that if this is introduced it will directly result in a reduction in overall survival in patients not fit enough to receive R-CHOP and is directly discriminatory against more frail and elderly patients. There is a wealth of evidence to support this statement. We also feel there is a high risk of harm if rituximab is removed from the management of stage I DLBL. Although harder to prove, the supportive evidence from so much DLBL data would be enough to keep rituximab in the treatment regimen for these patients. 2. Removal of staging PET/CT for DLBL will compromise the interpretation of subsequent scans. It will also result in under-staging a significant number of patients which could have implications for use of prophylactic CNS directed therapy and choice of regimen (e.g R-CODOXM)	It was our intention at scoping to include TA65 in the guideline but we have now agreed to omit it as it no longer reflects current practice. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the linking evidence to

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						recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.
					3. The lack of flexibility with regards to any other chemotherapy regimen for DLBL and subtypes of DLBL is very disappointing. There are many different clinical scenarios where the use of different regimens such as R-GCVP / R-CEOP / R-CODOXM-RIVAC / R-DA-EPOCH / R-HDMTX-CYT can be justified and the lack of any flexibility in this document is profoundly worrying for clinicians trying to optimise patient care for an individual patient's circumstances.	The guideline committee are unable to cover everything that can and cannot be done. There are endless possible alternatives to CHOP. However, due to the absence of good data we are unable to list them.
					4. A lack of discussion or recommendation of R-Bendamustine in the management of indolent NHL. This is one of the biggest changes in international practice in recent years, and producing an NHL guideline that does not include guidance on when and how best to use this chemotherapy regimen is simply incomplete.	Thank you for your comment. We are aware of the data for R-bendamustine but we did not include it as an intervention in this topic as it is a regimen currently undergoing a NICE technology appraisal. We have added the following text in both the Short version of the guideline and in the LETR paragraph of the Full guideline to explain this omission: 'The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with follicular lymphoma , because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first line treatment of advanced indolent non-Hodgkin's lymphoma' was in development. This technology appraisal is currently in development.
					5. There is no flexibility in managing T-cell lymphoma. There is extensive discussion in	The guideline committee are unable to cover everything that can and cannot be done.

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					the document about the lack of firm data and consensus on treatment 'In the UK the use of CHOP / CHOEP / gemcitibine-containing regimens is highly variable'. There is therefore no evidence to restrict therapy to CHOP and potentially discriminate against patients not fit enough to receive anthracycline, or remove the option to treat fitter younger patients with CHOEP We have additional concerns about the following areas, but accept that we need to prioritise the above 5 points that are most likely to directly impact on patient care and survival 1. The GC appear to have carried out a mini technology appraisal for R-monotherapy (x4 doses) in asymptomatic FL and recommended its introduction into UK practice. This is a non-licensed indication for this drug. It is against accepted international standard practice, has unknown consequences for future lines of therapy and we are not aware of any pressure from UK clinicians or patients to adopt this strategy. 2. Rituximab maintenance after 'CHOP-based' induction in Mantle Cell Lymphoma. Does that include the recently NICE-approved bortezomib-based chemotherapy? If we are concerned about recommending R-maintenance after R-bedamustine because of the lack of published prospective data, shouldn't we also be concerned about R-maintenance post bortezomib-based chemotherapy? 3. There was no section on relapsed MCL. We	There are endless possible alternatives to CHOP. However, due to the absence of good data we are unable to list them. The recommendation was based on the assessment of the clinical data and a rigorous health economic assessment. The guideline committee agree that it is possible that rituximab maintenance is of value after regimens other than R-CHOP. The guideline committee also agree that t there is a lack of published prospective data. Thank you for your comment. We acknowledge that the role of ibrutinib in

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					remain unclear about the role of ibrutinib in patients who relapse late post R-chemo based treatment. There is no prospective trial of ibrutinib vs R-chemo (and there won't be). This is a challenging area that may benefit from expert guidance. 4. Removal of interim PET/CT in DLBL. There is universal consensus that interim PET is a very strong prognostic tool in DLBL. The argument against it appears to be cost-based. We agree that we do not change therapy on most iPET2+ patients. However, with certain patients an iPET+ scan will influence decisions re: biopsy. Furthermore, as iPET negative patients (approx. 2/3 DLBL) have such a good prognosis, this will impact on future follow-up / scan strategies. We would argue that getting this early powerful prognostic information can be very helpful for patients. From a cost-effectiveness perspective, as 2/3 patients are iPET-, these patients will not have an additional end of treatment scan, therefore with interim PET scanning, only 1/3 of patients have an additional scan. Signatory hospitals and named clinician who has signed on behalf of colleagues [redacted]	patients who relapse late post R-chemo based treatment is unclear. However this topic was not within the scope of the guideline. Therefore the evidence was not reviewed by the Guideline Committee and we are unable to make recommendations in this area.

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					[redacted]	
103	Association for Palliative Medicine of Great Britain & Ireland	Short	General	General	When discussing treatment of advanced stage symptomatic lymphoma, should there be a brief mention to consider referral to palliative care services as this, alongside active treatments, can be beneficial for the patient?	Thank you for this comment. Acute symptom control was not included within the scope of this guideline.
4	Bristol-Myers Squibb Pharmaceuticals Ltd	Full	General	General	BMS feels that the Guideline is very comprehensive and well researched. However, we did feel that the treatment recommendations were very specific and left little room for therapies currently under development. Given the significant number of therapies for NHL that are in late stage development (including promising new modalities, such as the novel immune-oncology agents, which could be a potential treatment option for NHL patients), we would like to suggest that a degree of flexibility is written into the guidelines allowing for future NICE recommended treatments to be included in the pathway at the appropriate point. *e.g. For DLBCL Salvage Therapy, another recommendation could be added: 'Offer salvage therapy with therapies that have been approved by NICE subsequent to the publication of these guidelines. Usage should be according to label and NICE recommendation.'*	Thank you for your comments. We fully recognise that the guideline does not comment on therapies currently under development and this underlines the importance that must be attached to regular update of these guidelines. NICE will routinely review their published guidelines to assess if an update is necessary.

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1	British HIV Association (BHIVA)	Full	General	General	BHIVA is concerned that the NICE guidelines make no mention of HIV testing for NHL. All patients should be tested following a diagnosis of NHL as this influences the treatment (requiring antiretrovirals and OI prophylaxis) as per BHIVA malignancy guidelines. BHIVA strongly recommends this in view of the BHIVA (NICE accredited) malignancy guidelines '*BHIVA guidelines for HIV-associated malignancies 2014*', *HIV Medicine* (2014), **15** (Suppl. 2), 1–92. Available to download at: http://www.bhiva.org/malignancy-guidelines.aspx	Thank you for your comments on HIV testing. The committee only reviewed those areas of practice deemed to be controversial. It was fully accepted that HIV testing is a routine procedure in patients with Lymphoma.
9	British Nuclear Medicine Society	Full	40-51 Appendix G Evidence review	General	There may be a role for PET-CT in staging and remission assessment of some T cell lymphoma subtypes and to assess patients with cutaneous lymphomas for systemic involvement. The attention of the GC is drawn to the studies below not considered in the documentation. **NK T cell** Moon SH, Cho SK, Kim WS, et al: The role of 18F-FDG PET/CT for initial staging of nasal type natural killer/T-cell lymphoma: a comparison with conventional staging methods. J Nucl Med 54:1039-44, 2013 Khong PL, Huang B, Lee EY, Chan WK, Kwong YL: Midtreatment (1)(8)F-FDG PET/CT Scan for Early Response Assessment of SMILE Therapy in Natural Killer/T-Cell Lymphoma: A Prospective Study from a Single Center. J Nucl Med 55:911-6, 2014 **PTCL** Casulo C, Schoder H, Feeney J, et al: FDG-PET in the Staging and Prognosis of T cell Lymphoma Leukemia & lymphoma Leukemia & lymphoma,	Thank you for your comment. We have amended the recommendation so that it includes all other sub types not included in recommendation 1.2.1. The recommendation now states: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation, consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The El-Galaly et al (2015) study is relevant but was not included because it was published after our final literature search in September 2015. Moon (2013) and Khong (2014) were not identified by our literature searches. Casulo (2013) was included in our evidence review.

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					54(10), 2163-2167, 2013. El-Galaly TC, Pedersen MB, Hutchings M, et al: Utility of interim and end-of-treatment PET/CT in peripheral T-cell lymphomas: A review of 124 patients. American journal of hematology 90:975-80, 2015 Feeney J, Horwitz S, Gonen M, et al: Characterization of T-cell lymphomas by FDG PET/CT. AJR. 2010; 195:333-40. Kolstad A, Laurell A, Jerkeman M, et al: Nordic MCL3 study: 90Y-ibritumomab-tiuxetan added to BEAM/C in non-CR patients before transplant in mantle cell lymphoma. Blood 123:2953-9, 2014	Feeney (2010) includes some patients also in Casulo (2013). Kolstad (2014) this study examines pre-transplant PET-CT as a prognostic factor in the Nordic MCL3 study – however our clinical review question on interim PET-CT was limited to DLBCL.
15	British Nuclear Medicine Society	Full	40	General	(p40-51) It is widely accepted in clinical practice for Non-Hodgkin's Lymphoma in the UK that F18 FDG PET-CT scans are a vital step in the assessment of patients for initial staging as well as for assessment of treatment response. This also has the effect of providing a mechanism for selection of patients into clinical trials with newer treatment approaches where appropriate. It is well accepted that most patients with a diagnosis of Non-Hodgkin's Lymphoma would be rendered eligible for clinical trials based on histological sub-type and receptor expression. The loss of FDG PET-CT scans in this context could result in patients having to undergo these same scans under a research pathway which is likely to add complexity as well as cost to the system. International consensus guidelines also recommend interim PET-CT scans as a means of	Thank you for your comment. We accept that a recommendation not to do staging FDG-PET causes difficulty with entering patients into clinical trials but this is an inadequate reason for making a positive recommendation in the guideline. There is an increasing body of data suggesting that interim PET-CT scan is not helpful in staging diffuse large B-Cell Lymphoma. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-

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					ensuring that patients are on the correct treatment pathway and this allows modification of treatment if appropriate. BNMS recognises the role of [redacted] who has prepared a response on behalf of the Royal College of Physicians and fully endorses her comments as listed below.	CT imaging to confirm staging if the results will alter management'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.
16	British Nuclear Medicine Society	Full	40	Page 42 Box 1, line 1 Page 43 Box 1, line 6	(p40-51) Question 1 We are concerned that the following recommendations represent a challenging change in practice (page 42, line 1): '*Offer FDG-PET-CT imaging to confirm staging for people diagnosed with:* *stage I diffuse large B-cell lymphoma by clinical and CT criteria* *stage I or localised stage II follicular lymphoma if disease is thought to be encompassable within a radiotherapy field* *stage I or II Burkitt lymphoma with other low-risk features.*' The NICE documentation (page 43 line 6) states that : '*The GC thought … baseline FDG PET-CT rarely had an influence on management when assessing end of treatment FDG PET-CT scan and is not essential for interpreting end of treatment FDG PET-CT'.* The GC had a single representative from the imaging community and should be aware that this is NOT a commonly held view in clinical practice nor in clinical trials.	Thank you for your comments. Membership of the Guideline Committee included a very experienced consultant radiologist. However the guideline was issued for consultation with stakeholders, which included several organisations representing the interest of radiology and nuclear medicine. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above

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					It is acknowledged in international consensus guidelines (as above point 1) but not in the NICE documentation that a staging scan is necessary for the purpose of accurate interpretation of response scans in all stages of disease, in particular for patients with extranodal disease which is not adequately assessed on staging CT. We suggest a baseline scan should be recommended in all stages of DLBCL, Burkitt's lymphoma and high tumour burden or advanced symptomatic FL treated with induction immune-chemotherapy for the following reasons: Although DLBCL is routinely FDG-avid, assessment of extranodal sites, especially those that can have high physiological uptake and which often have increased uptake in response to treatment relies on the identification of involvement on a baseline scan [Barrington, et al. 2014]. The incidence of extranodal disease in DLBCL can be as high as 66% [El-Galaly, et al. 2015]. Sites with high physiological uptake include bone marrow, stomach, gut, Waldeyers ring. In particular, assessment of bone marrow involvement can be problematic, with ablation of normal marrow at disease sites successfully treated which becomes 'cold' on a response scan and increased uptake within normal and diseased marrow which becomes 'hot' on a response scan. Without a baseline scan to refer to, it can be difficult to be sure if 'hot' focal uptake represents normal reactive marrow with ablated adjacent marrow or residual marrow disease. Reactive and inflammatory changes are common	recommendation, consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the linking evidence to recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area. Barrington (2014) was not included as evidence because it is an expert consensus guideline. The El-Galaly et al (2015) study is relevant but was not included because it was published after our final literature search in September 2015. Barrington (2010 & 2011) and Meignan (2009) were not included because they are Hodgkin Lymphoma studies. Thank you for this information.

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					at some sites including the lung hila which cannot be distinguished from initial sites of disease involvement without reference to a baseline scan. In early stage Hodgkin Lymphoma (HL), in the RAPID trial there was uncertainty how to interpret FDG uptake in 19% patients who did not demonstrate complete metabolic response where FDG uptake occurred at sites where lymphadenopathy was not reported on the staging CT scan [Barrington, et al. 2011]. This incidence of uncertainty in interpretation of response occurred in a group of patients who uncommonly have extranodal disease and was carried out using central review by 2 experienced observers. Differentiating inflammatory related treatment effects is a challenging area that has been reported to impact on interobserver agreement, in reporting Hodgkin Lymphoma [Barrington, et al. 2010] and which also affects reporting in NHL. Interobserver agreement in DLBCL is reported to be better when a direct comparison can be carried out with the baseline scan for response assessment [Meignan, et al. 2009]. In a small study in lymphoma, addition of baseline to post treatment PET evaluation affected the classification of metabolic response in 34% of malignant lymphoma patients treated with first-line chemotherapy, leading to opposite conclusions regarding response in 1 out of 7 patients [Quarles van Ufford, et al. 2010].	With regards to ambiguous findings on end of treatment PET-scans, good practice would be to either biopsy the lesion or repeat the scan after a short-interval.
17	British Nuclear Medicine Society	Full	40	General	(p40, 43) Question 1 We are concerned that the absence of a baseline PET-CT will adversely affect patients who	Thank you for your comment. We acknowledge that some radiotherapy guidelines recommend baseline PET scanning to facilitate radiotherapy planning. However

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					undergo radiation planning, this includes not only patients with limited disease but also patients requiring consolidation radiotherapy. Modern radiotherapy uses smaller volumes (e.g. involved-site and involved-node radiotherapy) which are based on accurate mapping of exact disease involvement rather than anatomical sites (involved-field radiotherapy). International guidelines produced by the International Lymphoma Radiation Oncology Group recommend the use of PET-CT for radiation planning [Illidge, et al. 2014] and there is plenty of evidence that PET-CT information changes the volume to be irradiated in a significant proportion of patients.	this topic was not within the scope of the guideline. Therefore the evidence was not reviewed by the Guideline Committee and we are unable to make recommendations in this area. However we would point out that the International Radiation Oncology Group guidelines does not specify the need for baseline PET-CT scanning. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.
18	British Nuclear Medicine Society	Full	40	General	(p40, 43) Question 1 We are concerned that implementation of the recommendation with respect to staging in DLBCL will have an adverse effect on patient management and evaluation of prognosis for the following reasons: The incidence of extranodal disease in DLBCL is high. In a recent study with 443 patients included from Canada and Denmark, 2/3 patients had extranodal disease on PET [El-Galaly, et al. 2015]. This study was not included in the NICE	Thank you for your comment. The Guideline Committee acknowledged that in some circumstances carrying out a staging PET-CT scan may result in a change of stage, IPI status and a need for CNS prophylaxis but there is no high quality evidence to support this. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised

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					evaluation. In multivariate analysis, stage IV disease, the presence of extranodal disease on PET-CT and the number of extranodal sites were predictive of PFS and OS independent of LDH, PS and age. More treatment failures occurred with an increasing number of extranodal sites. Particular sites were identified with adverse prognosis including bone marrow, pleura, gynaecological organs. Although not reported by the studies assessed in the NICE guidance, upstaging has treatment implications for advanced vs limited stage with longer course chemotherapy. Patients with stage II disease may be upstaged according to PET and there is a high incidence of stage III/IV disease using PET-CT as suggested by the study above. Improved accuracy of staging is likely to result in fewer patients being undertreated or overtreated and this was the recommendation in recent international guidelines for staging scans. There may also be implications for CNS prophylaxis.	the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area. El-Galaly et al (2015) was a study of the prognostic value of the baseline PET-CT scan, whereas our review question concerned the staging accuracy of baseline PET-CT. This paper was also published after our last literature search in September 2015.
19	British Nuclear Medicine Society	Full Appendix G	40	Table of excluded studies relating to PET	(p40-51) PET-CT is more accurate for staging aggressive non-Hodgkin lymphomas (NHL) and Follicular Lymphomas (FL) than CT, as acknowledged in the NICE documentation. Limited data are presented because all studies that were not PET-CT were excluded, which is inappropriate. PET-CT has improved specificity compared to PET alone, but sensitivity is similar. Excluding all studies reporting PET only (or studies with a proportion of patients scanned on PET only cameras) ignores much of the evidence base established before PET-CT became widespread in the period between 2005-2010. This applies also to response assessment.	Thank you for your comment. PET only scanners are no longer manufactured and all radiology departments in the UK now use PET-CT. The Guideline Committee did not assess or investigate evidence on the use of PET as this technology has been surpassed and is no longer used in current clinical practice. Combined PET-CT affords better accuracy and the PET-CT evidence has been reviewed in detail within this section of the guideline. The GC agreed that the evidence review

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						should be limited to PET-CT studies only for the reasons outlined above (PET only is no longer available and PET-CT has superior accuracy).
27	British Nuclear Medicine Society	Full	41	33	Question 1 Further support for our view that staging scans are required in all stages of DLBCL is that studies supporting remission assessment in patients with DLBCL using PET and included in the NICE draft documentation relied on having baseline scans for proper remission assessment. The reason why the 16 observational studies used baseline and response scans but did not directly report the use of baseline scans in evaluating response (p41, line33, section 3.1.1.5) is because it is (almost) universally accepted that baseline scans are required for proper interpretation of response scans. The recommended criteria for response assessment are Deauville criteria (DC) which are in widespread clinical use and in clinical trials. They are recommended based on improved interobserver agreement and better positive predictive value compared to older International Harmonisation Project (IHP) Criteria[Barrington, et al. 2014]. DC rely on scoring ' the most intense uptake in a site of initial disease' with reference regions in the normal mediastinum and the liver [Meignan, et al. 2009] and require a baseline scan to determine that the most intense uptake corresponds to a site of initial disease. This is not always apparent on a CT scan which is a less sensitive test. Determining whether there is progressive metabolic disease (or not) also relies	Thank you for your comments. The GC concluded there was inadequate high quality data to support your assertion. We agree that a staging scan is required to distinguish the different categories of metabolic response but we were unable to find data that this is of any clinical value. Further, the key clinical question on the end of treatment PET-CT scan is whether lymphoma is 'present or not' (not the quality of response). Good clinical practice mandates that equivocal abnormalities on an end of treatment PET-CT scan should be investigated on merit (usually with interval repeat imaging and/ or biopsy). The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'Consider FDG-PET-CT imaging to confirm staging if the results will alter management for people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation'. The GC have amended the LETR paragraph to explain the rationale behind this decision Due to the uncertainty and lack of evidence as to whether a baseline PET scan is actually required to interpret an

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					on having a clear map of initial disease sites. New response categories proposed in international guidance rely on baseline scans to assess change in uptake to categorise response into partial metabolic response, stable metabolic disease and progressive metabolic disease[Cheson, et al. 2014]. Again this is not possible without a baseline scan. Without a baseline scan only complete metabolic response can be assigned in the presence of no abnormal uptake.	end of treatment scan, the GC have also proposed the following research recommendation – "In people with Diffuse large B-cell lymphoma stage II or above, does a FDG-PET CT scan have any advantages over the availability of a baseline CT-scan in the correct interpretation of the end of FDG-PET-CT scan". We disagree that staging and interim scans are required to report the Deauville score on an end of treatment scan. The Deauville score is calculated using the PET-CT data within an end of treatment scan, relative to the mediastinal blood pool and physiological liver activity level calculations on that particular scan. Barrington (2014) and Cheson (2014) were not included as evidence because they are expert consensus guidelines. Meignan (2009) was not included because it is a Hodgkin Lymphoma study.
33	British Nuclear Medicine Society	Full	42	Boxes All entitled trade off between clinical benefits and harms	(p42, 43, 47) Question 3 From our experience in scanning patients with CT and PET-CT we are concerned about statements made in the NICE documentation about concerns with respect to radiation exposure (page 42,45,47) to the effect that '*limiting the use of FDG PET CT staging .. would result in a reduction in radiation exposure*' and '*it was the consensus of the GC that the recommendation* (not to offer FDG PET CT imaging for interim assessment in DLBCL)	Thank you for your comment. The major reason for omitting interim scans was the lack of evidence that they are of any clinical benefit and we have removed the statements about reduced radiation dose from the LETR. The Mamot (2015) and Carr (2014) studies were included in the evidence review, the Huntington (2015) paper identified in our search was excluded from the clinical

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					would stop inappropriate therapy changes and reduce radiation exposure and discomfort from FDG PET CT' and '*there could be increased radiation exposure for patients*'. The effective dose associated with contrast-enhanced CT scan of chest abdomen and pelvis is in the order of 16mSv which is the same or lower for a PET-CT scan (with modern cameras in the region of 10-16mSv), which is commonly performed using a lower dose non contrast enhanced CT with improved staging and response assessment compared to CT. Therefore if a PET-CT scan replaces CT at staging, at interim or end of treatment assessment it would not result in an increase in radiation exposure. Patients experiencing an early complete metabolic response on interim imaging (approximately 60-79%)[Mamot, et al. 2015,Carr, et al. 2014,Huntington, et al. 2015] do not require an end of treatment scan which may result in a reduction in radiation exposure compared to a strategy recommended by NICE of staging CT, interim CT and end of treatment PET CT in patients with DLBCL.	evidence review because it was a cost-effectiveness analysis.
34	British Nuclear Medicine Society	Full	42	Box entitled recommendation	With respect to MALT lymphomas the GC may wish to take into account the following publication that demonstrated that FDG avidity was related to site of disease and staging may be appropriate in some MALT lymphomas. Treglia G, Zucca E, Sadeghi R, et al: Detection rate of fluorine-18-fluorodeoxyglucose positron emission tomography in patients with marginal zone lymphoma of MALT type: a meta-analysis.	The Treglia paper included both PET and PET-CT studies. However our evidence review was limited to PET-CT studies and therefore PET only studies were excluded. In addition this study only reported detection rate (sensitivity) whereas false positives are an important issue with PET-CT. Both sensitivity and specificity were needed for meaningful interpretation, because studies could adopt a test threshold with high

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					Hematological Oncology 33:113-24, 2015	sensitivity but unacceptable specificity.
44	British Nuclear Medicine Society	Full	43	Page 43, Recommendation box 1 Page 48, Line11	(p43, 48) Question 1 and Question 2 We are concerned that there may be adverse effects on patients and cost implications if a baseline PET-CT scan is not available. The absence of a baseline scan will lead to uncertainty in interpreting response and rather than the premise that '*any abnormalities identified on end of treatment FDG-PET-CT can be investigated on merit*' (page 43, Other considerations box line 11) could result in unnecessary biopsies or interval scans. There may be delay in treatment for some patients (who turn out to have disease requiring treatment) and anxiety in others (who turn out to have uptake related to treatment related inflammation or another cause). The potential cost savings associated with a reduction in over- and under-treatment referred to in the NICE consultation document (p48) are likely to be reduced if there is clinical uncertainty.	Thank you for your comments. We are unaware of any data showing that carrying out a PET-CT scan is cost saving. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the linking evidence to recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area. It is the belief of the Guideline Committee that the distinction of persisting disease and disease at a new site is of little clinical impact (both of course indicate active lymphoma on an end of treatment scan, requiring further treatment) and where there is uncertainty good clinical practice should be to carry out a biopsy or interval scan.
45	British Nuclear Medicine Society	Full	43	Box entitled other consider	Question 1 The absence of a baseline scan (as acknowledged by the GC) will significantly disadvantage the UK in the ability to perform	Thank you for your comment. The Guideline Committee accept that in the absence of any high quality data decisions

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				ations	research in the field of PET and lymphoma, which has previously been a strength.	about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management.'. The GC have amended the linking evidence to recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.
48	British Nuclear Medicine Society	Full	44	Box entitled trade off between clinical benefits and harms	(p44-45) Question 1 and Question 3 With respect to interim PET and DLBCL we are concerned that whilst the guidance acknowledges '*The evidence concerned the prognostic utility of interim FDG-PET-CT'* the statement that *'it was the consensus of the GC that the recommendation would stop inappropriate therapy changes and reduce radiation exposure and discomfort from FDG-PET-CT* does not take account i) of the importance of the prognostic utility of interim PET on patient management ii) that the majority of patients with complete metabolic response on interim scanning do not require and end of treatment PET-CT (or CT) scan iii) the radiation exposure associated with the use of interim PET has been overestimated. The GC states that 'CT is conventionally used for interim response evaluation, assessing changes	Thank you for your comments. We have removed commentary on radiation exposure from this section of the guideline. The Guideline Committee do not accept the clinical utility of interim PET scanning for DLBCL, and we think it would be improper or unsafe to abandon end of treatment PET-scanning on the basis of a negative interim PET scan after 2 cycles of therapy. The Mamot (2015) and Carr (2014) studies were included, the Huntington (2015) paper identified in our search was excluded from the clinical evidence review as it was a cost-effectiveness analysis. The Strobel (2007) study was not included as it was mixed HD and NHL and results were not reported separately.

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					in lesions size' implying this is good practice. PET-CT is a more appropriate use of resources than using interim CT for which there is no published evidence, if interim scanning is performed. Interim PET has a high negative predictive value in DLBCL, as acknowledged in the NICE consultation. Whilst it may not influence treatment decisions, this is useful information for patients and clinicians. Patients showing remission early can be reassured whilst still having treatment. Patients with early and late complete metabolic response (CMR)on PET-CT had a 2-y EFS of 97% (95% CI 92,98) in a recent study involving 327 patients [Carr, et al. 2014]. In addition, PET-CT may detect early progression in a small proportion of patients for whom treatment may need to be changed. If interim imaging is performed, PET-CT should be used in preference to CT for the above reasons. The majority of patients have complete metabolic response at interim (60% in study by Mamot et al; 79% in study by Huntingdon et al; 62% in study by Carr et al). All patients in the studies by Mamot et al[Mamot, et al. 2015] and Huntingdon et al[Huntington, et al. 2015] and in an earlier smaller study by Strobel et al[Strobel, et al. 2007] and 96% of patients in the study by Carr et al[Carr, et al. 2014] with early CMR on interim PET had CMR on the EOT-PET. This means that with early CMR at interim an EOT PET is not required, which saves resources, inconvenience and reduces radiation dose. If an interim PET scan does not show CMR, there	

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					is no indication to change treatment, unless there is evidence of progression or lack of any response but closer monitoring of these patients during treatment may be warranted, as a proportion will progress, especially those with initial poor risk disease .	
50	British Nuclear Medicine Society	Full	46 Appendix G	Box entitled recommendations Excluded studies	We are concerned about the impact of the following recommendation on clinical practice with respect to remission assessment in patients with Follicular Lymphoma (FL) treated for high tumour burden or advanced symptomatic disease with R-chemotherapy : '*Do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with:* *follicular lymphoma* *mantle cell lymphoma* *MALT lymphoma.'* PET should be considered for Remission assessment in FL in addition to DLBCL for the following reasons: PET is predictive of outcomes in patients treated with high tumour burden FL with R-chemotherapy improving response assessment compared with FLIPI, FLIPI2 and CT. PET-CT identifies a poor prognostic group [Trotman, et al. 2014] in whom closer monitoring or second line treatment may be indicated [Casulo, et al. 2015]. For this reason, PET-CT is recommended in international guidelines for response assessment in FL based on three multicentre studies which included 122 [Trotman, et al. 2011], 112 [Dupuis, et al.	Thank you for your comment. Please note we have amended our recommendation to make it clear that there are circumstances when an end of treatment scan should be performed in follicular lymphoma but suggest that this should only be when treatment decisions would be changed as a result of that scan. The recommendation now reads as follows: 'For people with subtypes of non-Hodgkin's lymphoma not listed in the above recommendation (1.2.4), do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management.' The Luminari (2013) Casulo (2013) Trotman (2014) studies were included. An alternative publication from the Dupuis (2012) study was included (Safar 2012)

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					2012]and 205 [Luminari, et al. 2014] patients respectively. All reported EOT PET-CT to be predictive of PFS, independent of the FLIPI, and superior to CT-based response. Only one of these studies was included in the NICE documentation. Dupuis was excluded because not all studies were PET-CT but all were attenuation corrected and therefore appropriate for inclusion in this context even if attenuation corrected with a radioactive source rather than CT. The study by Luminari et al and the pooled analysis below were not evaluated. The conclusions of the Trotman publication were considered to be biased in part due to its reliance on local physician interpretation of results. A pooled analysis of the 3 prospective studies referred to, but not considered in the NICE documentation, using central scan review and DC was published in 2014 [Trotman, et al. 2014]. The analysis included 246 patients all with PET-CT scans available for review. Median FU was 54.8m. 73% of patients were treated with R-CHOP, 15% R-CVP and 12% R-FM. 83% of patients had a negative scan (DS 1-3). The study revealed a significant number of patients had their response re-classified with PET compared to CT-based International Working Group (IWC) criteria, PET-based response was more predictive of PFS and OS than IWC, in the whole group, in the RCHOP-treated patients and in the responding patients according to IWC. In the whole group, 4y-PFS was 63.4 % (95% CI 55.9, 70.0) for patients with CMR, compared with 23.2% (95% CI 11.1,37.9) for patients without CMR [HR 3.9 (2.5,5.9) $p < 0.0001$]. The difference in median	

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					PFS was very large; 74 and 16.9 months for patients with scans showing CMR and no CMR respectively.	
84	British Nuclear Medicine Society	General	General	General	References related to comments above **REFERENCES** Barrington SF, Mikhaeel NG, Kostakoglu L, et al: Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. Journal of clinical oncology. 2014; 32:3048-58. Barrington S, Qian W, Somer EJ, et al: Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. European Journal of Nuclear Medicine and Molecular Imaging. 2010; 37:1824-1833.Barrington SF, MacKewn JE, Schleyer P, et al: Establishment of a UK-wide network to facilitate the acquisition of quality assured FDG-PET data for clinical trials in lymphoma. Annals of Oncology. 2011; 22:739-745. Carr R, Fanti S, Paez D, et al: Prospective international cohort study demonstrates inability of interim PET to predict treatment failure in diffuse large B-cell lymphoma. Journal of nuclear medicine. 2014; 55:1936-44. Casulo C, Byrtek M, Dawson KL, et al: Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. Journal of clinical oncology. 2015; 33:2516-22.	Thank you for your list of references to aide with your comments.

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					Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. Journal of clinical oncology. 2014; 32:3059-68. Dupuis J, Berriolo-Riedinger A, Julian A, et al: Impact of [18F]Fluorodeoxyglucose Positron Emission Tomography Response Evaluation in Patients With High-Tumor Burden Follicular Lymphoma Treated With Immunochemotherapy: A Prospective Study From the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. Journal of clinical oncology. 2012; 30:4317-22. El-Galaly TC, Villa D, Alzahrani M, et al: Outcome prediction by extranodal involvement, IPI, R-IPI, and NCCN-IPI in the PET/CT and rituximab era: A Danish-Canadian study of 443 patients with diffuse-large B-cell lymphoma. Am J Hematol. 2015; 90:1041-6. Huntington SF, Nasta SD, Schuster SJ, et al: Utility of interim and end-of-treatment [(18)F]-fluorodeoxyglucose positron emission tomography-computed tomography in frontline therapy of patients with diffuse large B-cell lymphoma. Leuk Lymphoma. 2015; 56:2579-84. Illidge T, Specht L, Yahalom J, et al: Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2014; 89:49-58. Luminari S, Biasoli I, Versari A, et al: The prognostic role of post-induction FDG-PET in patients with follicular lymphoma: a subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi (FIL). Annals of oncology. 2014;	

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					25:442-7. Mamot C, Klingbiel D, Hitz F, et al: Final Results of a Prospective Evaluation of the Predictive Value of Interim Positron Emission Tomography in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP-14 (SAKK 38/07). Journal of clinical oncology. 2015; 33:2523-9. Meignan M, Gallamini A, Haioun C: Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leuk Lymphoma. 2009; 50:1257-60. Meignan M, Itti E, Bardet S, et al: Development and application of a real-time on-line blinded independent central review of interim PET scans to determine treatment allocation in lymphoma trials. Journal of clinical oncology. 2009; 27:2739-41. Quarles van Ufford H, Hoekstra O, de Haas M, et al: On the added value of baseline FDG-PET in malignant lymphoma. Molecular imaging and biology. 2010; 12:225-32. Strobel K, Schaefer NG, Renner C, et al: Cost-effective therapy remission assessment in lymphoma patients using 2- fluorine-18 fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography: is an end of treatment exam necessary in all patients? Annals of Oncology. 2007; 18:658-664. Trotman J, Luminari S, Boussetta S, et al: Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. The Lancet Haematology. 2014; 1:e17-e27. Trotman J, Fournier M, Lamy T, et al: Positron Emission Tomography-Computed Tomography	

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					(PET-CT) After Induction Therapy Is Highly Predictive of Patient Outcome in Follicular Lymphoma: Analysis of PET-CT in a Subset of PRIMA Trial Participants. Journal of Clinical Oncology. 2011; 29:3194-3200. Zelenetz AD, Gordon LI, Wierda WG, et al: Non-Hodgkin's lymphomas, version 4.2014. J Natl Compr Canc Netw. 2014; 12:1282-303.	
2	British Society for Haematology	Full	General	General	The BSH has consulted its members as well as UK lymphoma specialists more broadly in drawing up this response. We have printed below a list of names who have expressed strong support for the points made above, reflecting widespread and deeply-held concern across the country for the implications of these aspects of the draft NICE guidance. The BSH, following its consultation, feels strongly that these issues represent significant variation from the current UK and international best practice, and in some cases seem to ignore crucial evidence. Unless they are addressed, we are concerned that implementation of the proposed guideline will unjustifiably deny patients access to diagnostic and therapeutic modalities of proven efficacy. This would be a retrograde step and result in significantly poorer patient outcomes than we currently achieve. We feel that these issues need to be resolved before the proposed guidance can be endorsed by UK haematologists looking after patients with NHL. We would therefore be grateful if you could address these key issues before the guidelines	Thank you for your comments, all of which have been addressed elsewhere in response to other comments you have raised.

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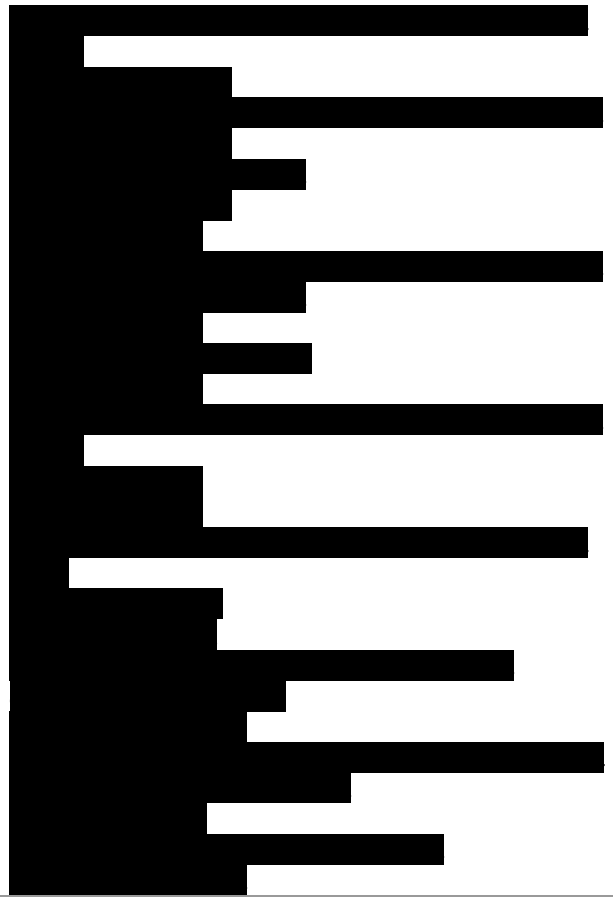
					are finalised. **The following UK consultants who treat patients with lymphoma have expressed strong support for the concerns raised above (emails on file)** 	

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					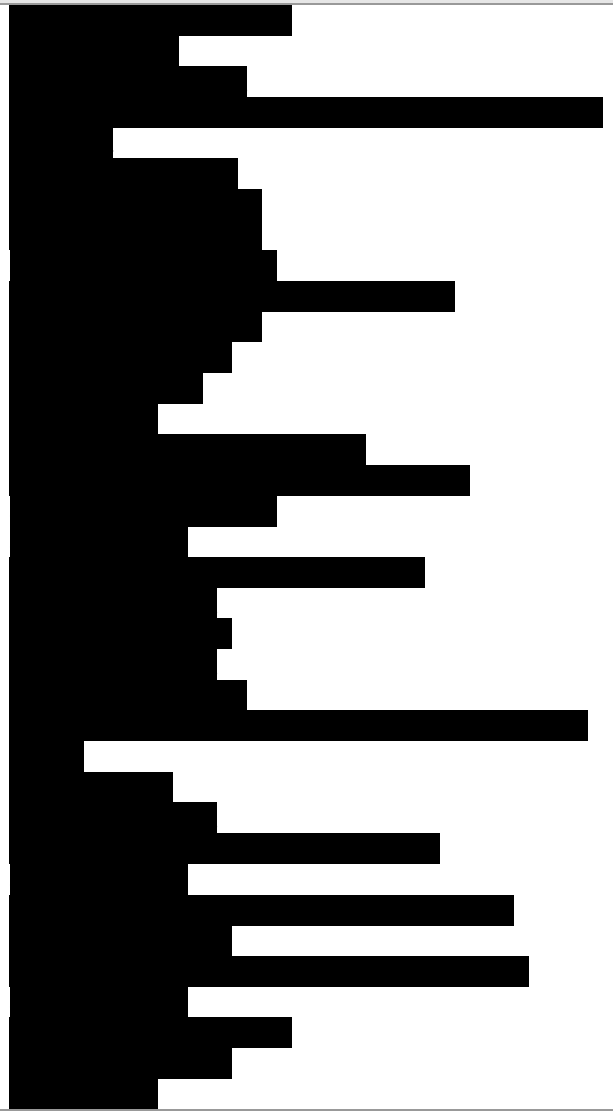	

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					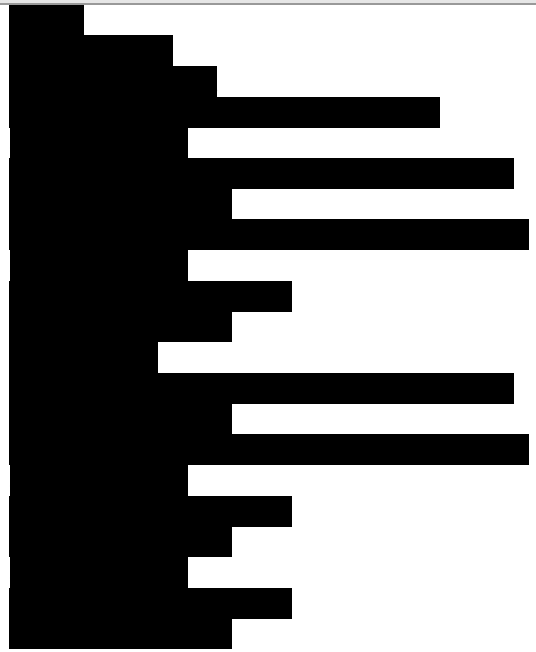	
35	British Society for Haematology	Full	42	Whole page	The draft guideline states: '*do not routinely offer FDG-PET-CT imaging to confirm staging for people diagnosed with: diffuse large B-cell lymphoma that is stage II or above; follicular lymphoma that is non-localised stage II or above; mantle cell lymphoma; MALT lymphoma; Burkitt lymphoma with high-risk features, or stage III or IV*'. These criteria are unnecessarily prescriptive, they directly contradict the 2014 International Recommendations (the Lugano Classification), and are likely to impact negatively on patient outcomes in several ways. First, in DLBCL the	Thank you for your comment. We acknowledge that some radiotherapy guidelines recommend baseline PET scanning to facilitate radiotherapy planning. However this topic was not within the scope of the guideline. Therefore the evidence was not reviewed by the Guideline Committee and we are unable to make recommendations in this area. However we would point out that the International Radiation Oncology Group guidelines does not specify the need for baseline PET-CT scanning. The Guideline Committee accept that in the

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					additional sensitivity of PET-CT compared to conventional CT, particularly in detecting extranodal and bone marrow disease, is critically important – especially in aiding the decision-making with respect to CNS-direct chemoprophylaxis. Recent data indicate that in patients with DLBCL the number of extranodal sites of disease, as detected by PET-CT, is highly predictive of the risk of CNS relapse: omitting PET-CT at diagnosis will make it more difficult for us to reduce the risk of this devastating complication of DLBCL. . Second, these proposals will delay the initiation of chemotherapy for patients with localised disease. To comply with the proposed guidance all patients will first undergo CT and bone marrow biopsy to establish whether they have localised disease, before their eligibility for PET-CT scanning can be determined. Patients with localised disease will then have to wait for the PET-CT to be performed before starting therapy. We are concerned that these patients' treatment will be significantly delayed as a consequence of the proposed guidelines, and they will also receive additional radiation exposure because of the need for a CT before undergoing a PET-CT.	absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management.'. The GC have amended the linking evidence to recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area. With regard to extra nodal sites and CNS risks we are unaware of any data comparing PET CT and standard CT on the risk of CNS relapse. There is very little published evidence(with no good quality evidence) to support the assertion that a baseline PET-CT scan is required to interpret an end of treatment PET-CT scan, the key question on the end of treatment PET-CT scan being whether lymphoma is 'present or not' (not the quality of response). Good clinical practice mandates that equivocal abnormalities on an end of treatment PET-CT scan should be clinically investigated on merit (usually with interval repeat imaging and/ or biopsy). Due to the uncertainty and lack of evidence as to whether a baseline PET scan is actually required to interpret an end of treatment scan, we have proposed a research recommendation – "In people with Diffuse

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					Third, evaluating the end-of-treatment PET-CT in DLBCL and BL (as recommended on page 46) using the Deauville criteria is dependent on a baseline scan for comparison. Those of us who regularly review post-therapy PET-CT imaging in lymphoma MDT meetings know the value of having a pre-treatment PET-CT when assessing the significance of residual areas of abnormal FDG uptake. In the absence of a baseline scan, it is likely that many of the patients with equivocal post-therapy PET-CT appearances will require serial scanning to document resolution of the abnormalities. This will both increase radiation exposure, and generate avoidable anxiety in these patients, with resulting long-term psychological morbidity. This runs completely against the current emphasis on minimising the psychological impact of lymphoma diagnosis. Finally, a baseline PET-CT can be extremely useful in identifying areas of possible high-grade transformation for patients with known indolent lymphomas, and may guide biopsy. Effective management of these patients is therefore dependent on having access to routine baseline PET-CT imaging for patients with indolent lymphomas. In view of all these issues, the forthcoming BCSH guidelines on the management of DLBCL in adults specifically recommend that 'where possible, a staging PET-CT scan is recommended for all patients'. Similarly the 2014 Lugano Classification recommends that, at diagnosis, 'PET-CT is the standard for FDG-avid lymphomas'. We urge the Guidelines Committee to reconsider their	large B-cell lymphoma stage II or above, does a FDG-PET CT scan have any advantages over the availability of a baseline CT-scan in the correct interpretation of the end of treatment FDG-PET-CT scan". The Guideline Committee agreed that the distinction of persisting disease and disease at a new site is of little clinical impact (both of course indicate active lymphoma on an end of treatment scan, requiring further treatment) and where there is uncertainty good clinical practice should be to carry out a biopsy or an interval scan. We do not accept that a PET-CT is a reliable means of diagnosing high grade transformation of non-transformed FL, Follicular lymphoma paradoxically demonstrates intense FDG uptake (with high SUVmax levels) on a PET-CT scan, high grade lymphomas also demonstrate intense

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					recommendations so that they are in line with national and international guidance.	FDG uptake, therefore high grade transformation of follicular lymphoma cannot be detected using PET SUVmax levels. We would make the point that good practice is to biopsy in cases of suspected transformation based on clinical grounds, including biopsy as required of any disproportionate sites of disease volume increase or change in morphology of lesion/s on imaging.
51	British Society for Haematology	Full	46	35	The draft guideline states: '*offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with: diffuse large B-cell lymphoma and Burkitt lymphoma. Do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with follicular lymphoma, mantle cell lymphoma and MALT lymphoma'*. The data presented on page 46 (lines 17-28) clearly demonstrate the predictive value of PET-CT at the end of induction therapy for FL. Conventional CT is often unhelpful in these cases in distinguishing between fibrotic post-therapy masses and residual viable lymphoma. Patients with residual post-induction FDG-avid masses have poorer outcomes following rituximab maintenance compared to those in complete remission post-therapy. Significant FDG uptake on the post-treatment PET-CT often prompts a biopsy of the avid area, with a view to second-line chemotherapy if viable lymphoma is detected. Omitting the end-of-treatment PET-CT in patients with FL will therefore potentially disadvantage the approximately 20% of patients with FDG-avid masses, who might benefit from more intensive therapy than routine rituximab maintenance.	Thank you for your comment. We have amended our recommendation to make it clear that there are circumstances when an end of treatment scan should be performed in follicular lymphoma but suggest that this should only be when treatment decisions would be changed based on the result of that scan. The recommendation now reads as follows: 'For people with subtypes of non-Hodgkin's lymphoma not listed in the above recommendation (1.2.4), do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management.'

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					This recommendation also contradicts the Lugano Classification guidance that 'PET-CT should be used for response assessment in FDG-avid histologies', and we again ask the Guidelines Committee to revise their recommendations accordingly.	
58	British Society for Haematology	Full	53 (82)	41	The draft guideline states: '*rituximab, in combination with: CVP, CHOP, MCP, CHVPi or Chlorambucil is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people*'. It is surprising that rituximab in combination with Bendamustine (R-Bendamustine) is not given as an option, There are clear data demonstrating that rituximab plus Bendamustine is more effective (in terms of PFS) and less toxic than R-CHOP, which was hitherto considered to be the most effective first-line therapy for FL. Delaying the need for second-line therapy is especially important for this group of patients, for whom the next treatment regimen would typically include a stem cell transplant. For this reason, the majority of UK lymphoma specialists advocate R-Bendamustine for initial therapy of FL in patients who are sufficiently fit to tolerate it. The availability of generic Bendamustine makes the argument for using this cost-effective, efficacious and relatively non-toxic agent especially compelling. It is understood that the draft guidance has not formally re-evaluated the issue of initial therapy in FL, and the recommendation relating to this reflects previous guidance (NICE technology	Thank you for your comment. We are aware of the data for R-bendamustine but we did not include it as an intervention in this topic as it is a regimen currently undergoing a NICE technology appraisal. We have added the following text in both the Short version of the guideline and in the LETR paragraph of the Full guideline to explain this omission: 'The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with follicular lymphoma , because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first line treatment of advanced indolent non-Hodgkin's lymphoma' was in development. This technology appraisal is currently in development.

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					appraisal guidance 243). Nonetheless, the omission of R-Bendamustine is very disappointing and we feel strongly it should be included on this list, at least until the technology appraisal has been completed. Equally there are persuasive data for the use of R-Bendamustine across the range of indolent lymphomas and we urge the committee to include this regimen as a treatment option in all types of indolent lymphomas.	
72	British Society for Haematology	Full	116	9	The draft guideline states: '*rituximab is recommended for use in combination with a regimen of CHOP for the first-line treatment of people with CD20-positive diffuse large-B-cell lymphoma at clinical stage II, III or IV. Rituximab is not recommended for use when CHOP is contraindicated*'. As for point 3, this section of the guideline cites previous guidance (NICE technology appraisal guidance 65). There is clear, published evidence that R-GCVP is an effective regimen for patients with DLBCL for whom anthracycline is contra-indicated, and that R-miniCHOP is effective and well tolerated in older patients. Likewise, recent data indicate that R-CODOXM/R-IVAC is highly effective in fit patients with high-IPI DLBCL. All these studies were large, phase 2 studies demonstrating the safety and efficacy of rituximab with non-CHOP based regimens, and it is important that the proposed guidance incorporates the latest data. These studies appear not to have been evaluated in the NICE assessment and the exclusion of these regimens will potentially disadvantage the groups of patients	Thank you for your comments. It was our intention at scoping to include TA65 in the guideline but we have now agreed to omit it as it no longer reflects current practice.

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					who would most benefit from them – i.e. the elderly and those with chronic co-morbidities, for whom CHOP is not a suitable backbone regimen. We are consequently very concerned that this guidance will negatively affect these patients' outcomes, and could in practice prove to be highly discriminatory against older patients and those with chronic illnesses. We would urge the guidelines committee to re-examine this evidence and acknowledge that that rituximab should be offered with non-CHOP regimens for the treatment of DLBCL.	
13	Celgene Ltd	Full	32	30 onwards (contents of recommendations box)	(p32-33) We have some suggestions regarding the guideline relating to: stratifying high grade B-cell lymphomas using laboratory techniques. While we agree with the conclusion that immunohistochemistry (IHC) is not ideal for assessing the prognostic value associated with cell of origin in people with diffuse large B-cell lymphoma (DLBCL), we are concerned that the guideline does not recommend an alternative to IHC. Should a treatment become available for patients in specifically either the GCB or non-GBC/ABC subgroups, clinicians will need some guidance to suggest how cell of origin should be determined. We therefore recommend that the guideline conclude 'should differentiation by cell of origin be needed to guide treatment, gene expression profiling (GEP) should be used over IHC, given that GEP is a highly effective technique with consistent results across the major studies, but	Thank you for your comments. We agree that an alternative to immunohistochemistry needs to be introduced but at present such a test (e.g. GEP) is not routinely available. There was a lack of consensus on the methodology of gene expression profiling (GEP); although the various systems worked in research settings they were not yet robust

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					that the exact technique/GEP panel cannot yet be recommended'. In addition, the guideline could elaborate on the options available for GEP currently and make it clear that if cell of origin is needed in the future to guide treatment, that the panel used for this should be selected at the discretion of individual hospital trust/clinicians until further evidence is available for review to allow NICE to make a firm recommendation on this point. We agree with NICE that this is a 'rapidly changing' field and NICE should therefore commit to update guidance on this in a timely manner.	enough to be used in routine practice. Research is moving towards newer practices so efforts are now being made to establish the best GEP platforms. Therefore the GC decided not to recommend GEP. We agree that this is a rapidly changing field and that an update will be necessary in due course. NICE review published guidelines to assess if an update is necessary.
92	Department of Health	General	General	General	Thank you for the opportunity to comment on the draft for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you.
36	Guys and St Thomas` Foundation NHS Trust	Full	42	Section 3.1.1.2	*The draft guideline states: "not to routinely offer FDG-PET-CT imaging to confirm staging with DLBCL Stage II or above, FCL that is non-localised stage II or above; mantle cell lymphoma; MALT lymphoma; Burkitt with high risk features or stage III/IV"* We believe a baseline scan should be performed for all stages of DLBCL, Burkitt Lymphoma and high tumour burden advanced symptomatic FL treated with immuno-chemotherapy. In DLBCL, the additional sensitivity of PET-CT compared to conventional CT, is particularly useful for the detection of extra nodal disease where the	Thank you for your comment. The Guideline Committee acknowledged that in some circumstances carrying out a staging PET-CT scan may result in a change of stage, IPI status and a need for CNS prophylaxis but there is insufficient high quality data to support this. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above

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					incidence is increased in DLBCL, or patients with bone marrow based disease. It is especially helpful to guide treatment decisions around CNS prophylaxis and in patients with extensive extra nodal disease which conveys a worse disease prognosis. Also the use confined only to those with localised disease will delay treatment initiation as other investigations will need to be carried out before a PET-CT will be able to be performed. The improved accuracy of staging offered by PET-CT will mean fewer patients are inappropriately over or under treated. Furthermore the use of PET-CT after CT will result in unnecessary radiation exposure. Baseline PET-CT is especially useful for patients requiring radiotherapy treatment as modern radio therapy techniques use smaller volumes for which assessment of, is optimal with the use of PET-CT. The International lymphoma radiation oncology group (Illidge T, et al 2014) recommend the use of PET-CT for radiation planning. The use of a baseline scan is essential in interpreting the end of treatment PET-CT in DLBCL and BL when using the internationally established Deauville criteria. For patients where there is no baseline scan to compare, this may result in patients having several unnecessary serial scans to document disease regression. A further advantage of the baseline PET-CT is its use in suspected cases of transformed follicular cell lymphoma, where highly FDG avid lesions can inform appropriate biopsy targeting and appropriate clinical decision making.	recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the linking evidence to recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.

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					We would strongly recommend that all patients should receive a baseline PET-CT in keeping with the International consensus Lugano published recommendations (Cheson B, Barrington S et al 2014) where PET-CT is the recommended standard for FDG avid lymphomas. Further considerations are that the absence of a baseline PET-CT will lead to an inability to perform clinical research in PET–CT directed lymphoma studies, in which the UK has taken a leading role Internationally.	
52	Guys and St Thomas` Foundation NHS Trust	Full	46	Section 3.1.3.2	*The draft guideline recommends "not to routinely offer FDG-PET –CT imaging to assess response at completion of planned treatment for people with: Follicular lymphoma, mantle cell lymphoma, and MALT lymphoma".* We recommend that PET-CT should be used for remission assessment to induction treatment for FL in addition to DLBCL. The full draft guidance (p46, L 17-28) cites the evidence to support the use of the end of treatment assessment in FL. In the international consensus guidelines, the use of PET-CT is recommended based on 3 multicentre studies. When FDG avidity is observed, a strong clinical suspicion of residual disease is raised and a biopsy should be performed in case further intensive treatment may be required, The International consensus guidelines recommend that PET-CT be used for response assessment in all FDG avid histologies. We ask the guideline committee to consider to revise their recommendations.	Thank you for your comment. Please note we have amended our recommendation to make it clear that there are circumstances when an end of treatment scan should be performed in follicular lymphoma but suggest that this should only be when treatment decisions would be changed as a result of that scan. As detailed in the Guideline clinical evidence section and the LETR (please see evidence statements within full Guidelines), there is currently only limited retrospective evidence in this area, in addition the GC note there is uncertainty about whether additional treatment should be given according to results of post-induction FDG-PET-CT, with no evidence that this may improve patient outcomes. Prospective trials are required/ being conducted in this area. The recommendation now reads as follows: 'For people with subtypes of non-Hodgkin's lymphoma not listed in the above recommendation (1.2.4), do not routinely offer

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						FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management.'
65	Guys and St Thomas` Foundation NHS Trust	Full	82	Section 4.1.4.1	The draft guideline states that "*Rituximab in combination with : CVP, CHOP, MCP ,CHVPi or Chlorambucil is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people".* We would recommend that Bendamustine is given as an option in combination with rituximab. There is a strong evidence base for this combination demonstrating superior efficacy, and less toxicity when compared to R-CHOP. R-Bendamustine on the basis of the published data (Rummel M et al, 2013) has largely become a standard of care for many UK based haematologists. We acknowledge that the previous technology appraisal (TA, 2011) regarding the use of Bendamustine stalled for unknown reasons, but we feel strongly that Bendamustine should be included as an option in the first line chemo-immunotherapy treatment option. Bendamustine is now available as a generic drug which should minimise cost implications.	Thank you for your comment. We are aware of the data for R-bendamustine but we did not include it as an intervention in this topic as it is a regimen currently undergoing a NICE technology appraisal. We have added the following text in both the Short version of the guideline and in the LETR paragraph of the Full guideline to explain this omission: 'The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with follicular lymphoma , because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first line treatment of advanced indolent non-Hodgkin's lymphoma' was in development. This technology appraisal is currently in development.
73	Guys and St Thomas` Foundation NHS Trust	Full	116	Section 4.4.2.1	*The draft guideline recommends "the use of Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) for the first line treatment of people with CD20 positive diffuse large B cell lymphoma at clinical stage II, III, or IV. Rituximab is not recommended when CHOP is contra indicated".* Since the publication of the original TA 65 in 2003,	Thank you for your comments. It has been agreed with NICE that all references to TA65 can be removed from the guideline.

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					which is now out of date, the field has changed rapidly and the efficacy of Rituximab in combination with other chemotherapy backbones has been demonstrated. This is particularly important for groups where the use of the CHOP is contraindicated or futile, such as the co-existence of cardiac co-morbidity or the high risk DLBCL case such as IPI ≥ 3. Such regimens such as R-GCVP (Fields P et al, 2014), R-mini CHOP (Peyrade F et al, 2011), are particularly useful in high risk cardiac or elderly patients with a strong published evidence base. The use of more intensive regimens such R-LMB or R-CODOX-IVAC should be given strong consideration in high risk cases of DLBCL such as high IPI (≥3). We would also recommend that previous TA are regularly reviewed, given this rapidly changing clinical field.	
20	Imperial College Healthcare NHS Trust	Full	40	General	Radiotherapy planning would be adversely effected by absence of PET baseline scans as modern radiotherapy low volume techniques (involved node/site radiotherapy) rely on accurate assessment disease involvement . The International Oncology Group Radiation guidelines recommend the use of baseline CT PET for radiation planning. Ref : Illidge et al 2014	Thank you for your comment. We acknowledge that some radiotherapy guidelines recommend baseline PET scanning to facilitate radiotherapy planning. However this topic was not within the scope of the guideline. Therefore the evidence was not reviewed by the Guideline Committee and we are unable to make recommendations in this area.. However we would point out that the International Radiation Oncology Group guidelines does not specify the need for baseline PET-CT scanning. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised

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						the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.
28	Imperial College Healthcare NHS Trust	Full	41	14-17	PET imaging has the ability to detect extranodal disease at presentation that would not be picked at by CT imaging – extranodal DLBCL is a risk factor for CNS involvement and this directly informs our decision to use additional CNS directed chemo-prophylactic treatment for these patients	Thank you for your comment. The Guideline Committee acknowledged that in some circumstances carrying out a staging PET-CT scan may result in a change of stage, IPI status and a need for CNS prophylaxis but there is insufficient high quality data to support this. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'Consider FDG-PET-CT imaging to confirm staging if the results will alter management for people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.
29	Imperial College Healthcare NHS Trust	Full	41	32-36	The Deauville criteria is the internationally accepted scale for interpreting response to	Thank you for your comment. We disagree that staging and interim scans are required to

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					treatment by FDG PET scan. Assessment relies on comparison of interim and end of treatment scans to baseline scans. In the absence of baseline PET, end of treatment PET scans will be harder to interpret and patients with equivocal end of treatment scans may well require increased serial radiological monitoring or unnecessary biopsies with potential uncertainty and anxiety to patients	report the Deauville score on an end of treatment scan. The Deauville score is calculated using the PET-CT data within an end of treatment scan, relative to the mediastinal blood pool and physiological liver activity level calculations on that particular scan. There is very little published evidence (and no good quality evidence) to support the assertion that a baseline PET-CT scan is required to interpret an end of treatment PET-CT scan, the key question on the end of treatment PET-CT scan being whether lymphoma is 'present or not' (not the quality of response). Good clinical practice mandates that equivocal abnormalities on an end of treatment PET-CT scan should be clinically investigated on merit (usually with interval repeat imaging and/ or biopsy). Due to the uncertainty and lack of evidence as to whether a baseline PET scan is actually required to interpret an end of treatment scan, the Guideline Committee have proposed a research recommendation – "In people with Diffuse large B-cell lymphoma stage II or above, does a FDG-PET-CT scan have any advantages over the availability of a baseline CT-scan in the correct interpretation of the end of treatment FDG-PET-CT scan".
32	Imperial College Healthcare NHS Trust	Full	42	General	(and page 46) End of treatment FDG-PET scans in FL have prognostic value as demonstrated by studies (line 17-28 p46) and can identify patients who would benefit from further 2nd line chemotherapy rather than standard rituximab maintenance.	After reviewing the evidence the Guideline Committee concluded there was insufficient high quality data to make a recommendation for the use of interim PET-CT. The evidence showed that end of treatment scans were better predictors than interim ones for these subtypes.

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						With regard to end of treatment scans for Follicular lymphoma and MALT there is a lack of evidence but we are not suggesting that there are no circumstances in which a PET-CT scan should be performed. We have amended the recommendation to say that they should be carried out only if they change therapy. The recommendation now states,: • **'For people with other subtypes of non-Hodgkin's lymphoma not listed in the above recommendation (1.2.4), do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management**'. We have also stressed in the linking evidence to recommendations (LETR) table that this is an evolving field and the situation could change as data emerges from recent and ongoing trials, particularly if there is a change of practice with regards to maintenance rituximab therapy.
37	Imperial College Healthcare NHS Trust	Full	42	General	We are concerned that the recommendation to limit the use of baseline PET imaging only to patients with Stage I DLBCL/FL stage I and localised stage II contradicts current international recommendations – National Comprehensive Cancer Network and Lugano Classification Refs NCCN NHL guidelines Zelenetz 2014 Cheson et al 2014 – Recommendations for the	Thank you for your comment. The guideline committee have removed the following recommendation, 'Do not routinely offer FDG-PET-CT imaging to confirm staging for people diagnosed with: • diffuse large B-cell lymphoma that is stage II or above • follicular lymphoma that is non-localised stage II or above • mantle cell lymphoma • MALT lymphoma (extra nodal marginal zone

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					initial evaluation, staging and response assessment of Hodgkin's and Non-Hodgkin's lymphoma: The Lugano Classification. JCO(32) 27 (3059-3065)	lymphoma of mucosa-associated lymphoid tissue) • Burkitt lymphoma with high-risk features, or stage III or IV' The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area. The Zelenetz (2014) Cheson (2014) papers were not included in the evidence review because they are guidelines rather than primary studies.
38	Imperial College Healthcare NHS Trust	Full	42	General	(and pages 43 & 47) The guidelines imply limiting the use of FDG PET would reduce radiation exposure. In our centre we perform PET/CT at baseline, interim and end of treatment in NHL subgroups known to be FDG avid. We do not perform CECT at these time points. The radiation dose of a CECT NCAP (12 mSv) is similar to that of FDG PET/CT (approx.13 mSv). The new proposed guidelines would not reduce radiation dose as it is likely patients will end up having more imaging as there will be equivocal reports at	Thank you for your comment. We have removed statements regarding radiation dose from this section of the guideline.

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					interim and end of treatment assessments if CECT is used.	
39	Imperial College Healthcare NHS Trust	Full	42	General	(and page 46) The recommendation not to offer baseline or assessment response FDG-PET for patients with low grade lymphoma is not in line with the Lugano Classification which states that FDG-PET is the standard for FDG avid lymphomas. Baseline FDG PET is useful in identifying areas of high grade transformation in low grade lymphoma, can help identify best area for biopsy and can influence treatment planning from the start.	Thank you for your comment. Please note we have amended our recommendations on baseline and end of treatment staging with PET-CT to the following: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation, consider FDG-PET-CT imaging to confirm staging if the results will alter management'; and 'For people with subtypes of non-Hodgkin's lymphoma not listed in the above recommendation (1.2.4), do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management. The Guideline Committee does not accept that FDG-PET is useful in identifying areas of high grade transformation as non-transformed follicular lymphoma is typically FDG avid.
74	Imperial College Healthcare NHS Trust	Full	116	9	Rituximab is recommended for use in combination with a regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) for the first-line treatment of people with CD20-positive diffuse large-B-cell lymphoma at clinical stage II, III or IV. Rituximab is not recommended for use when CHOP is contraindicated . Concern: There is no provision in the guideline for patients for whom anthracyclines are contra-indicated – recently published evidence demonstrates the efficacy of R-GCVP in this group of patients.	Thank you for your comments. It was our intention at scoping to include TA65 in the guideline but we have now agreed to omit it as it no longer reflects current practice..

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					Ref Fields et al JC0 2014	
40	Lymphoma Association	Full	42	Section 3.1.1.2	Baseline FDG-PET-CT scanning is seen as standard clinical practice around the world. The recommendation not to offer FDG-PET-CT for certain subtypes and stages would put UK practice out of step with the rest of the world (following international consensus at the Lugano International Conferences on Malignant Lymphomas – see the Lugano classification and the Cheson criteria covered in *Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification* (Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister, 2014 J Clin Oncol 32)). We appreciate that the evidence concerning the routine use of staging by PET scanning is very limited (either for or against), and the views expressed in the draft guideline are thus a reflection of the personal opinions of the committee. As such, it is essential that these personal views are not out of step with the views of the large majority of experts in the field and nearly all other international guidelines. Furthermore, not carrying out baseline PET scans could have an impact on the UK's leading role in clinical research. This is because any properly constituted trials will need to comply with the Lugano/Cheson criteria and, if baseline scanning isn't the norm, then the additional costs of such scans will have to be met from research budgets. This may mean the UK will be a less attractive place for trials, which will have a number of	Thank you for your comment. We acknowledge that some radiotherapy guidelines recommend baseline PET scanning to facilitate radiotherapy planning. However this topic was not within the scope of the guideline. Therefore the evidence was not reviewed by the Guideline Committee and we are unable to make recommendations in this area. However we would point out that the International Radiation Oncology Group guidelines does not specify the need for baseline PET-CT scanning. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management.'. The GC have amended the linking evidence to recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.

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					significant knock-on effects, including reducing access to new and innovative treatments for patients. Finally, clearly the above points apply to the treatment of all forms of lymphomas, but will be particularly damaging in relation to high grade or aggressive subtypes.	
66	Lymphoma Association	Full	82	Section 4.1.4	Follicular lymphoma – Bendamustine is widely used in the treatment of FL, but is not covered in the guideline. In the views of some clinicians, Bendamustine is more effective than R-CHOP or at least as good. While we appreciate that Bendamustine is currently the subject of a NICE TA (started in 2011, but which appears to have been suspended), and therefore cannot be covered in a guideline (although patients don't really understand why current TAs can't at least be acknowledged in guidelines), we are concerned that no mention of the treatment will lead to it not being available to patients in the future. Perhaps the guideline could indicate that just because certain treatments aren't included in the guideline, they shouldn't automatically be excluded from consideration. Similarly, it should also be noted that Bendamustine is now available as a generic drug, which means it is significantly cheaper than it was previously.	Thank you for your comment. We are aware of the data for R-bendamustine but we were unable to include it as an intervention in this topic as it is a regimen currently undergoing a NICE technology appraisal. We have added the following text in both the Short version of the guideline and in the LETR paragraph of the Full guideline to explain this omission: 'The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with follicular lymphoma , because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first line treatment of advanced indolent non-Hodgkin's lymphoma' was in development. This technology appraisal is currently in development.
75	Lymphoma Association	Full	116	Section 4.4.2	First line treatment of CD20+ DLBC Lymphoma – the recommendations in this section re not considering rituximab for patients where CHOP is contra-indicated are based on appraisal guidance (NICE TA Guidance 65) that is nearly 13 years old and does not reflect current practice and the current standard of care. In such a fast-changing area of clinical practice, patients would simply not understand or accept current treatment practice	Thank you for your comments. It was our intention at scoping to include TA65 in the guideline but we have now agreed to omit it as it no longer reflects current practice. NICE has a process for updating technology appraisals more information can be found on the NICE website https://www.nice.org.uk/About/What-we-

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					and decisions being informed by an out-of-date and inaccurate piece of guidance, which should in fact be withdrawn. We are concerned that these recommendations would reflect badly on UK clinical practice across the world, given that they do not reflect contemporary practice. In addition, the recommendations are highly discriminatory to the elderly and the less fit who may be denied the most effective treatments. Should TA guidance have some form of expiry date system or "Best Before" or "Use By" date, so as to avoid situations like these?	do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance
82	Lymphoma Association	Full	159	Section 5	We're disappointed that this section doesn't appear to reference the high quality and accredited information and support that is available within the voluntary sector. Significant cost savings could be made if the NHS were to contract centrally with specialist lymphoma information and support organisations, rather than encouraging a multiple provision approach from individual hospitals, treatment centres and trusts.	Thank you for your comment. The full guideline does not signpost charitable organisations, but the lay version of the guideline 'information for the public' will sign post to the Lymphoma Association. The recommendations on information support were based on a comprehensive systematic review of the published evidence. However the GC did specifically look at the provision of information by relevant organisations with an interest in lymphoma.
93	NAPP Pharmaceuticals Limited	General	General	General	Please note that on this occasion Napp does not wish to comment on the draft guideline. Thank you for keeping us informed of the developments relating to this guideline.	Thank you.
5	NCRI-RCP-ACP	Full	General	General	References related to comments above REFERENCES Barrington SF, Mikhaeel NG, Kostakoglu L, et al: Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant	Thank you for the list of references that relate to your earlier comments.

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					Lymphomas Imaging Working Group. Journal of clinical oncology. 2014; 32:3048-58. Barrington S, Qian W, Somer EJ, et al: Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. European Journal of Nuclear Medicine and Molecular Imaging. 2010; 37:1824-1833.Barrington SF, MacKewn JE, Schleyer P, et al: Establishment of a UK-wide network to facilitate the acquisition of quality assured FDG-PET data for clinical trials in lymphoma. Annals of Oncology. 2011; 22:739-745. Carr R, Fanti S, Paez D, et al: Prospective international cohort study demonstrates inability of interim PET to predict treatment failure in diffuse large B-cell lymphoma. Journal of nuclear medicine. 2014; 55:1936-44. Casulo C, Byrtek M, Dawson KL, et al: Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. Journal of clinical oncology. 2015; 33:2516-22. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. Journal of clinical oncology. 2014; 32:3059-68. Dupuis J, Berriolo-Riedinger A, Julian A, et al: Impact of [18F]Fluorodeoxyglucose Positron Emission Tomography Response Evaluation in Patients With High-Tumor Burden Follicular Lymphoma Treated With Immunochemotherapy: A Prospective Study From the Groupe d'Etudes	

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					des Lymphomes de l'Adulte and GOELAMS. Journal of clinical oncology. 2012; 30:4317-22. El-Galaly TC, Villa D, Alzahrani M, et al: Outcome prediction by extranodal involvement, IPI, R-IPI, and NCCN-IPI in the PET/CT and rituximab era: A Danish-Canadian study of 443 patients with diffuse-Glarge B-cell lymphoma. Am J Hematol. 2015; 90:1041-6. Huntington SF, Nasta SD, Schuster SJ, et al: Utility of interim and end-of-treatment [(18)F]-fluorodeoxyglucose positron emission tomography-computed tomography in frontline therapy of patients with diffuse large B-cell lymphoma. Leuk Lymphoma. 2015; 56:2579-84. Illidge T, Specht L, Yahalom J, et al: Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2014; 89:49-58. Luminari S, Biasoli I, Versari A, et al: The prognostic role of post-induction FDG-PET in patients with follicular lymphoma: a subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi (FIL). Annals of oncology. 2014; 25:442-7. Mamot C, Klingbiel D, Hitz F, et al: Final Results of a Prospective Evaluation of the Predictive Value of Interim Positron Emission Tomography in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP-14 (SAKK 38/07). Journal of clinical oncology. 2015; 33:2523-9. Meignan M, Gallamini A, Haioun C: Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leuk Lymphoma. 2009; 50:1257-60.	

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					Meignan M, Itti E, Bardet S, et al: Development and application of a real-time on-line blinded independent central review of interim PET scans to determine treatment allocation in lymphoma trials. Journal of clinical oncology. 2009; 27:2739-41. Quarles van Ufford H, Hoekstra O, de Haas M, et al: On the added value of baseline FDG-PET in malignant lymphoma. Molecular imaging and biology. 2010; 12:225-32. Strobel K, Schaefer NG, Renner C, et al: Cost-effective therapy remission assessment in lymphoma patients using 2- fluorine-18 fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography: is an end of treatment exam necessary in all patients? Annals of Oncology. 2007; 18:658-664. Trotman J, Luminari S, Boussetta S, et al: Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. The Lancet Haematology. 2014; 1:e17-e27. Trotman J, Fournier M, Lamy T, et al: Positron Emission Tomography-Computed Tomography (PET-CT) After Induction Therapy Is Highly Predictive of Patient Outcome in Follicular Lymphoma: Analysis of PET-CT in a Subset of PRIMA Trial Participants. Journal of Clinical Oncology. 2011; 29:3194-3200. Zelenetz AD, Gordon LI, Wierda WG, et al: Non-Hodgkin's lymphomas, version 4.2014. J Natl Compr Canc Netw. 2014; 12:1282-303.	
21	NCRI-RCP-ACP	Full	40	General	(p40-51) Our experts are concerned that the	Thank you for your comment. We agree that

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					specialist imaging advice given to the Guidelines Committee (GC) does not reflect the opinions of the majority of imaging specialists practicing in the UK who regularly report PET-CT in Non-Hodgkin Lymphoma (NHL) and are members of multidisciplinary teams. This draft consultation document is out of step with guidelines widely used in clinical practice and clinical trials for the staging and response assessment of NHL. Our experts note that the GC may wish to take further advice with respect to the imaging recommendations for PET-CT. Draft NICE recommendations are counter to those recommended in internationally agreed consensus guidelines [Barrington et al 2014, Cheson et al 2014], UK Evidence based guidelines for the use of PET-CT in England [http://www.rcplondon.ac.uk/resources/evidence-based-indications-use-pet-ct-uk-2013] and US National Comprehensive Cancer Network guidelines [Zelenetz, et al. 2014]. These guidelines all recommend a baseline scan for proper interpretation of response in NHL. Our experts believe there are strong pragmatic reasons for the use of : • staging scans in all stages of Diffuse Large B cell Lymphoma (DLBCL), limited stage Follicular Lymphoma (FL) on CT, FL treated with chemo-immunotherapy • interim PET-CT, if interim scanning is undertaken, in preference to CT in addition to the groups for whom PET-CT is already	the recommendation in the consultation version of the guideline differed from some of the current international guidelines. However our recommendations were made following a thorough systematic review of the evidence for this topic, with a rigorous NICE quality assessment of published studies using the QUADAS-2 tool and GRADE methodology, much of the evidence in this area being of low to moderate quality; whether a Test Result leads to a treatment change (and potential improved patient outcomes) also being a key consideration by the Guideline Committee. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the linking evidence to recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area. The Guideline Committee have made a recommendation for end of treatment scans for limited stage Follicular lymphoma. After reviewing the evidence the Guideline Committee concluded there was insufficient

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					recommended in the draft NICE guidance. • End of treatment scans in patients with FL treated with induction chemo immunotherapy • Selected patients with Mucosa Associated Lymphoma Tissue (MALT) and some T cell lymphomas	high quality data to make a recommendation for the use of interim PET-CT. The evidence showed that end of treatment scans were better predictors than interim ones for these subtypes. With regard to end of treatment scans for Follicular lymphoma and MALT there is a lack of evidence but we are not suggesting that there are no circumstances in which a PET-CT scan should be performed. We have amended the recommendation to say that they should be carried out only if they change therapy. The recommendation now states,: • **'For people with subtypes of non-Hodgkin's lymphoma not listed in the above recommendation (1.2.4), do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management**'. We have also stressed in the LETR table that this is an evolving field and the situation could change as data emerges from recent and ongoing trials, particularly if there is a change of practice with regards to maintenance rituximab therapy.
22	NCRI-RCP-ACP	Full	40	Page 42 Box 1, line 1 Page 43 Box 1, line 6	(p40-51) We are concerned that the following recommendations represent a challenging change in practice. **Page 42, line 1: Offer FDG-PET-CT imaging to confirm staging for people diagnosed with:**	The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above

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					• **stage I diffuse large B-cell lymphoma by clinical and CT criteria** • **stage I or localised stage II follicular lymphoma if disease is thought to be encompassable within a radiotherapy field** • **stage I or II Burkitt lymphoma with other low-risk features.** The NICE documentation (page 43 line 6) states that : **The GC thought that the ability to make more appropriate management decisions outweighed the harms which would be experienced by a small proportion of patients** Our experts note that the GC had a single representative from the imaging community and should be aware that this is not a commonly held view in clinical practice or in clinical trials. It is acknowledged in international consensus guidelines (as above point 1) but not in the NICE documentation that a staging scan is necessary for the purpose of accurate interpretation of response scans in all stages of disease, in particular for patients with extranodal disease which is not adequately assessed on staging CT. Our experts suggest a baseline scan should be recommended in all stages of DLBCL, Burkitt's lymphoma and high tumour burden or advanced symptomatic FL treated with induction immune-chemotherapy for the following reasons: • Although DLBCL is routinely FDG-avid, assessment of extranodal sites, especially	recommendation, consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area. Membership of the Guideline Committee included a very experienced consultant radiologist. However the guideline was issued for consultation with stakeholders, which included several organisations representing the interest of radiology and nuclear medicine. Thank you for this information. With regards to ambiguous findings on end of treatment PET-scans good practice would be to either biopsy the lesion or repeat the scan after a short-interval. Barrington (2014) was not included as evidence because it is an expert consensus guideline. The El-Galaly et al (2015) study is relevant but was not included because it was published after our final literature search in September 2015. Barrington (2010 & 2011) and Meignan (2009)

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					those that can have high physiological uptake and which often have increased uptake in response to treatment relies on the identification of involvement on a baseline scan [Barrington, et al. 2014]. The incidence of extranodal disease in DLBCL can be as high as 66% [El-Galaly, et al. 2015]. Sites with high physiological uptake include bone marrow, stomach, gut, Waldeyers ring. In particular, assessment of bone marrow involvement can be problematic, with ablation of normal marrow at disease sites successfully treated which becomes 'cold' on a response scan and increased uptake within normal and diseased marrow which becomes 'hot' on a response scan. Without a baseline scan to refer to, it can be difficult to be sure if 'hot' focal uptake represents normal reactive marrow with ablated adjacent marrow or residual marrow disease. • Reactive and inflammatory changes are common at some sites including the lung hila which cannot be distinguished from initial sites of disease involvement without reference to a baseline scan. In early stage Hodgkin Lymphoma, in the RAPID trial there was uncertainty how to interpret FDG uptake in 19% patients who did not demonstrate complete metabolic response where FDG uptake occurred at sites where lymphadenopathy was not reported on the staging CT scan [Barrington, et al. 2011]. This incidence of uncertainty in interpretation of response occurred in a group of patients who uncommonly have extranodal disease	were not included because they are Hodgkin Lymphoma studies. Quarles van Ufford (2010) was excluded because it used PET alone (not PET-CT).

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					and was carried out using central review by 2 experienced observers. • Differentiating inflammatory related treatment effects is a challenging area that has been reported to impact on interobserver agreement, in reporting Hodgkin Lymphoma [Barrington, et al. 2010] and which also affects reporting in NHL. Interobserver agreement in DLBCL is reported to be better when a direct comparison can be carried out with the baseline scan for response assessment [Meignan, et al. 2009]. In a small study in lymphoma, addition of baseline to post treatment PET evaluation affected the classification of metabolic response in 34% of malignant lymphoma patients treated with first-line chemotherapy, leading to opposite conclusions regarding response in 1 out of 7 patients [Quarles van Ufford, et al. 2010].	
23	NCRI-RCP-ACP	Full	40	General	(p40, 43) Question 1 Our experts are concerned that the absence of a baseline PET-CT will adversely affect patients who undergo radiation planning, this includes not only patients with limited disease but also patients requiring consolidation radiotherapy. Modern radiotherapy uses smaller volumes (e.g. involved-site and involved-node radiotherapy) which are based on accurate mapping of exact disease involvement rather than anatomical sites (involved-field radiotherapy). International	Thank you for your comment. We acknowledge that some radiotherapy guidelines recommend baseline PET scanning to facilitate radiotherapy planning. However this topic was not within the scope of the guideline. Therefore the evidence was not reviewed by the Guideline Committee and we are unable to make recommendations in this area.. However we would point out that the International Radiation Oncology Group guidelines does not specify the need for baseline PET-CT scanning. The Guideline Committee accept that in the

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					guidelines produced by the International Lymphoma Radiation Oncology Group recommend the use of PET-CT for radiation planning [Illidge, et al. 2014] and there is plenty of evidence that PET-CT information changes the volume to be irradiated in a significant proportion of patients.	absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation, consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.
24	NCRI-RCP-ACP	Full	40	General	(p40, 43) Question 1 Our experts are concerned that implementation of the recommendation with respect to staging in DLBCL will have an adverse effect on patient management and evaluation of prognosis for the following reasons: The incidence of extranodal disease in DLBCL is high. In a recent study with 443 patients included from Canada and Denmark, 2/3 patients had extranodal disease on PET [El-Galaly, et al. 2015]. This study was not included in the NICE evaluation. In multivariate analysis, stage IV disease, the presence of extranodal disease on PET-CT and the number of extranodal sites were predictive of PFS and OS independent of LDH, PS and age. More treatment failures occurred with an increasing number of extranodal sites. Particular sites were identified with adverse	Thank you for your comment. The Guideline Committee acknowledged that in some circumstances carrying out a staging PET-CT scan may result in a change of stage, IPI status and a need for CNS prophylaxis but there is no high quality evidence to support this. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'Consider FDG-PET-CT imaging to confirm staging if the results will alter management for people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried

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					prognosis including bone marrow, pleura, gynaecological organs. Although not reported by the studies assessed in the NICE guidance, upstaging has treatment implications for advanced vs limited stage with longer course chemotherapy. Patients with stage II disease may be upstaged according to PET and there is a high incidence of stage III/IV disease using PET-CT as suggested by the study above. Improved accuracy of staging is likely to result in fewer patients being undertreated or overtreated and this was the recommendation in recent international guidelines for staging scans. There may also be implications for CNS prophylaxis.	out in this area.
25	NCRI-RCP-ACP	Full Appendix G	40	Table of excluded studies relating to PET	(p40-51) Our experts believe that PET-CT is more accurate for staging aggressive non-Hodgkin lymphomas (NHL) and Follicular Lymphomas (FL) than CT, as acknowledged in the NICE documentation. Limited data are presented because all studies that were not PET-CT were excluded, which is inappropriate. PET-CT has improved specificity compared to PET alone, but sensitivity is similar. Excluding all studies reporting PET only (or studies with a proportion of patients scanned on PET only cameras) ignores much of the evidence base established before PET-CT became widespread in the period between 2005-2010. This applies also to response assessment.	Thank you for your comment. PET only scanners are no longer manufactured and all radiology departments in the UK now use PET-CT. The Guideline Committee did not assess or investigate evidence on the use of PET as this technology has been surpassed and is no longer used in current clinical practice. Combined PET-CT affords better accuracy and the PET-CT evidence has been reviewed in detail within this section of the guideline.
26	NCRI-RCP-ACP	Full	40	General Appendix G evidence review	(p40-51) Our experts note that there may be a role for PET-CT in staging and remission assessment of some T cell lymphoma subtypes and to assess patients with cutaneous lymphomas for systemic involvement. The attention of the GC is drawn to the studies below not considered in	Thank you for your comment. We have amended the recommendation so that it includes some T-Cell lymphomas. The recommendation now states: 'For people diagnosed with subtypes or

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					the documentation. NK T cell Moon SH, Cho SK, Kim WS, et al: The role of 18F-FDG PET/CT for initial staging of nasal type natural killer/T-cell lymphoma: a comparison with conventional staging methods. J Nucl Med 54:1039-44, 2013 Khong PL, Huang B, Lee EY, Chan WK, Kwong YL: Midtreatment (1)(8)F-FDG PET/CT Scan for Early Response Assessment of SMILE Therapy in Natural Killer/T-Cell Lymphoma: A Prospective Study from a Single Center. J Nucl Med 55:911-6, 2014 PTCL Casulo C, Schoder H, Feeney J, et al: FDG-PET in the Staging and Prognosis of T cell Lymphoma Leukemia & lymphoma Leukemia & lymphoma, 54(10), 2163-2167, 2013. El-Galaly TC, Pedersen MB, Hutchings M, et al: Utility of interim and end-of-treatment PET/CT in peripheral T-cell lymphomas: A review of 124 patients. American journal of hematology 90:975-80, 2015 Feeney J, Horwitz S, Gonen M, et al: Characterization of T-cell lymphomas by FDG PET/CT. AJR. 2010; 195:333-40. Kolstad A, Laurell A, Jerkeman M, et al: Nordic MCL3 study: 90Y-ibritumomab-tiuxetan added to BEAM/C in non-CR patients before transplant in mantle cell lymphoma. Blood 123:2953-9, 2014	stages of non-Hodgkin lymphoma not listed in the above recommendation, consider FDG-PET-CT imaging to confirm staging if the results will alter management'. Khong (2014) was not included because it assesses mid-treatment PET-CT in NK/ T-Cell lymphoma. Our clinical question on mid-treatment PET-CT was limited to DLBCL only and the group did not address mid-treatment imaging for other sub-types of NHL. Moon (2013) was not identified in our literature search. This case series of patients with rare nasal NK/ T-Cell lymphoma, suggests PET-CT can detect sites of nodal and extra-nodal involvement This evidence is consistent with the recommendation to consider staging PET-CT in NHL if the results could alter management. El-Galaly (2015) was published after our literature search cut-off. The focus of this study was the prognostic value of baseline PET-CT in DLBCL, whereas the guideline review question addressed the diagnostic accuracy of PET-CT staging. If this study had been included it would not have changed the recommendation – which was to offer PET-CT for stage I DLBCL and to consider it for other DLBCL stages. Casulo (2013) was included in our evidence review. Feeney (2010) includes some patients also in

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						Casulo (2013). Kolstad (2014) this study examines pre-transplant PET-CT as a prognostic factor in the Nordic MCL3 study – however our clinical review question on interim PET-CT was limited to DLBCL.
31	NCRI-RCP-ACP	Full	41	33	Question 1 **Use of pretreatment FDG-PET-CT to evaluate post-treatment FDG-PET-CT** **Sixteen studies observational did baseline FDG-PET-CT as well as interim or end of treatment FDG-PET-CT.** Our experts note the following in response to the above: • Further support for the view that staging scans are required in all stages of DLBCL is that studies supporting remission assessment in patients with DLBCL using PET and included in the NICE draft documentation relied on having baseline scans for proper remission assessment. The reason why the 16 observational studies used baseline and response scans but did not directly report the use of baseline scans in evaluating response (p41, line33, section 3.1.1.5) is because it is (almost) universally accepted that baseline scans are required for proper interpretation of response scans. • The recommended criteria for response assessment are Deauville criteria (DC) which	Thank you for your comments. The GC concluded there was inadequate high quality data to support your assertion. We agree that a staging scan is required to distinguish the different categories of metabolic response but we were unable to find data that this is of any clinical value. Further, the key clinical question on the end of treatment PET-CT scan is whether lymphoma is present or not (not the quality of response). Good clinical practice mandates that equivocal abnormalities on an end of treatment PET-CT scan should be investigated on merit (usually with interval repeat imaging and/ or biopsy). The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'Consider FDG-PET-CT imaging to confirm staging if the results will alter management for people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation'. The GC have amended the LETR paragraph to explain the rationale behind this decision. Due to the uncertainty and lack of evidence as to whether a baseline PET scan is actually required to interpret an

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					are in widespread clinical use and in clinical trials. They are recommended based on improved interobserver agreement and better positive predictive value compared to older International Harmonisation Project (IHP) Criteria[Barrington, et al. 2014]. DC rely on scoring ' the most intense uptake in a site of initial disease' with reference regions in the normal mediastinum and the liver [Meignan, et al. 2009] and require a baseline scan to determine that the most intense uptake corresponds to a site of initial disease. This is not always apparent on a CT scan which is a less sensitive test. Determining whether there is progressive metabolic disease (or not) also relies on having a clear map of initial disease sites. • New response categories proposed in international guidance rely on baseline scans to assess change in uptake to categorise response into partial metabolic response, stable metabolic disease and progressive metabolic disease[Cheson, et al. 2014]. Again this is not possible without a baseline scan. Without a baseline scan only complete metabolic response can be assigned in the presence of no abnormal uptake.	end of treatment scan, the GC have also proposed the following research recommendation – "In people with Diffuse large B-cell lymphoma stage II or above, does a FDG-PET CT scan have any advantages over the availability of a baseline CT-scan in the correct interpretation of the end of FDG-PET-CT scan". We disagree that interim staging and interim scans are required to report the Deauville score on an end of treatment scan. The Deauville score is calculated using the PET-CT data within an end of treatment scan, relative to the mediastinal blood pool and physiological liver activity level calculations on that particular scan. Barrington (2014) and Cheson (2014) were not included as evidence because they are expert consensus guidelines. Meignan (2009) was not included because it is a Hodgkin Lymphoma study.
42	NCRI-RCP-ACP	Full	42	Boxes All entitled trade-off between clinical benefits and	(p42, 43, 47) Question 3 Our experts note that from experience in scanning patients with CT and PET-CT they are concerned about statements made in the NICE documentation about concerns with respect to	The Guideline Committee does not believe there is sufficient high quality data to make a recommendation for the use of interim PET-CT. With regard to end of treatment scans for Follicular lymphoma and MALT there is a lack of evidence but we are not suggesting that there are no circumstances in which a PET-

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				harms	radiation exposure (page 42,45,47) to the effect that 'limiting the use of FDG PET CT staging .. would result in a reduction in radiation exposure' and 'it was the consensus of the GC that the recommendation (not to offer FDG PET CT imaging for interim assessment in DLBCL) would stop inappropriate therapy changes and reduce radiation exposure and discomfort from FDG PET CT' and 'there could be increased radiation exposure for patients'. The effective dose associated with contrast-enhanced CT scan of chest abdomen and pelvis is in the order of 16mSv which is the same or lower for a PET-CT scan (with modern cameras in the region of 10-16mSv), which is commonly performed using a lower dose non contrast enhanced CT with improved staging and response assessment compared to CT. Therefore if a PET-CT scan replaces CT at staging, at interim or end of treatment assessment it would not result in an increase in radiation exposure. Patients experiencing an early complete metabolic response on interim imaging (approximately 60-79%)[Mamot, et al. 2015,Carr, et al. 2014,Huntington, et al. 2015] do not require an end of treatment scan which may result in a reduction in radiation exposure compared to a strategy recommended by NICE of staging CT, interim CT and end of treatment PET CT in patients with DLBCL.	CT scan should be performed. We have amended the recommendation to say that they should be carried out only if they change therapy. The recommendation now states,: • **'For people with subtypes of non-Hodgkin's lymphoma not listed in the above recommendation (1.2.4), do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management**'. We have also stressed in the linking evidence to recommendations (LETR) table that this is an evolving field and the situation could change as data emerges from recent and ongoing trials, particularly if there is a change of practice with regards to maintenance rituximab therapy. Thank you for your comment. We have removed statements regarding radiation dose from this section of the guideline. The Mamot (2015) and Carr (2014) studies were included, the Huntington (2015) paper identified in our search was excluded from the clinical evidence review as it was a cost-effectiveness analysis.
46	NCRI-RCP-ACP	Full	43	Page 43, Recommendation box 1 Page 48, Line11	(p43, 48) Question 1 and Question 2 **Page 43, Recommendation box 1: Offer FDG-PET-CT imaging to confirm staging for people**	Thank you for your comments. We are unaware of any data showing that carrying out a PET-CT scan is cost saving. It is the belief of the Guideline Committee that

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					diagnosed with: • **stage I diffuse large B-cell lymphoma by clinical and CT criteria** • **stage I or localised stage II follicular lymphoma if disease is thought to be encompassable within a radiotherapy field** • **stage I or II Burkitt lymphoma with other low-risk features.** • **Do not routinely offer FDG-PET-CT imaging to confirm staging for people diagnosed with:** • **diffuse large B-cell lymphoma that is stage II or above** • **follicular lymphoma that is non-localised stage II or above** • **mantle cell lymphoma** • **MALT lymphoma (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue)** • **Burkitt lymphoma with high-risk features, or stage III or IV.** **Page 48, line 11: There are potential cost savings downstream associated with a reduction in over- and under-treatment.** Our experts are concerned that there may be adverse effects on patients and cost implications if a baseline PET-CT scan is not available. The absence of a baseline scan will lead to uncertainty in interpreting response and rather than the premise that **'***any abnormalities identified on end of treatment FDG-PET-CT can be investigated on merit'* (page 43, Other considerations box line 14)	the distinction of persisting disease and disease at a new site is of little clinical impact and where there is uncertainty good clinical practice should be to carry out a biopsy or interval scan.

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					could result in unnecessary biopsies or interval scans. There may be delay in treatment for some patients (who turn out to have disease requiring treatment) and anxiety in others (who turn out to have uptake related to treatment related inflammation or another cause). The potential cost savings associated with a reduction in over- and under- treatment referred to in the NICE consultation document (p48) are likely to be reduced if there is clinical uncertainty.	
47	NCRI-RCP-ACP	Full	43	Box entitled other considerations	Question 1 **The GC did not make recommendations on CT as it is a routine and established test used in UK haematology and lymphoma units for staging and for assessment of iterim and end of treatment response. The GC noted, however, that the use of FDG-PET-CT in this context is variable across the UK and made the recommendations due to the need for guidance on the use of FDG-PET-CT for staging, interim response assessment and end of treatment response.** **The GC acknowledged there would be a considerable change in practice in centres that currently do baseline FDG-PET-CT scans in all patients with DLBCL. The GC thought, however, that baseline FDG-PET-CT rarely had an influence on management when assessing end of treatment FDG-PET-CT scan and is not essential for interpreting end of treatment FDG-PET-CT. Any abnormalities identified on end of treatment FDG-PET-CT can be investigated on merit.**	Thank you for your comment. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management.'. The GC have amended the linking evidence to recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.

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					The GC also acknowledged that these recommendations may disadvantage the position of the UK in international clinical trial participation where base line FDG-PET-CT is mandated but is not funded as it will no longer be the standard of care. Our experts believe that the absence of a baseline scan (as acknowledged by the GC) will significantly disadvantage the UK in the ability to perform research in the field of PET and lymphoma, which has previously been a strength.	
49	NCRI-RCP-ACP	Full	44	Box entitled trade-off between clinical benefits and harms	(p44, 45) Question 1 and Question 3 **The evidence concerned the prognostic utility of interim FDG-PET-CT rather than its direct impact on patient outcomes, however it was the consensus of the GC that the recommendation would stop inappropriate therapy changes and reduce radiation exposure and discomfort from FDG-PET-CT.** **No harms associated with the recommendation were identified. The GC thought that patients who would benefit from more intensive treatment would be identified on their post-treatment FDG-PET-CT scan.** With respect to interim PET and DLBCL our experts are concerned that whilst the guidance acknowledges *'The evidence concerned the prognostic utility of interim FDG-PET-CT'* the statement that 'it was the consensus of the GC	Thank you for your comments. We have removed commentary on radiation exposure from this section of the guideline. The Guideline Committee do not accept the clinical utility of PET scanning on DLBCL, and we think it would be improper or unsafe to abandon of end of treatment PET-scan on the basis of a negative interim PET scan after 2 cycles of therapy The Mamot (2015) and Carr (2014) studies were included in the evidence review, the Huntington (2015) paper identified in our search was excluded from the clinical evidence review because it was a cost-effectiveness analysis. The Strobel (2007) study was not included as it was mixed HD and NHL and results were not reported separately.

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					that the recommendation would stop inappropriate therapy changes and reduce radiation exposure and discomfort from FDG-PET-CT does not take account: • of the importance of the prognostic utility of interim PET on patient management • that the majority of patients with complete metabolic response on interim scanning do not require and end of treatment PET-CT (or CT) scan • the radiation exposure associated with the use of interim PET has been overestimated. The GC states that '*CT is conventionally used for interim response evaluation, assessing changes in lesions size*' implying this is good practice. Our experts believe that PET-CT is a more appropriate use of resources than using interim CT for which there is no published evidence, if interim scanning is performed. Interim PET has a high negative predictive value in DLBCL, as acknowledged in the NICE consultation. Whilst it may not influence treatment decisions, this is useful information for patients and clinicians. Patients showing remission early can be reassured whilst still having treatment. Patients with early and late complete metabolic response (CMR)on PET-CT had a 2-y EFS of 97% (95% CI 92,98) in a recent study involving 327 patients [Carr, et al. 2014]. In addition, PET-CT may detect early progression in a small proportion of patients for whom treatment may need to be changed. If interim imaging is	

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					performed, PET-CT should be used in preference to CT for the above reasons. The majority of patients have complete metabolic response at interim (60% in study by Mamot et al; 79% in study by Huntingdon et al; 62% in study by Carr et al). All patients in the studies by Mamot et al[Mamot, et al. 2015] and Huntingdon et al[Huntington, et al. 2015] and in an earlier smaller study by Strobel et al[Strobel, et al. 2007] and 96% of patients in the study by Carr et al[Carr, et al. 2014] with early CMR on interim PET had CMR on the EOT-PET. This means that with early CMR at interim an EOT PET is not required, which saves resources, inconvenience and reduces radiation dose. If an interim PET scan does not show CMR, there is no indication to change treatment, unless there is evidence of progression or lack of any response but closer monitoring of these patients during treatment may be warranted, as a proportion will progress, especially those with initial poor risk disease .	
54	NCRI-RCP-ACP	Full	46 Appendix G	Box entitled recommendations Excluded studies	**Offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with:** • **diffuse large B-cell lymphoma** • **Burkitt lymphoma.** • **Do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with:** • **follicular lymphoma**	Thank you for your comment. Please note we have amended our recommendation to make it clear that there are circumstances when an end of treatment scan should be performed in follicular lymphoma but suggest that this should only be when treatment decisions would be changed as a result of that scan. The recommendation now reads as follows:

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					• **mantle cell lymphoma** • **MALT lymphoma.** **Consider FDG-PET-CT imaging to assess response to treatment before autologous stem cell transplantation for people with high-grade non-Hodgkin's lymphoma.** Our experts are concerned about the impact of the following recommendation on clinical practice with respect to remission assessment in patients with Follicular Lymphoma (FL) treated for high tumour burden or advanced symptomatic disease with R-chemotherapy : • **Do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with:** • **follicular lymphoma** • **mantle cell lymphoma** • **MALT lymphoma.** Our experts believe that PET should be considered for remission assessment in FL in addition to DLBCL for the following reasons: • PET is predictive of outcomes in patients treated with high tumour burden FL with R-chemotherapy improving response assessment compared with FLIPI, FLIPI2 and CT. PET-CT identifies a poor prognostic group [Trotman, et al. 2014] in whom closer monitoring or second line treatment may be indicated [Casulo, et al. 2015]. For this reason, PET-CT is recommended in international guidelines for response	'For people with subtypes of non-Hodgkin's lymphoma not listed in the above recommendation (1.2.4), do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management.' The Luminari (2013) Casulo (2013) Trotman (2014) studies were included. An alternative publication from the Dupuis (2012) study was included (Safar 2012)

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					assessment in FL based on three multicentre studies which included 122 [Trotman, et al. 2011], 112 [Dupuis, et al. 2012]and 205 [Luminari, et al. 2014] patients respectively. All reported EOT PET-CT to be predictive of PFS, independent of the FLIPI, and superior to CT-based response. Only one of these studies was included in the NICE documentation. Dupuis was excluded because not all studies were PET-CT but all were attenuation corrected and therefore appropriate for inclusion in this context even if attenuation corrected with a radioactive source rather than CT. The study by Luminari et al and the pooled analysis below were not evaluated. The conclusions of the Trotman publication were considered to be biased in part due to its reliance on local physician interpretation of results. • A pooled analysis of the 3 prospective studies referred to, but not considered in the NICE documentation, using central scan review and DC was published in 2014 [Trotman, et al. 2014]. The analysis included 246 patients all with PET-CT scans available for review. Median FU was 54.8m. 73% of patients were treated with R-CHOP, 15% R-CVP and 12% R-FM. 83% of patients had a negative scan (DS 1-3). The study revealed a significant number of patients had their response re-classified with PET compared to CT-based International Working Group (IWC) criteria, PET-based response was more predictive of PFS and OS than IWC, in the whole group, in the RCHOP-treated patients and in the	

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					responding patients according to IWC. In the whole group, 4y-PFS was 63.4 % (95% CI 55.9, 70.0) for patients with CMR, compared with 23.2% (95% CI 11.1,37.9) for patients without CMR [HR 3.9 (2.5,5.9) p < 0.0001]. The difference in median PFS was very large; 74 and 16.9 months for patients with scans showing CMR and no CMR respectively. Our experts note that with respect to MALT lymphomas the GC may wish to take into account the following publication that demonstrated that FDG avidity was related to site of disease and staging may be appropriate in some MALT lymphomas, Treglia G, Zucca E, Sadeghi R, et al: Detection rate of fluorine-18-fluorodeoxyglucose positron emission tomography in patients with marginal zone lymphoma of MALT type: a meta-analysis. Hematological Oncology 33:113-24, 2015	
87	NCRI-RCP-ACP	General	General	General	The NCRI-RCP-ACP are grateful for the opportunity to respond to the above consultation. We have liaised with The Joint Speciality Committee for Nuclear Medicine and would like to make the following comments.	Thank you.
6	NHS England	Full	General	General	there seems to be a complete neglect of the fact that people do die from Non-Hodgkin's Lymphoma so I would have expected a cross-reference to palliative and end of life care guidance at least.	Thank you for your comment. The topics included in this NICE guideline were determined at a stakeholder workshop and during stakeholder consultation. End of life care was not a topic the guideline committee were requested to address. However we have included links to NICE guidelines on patient experience in adult NHS services, improving

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						outcomes in haematological cancers (patient-centred care), improving supportive and palliative care for adults with cancer and care of dying adults in the last days of life.
3	Nottingham University Hospitals NHS Trust	Full	General	General	The current draft guidance, exemplified by the issues above, represents significant variation from the current UK and international standards of care. Moreover, such changes in practice will negatively and significantly impact on the ability of the NCRI Lymphoma Clinical Study Group to participate in many national and international studies as a result of restrictions on aspects of care considered to be standard practice worldwide.	Thank you for your comments. The Guideline Committee have made amendments which we hope you will find acceptable. These include: • Revisions to the recommendations on confirmation of staging and end of treatment assessment • Deletion of TA65 recommendations from the guideline • Inclusion of TA226 • Supporting information to explain why evidence for bendamustine was not assessed within the guideline.
41	Nottingham University Hospitals NHS Trust	Full	42	General	We are very concerned that by NOT routinely offering baseline PET-CT for patients with Diffuse Large B cell lymphoma (DLBCL) we will consistently under-stage patients in turn impacting calculation of the prognostically valuable IPI score and importantly impact on making an informed decision on central nervous system (CNS) prophylaxis. Page 118, line 44 states that CNS relapse risk should be calculated by extra-nodal involvement and prophylaxis offered where increased risk exists. It is our experience that baseline PET-CT frequently detects additional areas of extra-nodal involvement with DLBCL, particularly adrenal and renal lesions that are missed by CT alone. Thus, in the absence of a baseline PET-CT, we risk not identifying patients with extra-nodal disease who fulfil the CNS prophylaxis criteria and consequently put patients at higher risk of the devastating consequences of	Thank you for your comment. The Guideline Committee acknowledged that in some circumstances carrying out a staging PET-CT scan may result in a change of stage, IPI status and a need for CNS prophylaxis but there is insufficient high quality data to support this. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management.'. The GC have amended the linking evidence to

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					lymphoma CNS relapse. This recommendation is therefore illogical set against the arguments (within this NICE guidance) supporting the use of CNS prophylaxis for patients at risk.	recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.
53	Nottingham University Hospitals NHS Trust	Full	46	35	We are concerned at the recommendation to NOT routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment (end of induction = EOI) for people with follicular lymphoma (FL). The evidence supporting the prognostic value of EOI PET-CT in FL is strong. Up to 1 in 5 patients have FDG-avid disease on EOI PET-CT and clearly have an inferior prognosis. Such patients should be informed of this and counselled appropriately .This finding is used to inform further treatment options, including the value of Rituximab-maintenance, re-biopsy, treatment intensification, frequency and nature of follow-up visits etc.	Thank you for your comment. Please note we have amended our recommendation to make it clear that there are circumstances when an end of treatment scan should be performed in follicular lymphoma but suggest that this should only be when treatment decisions would be changed as a result of that scan.
67	Nottingham University Hospitals NHS Trust	Full	82	10	It is concerning that patients will no longer have access to Bendamustine in combination with Rituximab as first-line therapy of Follicular lymphoma given the published disease control and toxicity benefits as compared to the other immuno-chemotherapy comparators, without significant cost differences. However this decision is explained (process or otherwise), patients will ultimately lose out and NHSE will gain nothing.	Thank you for your comment. We are aware of the data for R-bendamustine but we did not include it as an intervention in this topic as it is a regimen currently undergoing a NICE technology appraisal. We have added the following text in both the Short version of the guideline and in the LETR paragraph of the Full guideline to explain this omission: 'The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with follicular lymphoma , because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first line treatment of advanced indolent non-Hodgkin's lymphoma' was in

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						development. This technology appraisal is currently in development.
76	Nottingham University Hospitals NHS Trust	Full	116	9	It is very concerning that the draft guidance does not recommend Rituximab in combination with any regimen other than CHOP as first-line treatment of DLBCL. Clear evidence and experience exists supporting a number of regimens for DLBCL such as R-GCVP, R-EPOCH, R-CODOXM/RIVAC. We note that the original NICE RCHOP guidance has not been reviewed as planned.	Thank you for your comments. . It was our intention at scoping to include TA65 in the guideline but we have now agreed to omit it as it no longer reflects current practice.
10	Roche Products Limited	Full Full – Appendix B	80-81 34	12 3	In relation to the comment 'PRIMA data suggests no impact of prior rituximab maintenance on effectiveness of subsequent rituximab containing therapy' - extrapolations based on data from the PRIMA study (Salles et al 2013) of maintenance rituximab in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy induction, a very different trial population to the asymptomatic low tumour burden population under consideration in this section, may not be valid. This is a limitation of the analysis that should be considered. We also note the full guideline p. 74 line 12 reports use of the data based on van Oers et al. 2010 (EORTC study) rather than Salles et al. 2013.	Thank you for your comments. The guideline committee accept that there are limitations to making extrapolations from one trial situation to another. However, since the use of rituximab induction in this setting is not standard practice, there is no data available that has directly measured progression in subsequent lines. Therefore the committee considered the approach taken was was reasonable as it was thought to provide the best approximation currently available As discussed in response to comment 63, this aspect was subject to much discussion and extensive sensitivity analysis. In the sensitivity analysis, the results were found to remain unchanged in numerous conservative scenarios. Data from Salles *et al.* (2013) was used in the model and the text in the full guideline has now been updated to reflect this.
60	Roche Products Limited	Full	73	34	To improve clarity of the guideline on the asymptomatic patients suitable for rituximab	Thank you for your comment. Further detail on the study population has been added in the

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					induction, it would be helpful to describe the population in the Ardeshna et al 2014 study in more detail as this study formed the basis of the cost-effectiveness analysis.	relevant section of the economic report.
61	Roche Products Limited	Full	73	42	The study population in Ardeshna *et al* 2014) included >20% stage II patients. The study population also had a relatively high performance status (ECOG >1 were excluded). The absolute risk of progression in stage III/IV 'asymptomatic' patients in all arms (watch & wait, rituximab induction & maintenance) may therefore be under-estimated in the economic analysis.	Thanks for raising a very useful discussion point. Further detail has now been added on this in the discussion section of the full economic report (Appendix A). It should be noted however that if the risk of progression is higher than that suggested in Ardeshna *et al* (2014) then this would only strengthen the argument for intervention rather than observation.
62	Roche Products Limited	Full	73	45	(p73-74) The figures for the % of patients requiring new treatment after 3 years are given as 54% for the watchful waiting arm and 11% for rituximab induction arm; the use of rituximab induction with maintenance was said to further reduce the numbers of patients requiring new treatment to 19% after 3 years. Clearly this cannot be correct as 19% would be an increase not a reduction. In the Ardeshna 2014 publication the figures are: WW 54%, rituximab induction 22% and rituximab induction plus maintenance 12%	Thank you for bringing this to our attention. This was an error in the report with the induction and maintenance figures the wrong way around. It should be 19% for rituximab induction and 11% for rituximab induction with maintenance. The error has been corrected. The absolute values for the rituximab arms are slightly different to those reported in Ardeshna *et al* (2014). This is because the figures applied in the model were estimated using the reported hazard ratios rather than the absolute values.
63	Roche Products Limited	Full	74	9	Response to 2nd line treatment with a rituximab chemotherapy regimen (followed by maintenance) after rituximab monotherapy induction in this 'asymptomatic' low tumour burden patient population is not known. Using data from the van Oers et al. 2010 study of maintenance rituximab in	Thank you for your comment. Since the use of rituximab induction in this setting is not standard practice, there is no data available that has directly measured progression in subsequent lines.

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					previously-treated patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy induction to estimate progression may not be valid.	The data used in the model was thought to provide the best approximation currently available. However, the uncertainty around subsequent treatment lines was an area subject to much discussion at the guideline meetings. We also conducted extensive sensitivity analysis in this area and found that the conclusion remained unchanged. This was the case even when it was assumed that subsequent risk was 50% or even 100% higher for patients initially treated with rituximab.
64	Roche Products Limited	Full	80	12	We are surprised by the recommendation to 'Offer rituximab induction therapy to people with advanced stage (stages III and IV) follicular lymphoma who are asymptomatic.' This is a use of rituximab outside the licensed indications for rituximab, which has therefore not been subjected to the safety & efficacy assessment of the licensing authority and for which the supporting evidence is described in these guidelines as of 'low quality'. An additional area of uncertainty is the assumption on subsequent treatment lines (comments 7 & 9).	Thank you for your comment. It is not unusual for NICE to make recommendations outside the licence indications. The recommendation was based upon the results of the cost-effectiveness analysis, which strongly suggested that rituximab induction is the optimal strategy. Review questions about pharmacological management will usually only include medicines with a UK marketing authorisation for some indication, based on regulatory assessment of safety and efficacy. Use of a medicine outside its licensed indication (off-label use) may be considered in some circumstances; for example, if this use is common practice in the UK, if there is good evidence for this use, or there is no other medicine licensed for the indication. This conclusion was found to be robust as it was unchanged when making some extreme

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						assumptions around some of the key uncertainties (including subsequent treatment lines). The clinical study upon which the analysis was based was originally stated as low quality. However, while the guideline was out for consultation, it was decided that the study should be upgraded to moderate quality because although originally downgraded for imprecision the effect estimate was in fact precise according to our criteria.
69	Roche Products Limited	Full	82	10	We note (page 82, line 6) that recommendations in this guideline will complement existing technology appraisals. The recommendation to 'Offer rituximab maintenance therapy as an option for the treatment of people with follicular non‑Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy' [Technology Appraisal 226, 2011] should be included in this section. NICE guidance TA 226 was put on the static list in 2014 and the recommendation in this section should be in line with recommendations on rituximab maintenance in advanced-stage relapsed or refractory follicular lymphomas (page 82 line 20 of full guideline)	We agree. The recommendations from TA226 on maintenance therapy have now been incorporated into the Short and Full guideline.
110	Roche Products Limited	Short	6	17	The recommendation to offer Rituximab maintenance therapy as an option for the treatment of people with follicular non‑Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy (NICE Technology Appraisal 226) should be included in this section. NICE guidance TA 226 was put on the static list in 2014	Thank you for your comment. TA226 has now been incorporated into the guideline.

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					and the recommendation in this section should be in line with recommendations on rituximab maintenance in advanced-stage relapsed or refractory follicular lymphomas (p. 7 of short guideline). Rituximab maintenance in this indication is recommended in the British Committee for Standards in Haematology and European Society for Medical Oncology clinical practice guidelines.	
111	Roche Products Limited	Short	6	14	The introduction of rituximab induction for patients who would currently be considered for a 'watch and wait' strategy is new to common clinical practice. It would therefore be helpful to have a more detailed description of the patient characteristics of the 'asymptomatic' population in line with the study population in Ardeshna *et al* 2014, as this study formed a significant part of the evidence basis for this recommendation.	Thank you for your comment. The GC did not think it was necessary to add the patient characteristics from the trial to the recommendations. The recommendation in its current form was thought to be specific enough and refers to a group of patients that is well known by the clinical community.
85	Royal College of General Practitioners	General	General	General	The RCGP welcomes this document and has no comments at this stage other than to say it is specialist care.	Thank you.
94	Royal College of Nursing	General	General	General	This is just to let you know that the feedback I have received from nurses caring from people with Non-Hodgkin's lymphoma suggests that there is no additional comments to submit to inform on the consultation of the above draft guidelines. Thank you for the opportunity to review this document.	Thank you.
86	Royal College of Paediatrics and Child Health	General	General	General	Having liaised with the British and Irish Paediatric Pathology Association, we have been informed that members have highlighted that these guidelines should be more explicitly stated to apply to over 16s only. They note that also core biopsy is almost never an appropriate diagnostic investigation of suspected lymphoproliferative	We have included a statement in the methodology section making clear that these guidelines refer to adults (page 7 below line 10). The age that the guideline covers will also be made clear on the NICE website.

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					malignancy in a child.	
96	Royal College of Pathologists	General	**1.10.2**	**Follow up for DLBCL**	The risk of relapse beyond 2 years is <10%. Follow up beyond 2 years therefore will be of low clinical utility.	Thank you for your comment, however this recommendation reflects the evidence reviewed.
97	Royal College of Pathologists	General	**1.6.2**	**1st line treatment of DLBCL**	Rituximab must be recommended as a standard with regimens other than CHOP. R-CODOXM/R-IVAC, R-CHOEP14, DA-EPOCHR are regimens used in high IPI disease and RGCVP, RCEOP, R-miniCHOP used in frail patients with comorbid conditions. The current recommendation is discriminatory to these groups of patients.	Thank you for your comments. It has been agreed with NICE that all references to TA65 can be removed from the guideline.
98	Royal College of Pathologists	General	**1.3.6**	**Treatment of advanced stage asymptomatic FL**	We are surprised that the guideline says "offer rituximab induction therapy" to this group of patients. Whilst rituximab may delay time to chemotherapy there remain many unknowns with this approach including response to rituximab based chemotherapy at next disease progression. For this reason, we think it would be preferable to revise this to "consider rituximab induction therapy."	Thank you for the comment. The evidence underpinning this recommendation was of moderate quality according to GRADE. The strength of the recommendation was also supported by the accompanying cost effectiveness analysis which showed the rituximab induction therapy to be highly cost effective. Therefore the GC agreed that the use of the term 'offer' within this recommendation was appropriate.
99	Royal College of Pathologists	General	**1.6.3**	**1st line treatment of DLBCL**	RCHOP must be recommended as a standard for stage 1 DLBCL. This is standard of care worldwide and the current recommendation (to omit rituximab) would seriously disadvantage the UK NHS patient. It is neither ethically feasible nor desirable to conduct a phase 3 randomised study of CHOP with or without rituximab for stage 1 DLBCL in the current era.	Thank you for your comments. It has been agreed with NICE that all references to TA65 can be removed from the guideline.
100	Royal College of Pathologists	General	**1.3.7**	**Treatment of advance**	R-Bendamustine must be recommended as an option. This regimen is much better tolerated than RCHOP and has been shown to confer significant	Thank you for your comment. We are aware of the data for R-bendamustine but we did not include it as an intervention in this topic as it is

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				d stage sympto matic FL	PFS benefit. Rituximab maintenance is standard of care and must be recommended.	a regimen currently undergoing a NICE technology appraisal. We have added the following text in both the Short version of the guideline and in the LETR paragraph of the Full guideline to explain this omission: 'The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with follicular lymphoma , because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first line treatment of advanced indolent non-Hodgkin's lymphoma' was in development. This technology appraisal is currently in development.
101	Royal College of Pathologists	General	**1.2.1 & 1.2.2:**	**Staging PET scan**	The recommendations limiting the use of staging PET scan to early stage DLBCL, FL and BL is very restrictive. They are contradictory to the royal college of radiologists guidelines and the international consensus of the malignant lymphomas imaging working group both of which recommend staging PET scan for all FDG avid lymphomas. The BCSH DLBCL guidelines (in press) also recommend staging PET scan for all newly diagnosed DLBCL. A staging PET scan is superior to CT scan in: 1. identifying extranodal disease (which may change IPI and influence decision on CNS prophylaxis). 2. focal marrow involvement which may be missed by staging bone marrow examination. 3. areas of high grade transformation in indolent lymphomas	Thank you for your comment. We acknowledge that some radiotherapy guidelines recommend baseline PET scanning to facilitate radiotherapy planning. However this topic was not within the scope of the guideline. Therefore the evidence was not reviewed by the Guideline Committee and we are unable to make recommendations in this area. However we would point out that the International Radiation Oncology Group guidelines does not specify the need for baseline PET-CT scanning. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-

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					In addition a staging PET scan is valuable in assessing the significance of residual FDG avid areas on the end of treatment PET scan. A staging PET scan must therefore be recommended for all FDG avid lymphomas.	Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-CT imaging to confirm staging if the results will alter management.'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area. The guideline committee does not accept that FDG-PET is useful when identifying high grade transformation as non-transformed follicular lymphoma is typically FDG avid.
102	Royal College of Pathologists	General	**1.2.4 & 1.2.5**	**End of treatment PET scan**	Is only recommended for DLBCL and BL but not FL and other NHL. Again, this contradicts published national and international guidelines on imaging FDG avid lymphomas. The prognostic value of end of treatment PET scan is well documented in FL where it is a major predictor of PFS. It is also of considerable value in assessing response in other high grade histologies such as transformed indolent lymphomas. In mantle cell lymphoma, it may be of particular value in assessing for bowel involvement and to assess its response. An end of treatment PET scan must therefore be recommended for all FDG avid lymphomas.	After reviewing the evidence the Guideline Committee concluded there was insufficient high quality data to make a recommendation for the use of interim PET-CT. The evidence showed that end of treatment scans were better predictors than interim ones for these subtypes.. With regard to end of treatment scans for Follicular lymphoma and MALT there is a lack of evidence but we are not suggesting that there are no circumstances in which a PET-CT scan should be performed. We have amended the recommendation to say that they should be carried out only if they change therapy. The recommendation now states,: • **'For people with other subtypes of non-Hodgkin's lymphoma not listed in the above recommendation, do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter**

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						management'. We have also stressed in the linking evidence to recommendations (LETR) table that this is an evolving field and the situation could change as data emerges from recent and ongoing trials, particularly if there is a change of practice with regards to maintenance rituximab therapy. The guideline committee disagrees that there is strong evidence to assess bowel involvement and bowel response for Mantle cell lymphoma.
7	Royal College of Radiologists	Full	General	General	Not recommending staging PET is: 1. Against international guidelines 2. Limit UK ability to participate in trials 3. False economy as more patients will undergo further invasive tests following inconclusive response assessment PET	Thank you for your comment. We acknowledge that some radiotherapy guidelines recommend baseline PET scanning to facilitate radiotherapy planning. However this topic was not within the scope of the guideline. Therefore the evidence was not reviewed by the Guideline Committee and we are unable to make recommendations in this area. However we would point out that the International Radiation Oncology Group guidelines does not specify the need for baseline PET-CT scanning. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation (1.2.1), consider FDG-PET-

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						CT imaging to confirm staging if the results will alter management.'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area
12	Royal College of Radiologists	Full	29	9	*'Consider using FISH (fluorescence in situ hybridisation) to identify a MYC rearrangement in all people newly presenting with histologically high-grade B-cell lymphoma'*. This recommendation would be challenging because until we can routinely use GEP, we should continue to use IHC algorithms. This would put the country at variance with the upcoming WHO recommendations	Thank you for your comment. Gene expression profiling is a not a routine diagnostic test and there is continuing uncertainty around the most appropriate platform to use. IHC are not a surrogate for FISH tests and cannot be used to reliably identify tumours with MYC re-arrangements, which are a key diagnostic and prognostic marker in aggressive lymphoma. This conclusion is based on the evidence review undertaken by the group.
14	Royal College of Radiologists	Full	32	30	'*Do not use immunohistochemistry to assess the prognostic value associated with cell of origin in people with diffuse large B-cell lymphoma.'* This recommendation would be challenging because we use FISH only after IHC. This would again put us at variance with the upcoming WHO recommendations.	Thank you for your comment. The GC agreed that it is inappropriate to recommend IHC algorithms that have been repeatedly shown to have poor diagnostic and prognostic accuracy. The reliability of IHC based cell of origin was part of the evidence review. It is not clear how this relates to the use of FISH.
43	Royal College of Radiologists	Full	42	1	*'Do not routinely offer FDG-PET-CT imaging to confirm staging for people diagnosed with:* *• diffuse large B-cell lymphoma that is stage II or above* *• follicular lymphoma that is non-localised stage II or above* *• mantle cell lymphoma* *• MALT lymphoma (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue)*	Thank you for your comments. It is the belief of the Guideline Committee that the distinction of persisting disease and disease at a new site is of little clinical impact in this clinical context, and where there is uncertainty good clinical practice should be to carry out a biopsy or interval scan.

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					• *Burkitt lymphoma with high-risk features, or stage III or IV'* This recommendation would be challenging because it would be unclear which extra nodal sites (and some nodal sites) were positive before starting therapy. Anything that is positive after therapy therefore could either be a new site or persistent disease. This would potentially influence the need for biopsy, and would change the recommendation for salvage therapy.	
55	Royal College of Radiologists	Full	46	35	*'Offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with: diffuse large B-cell lymphoma or Burkitt lymphoma'.* This recommendation would be challenging because PET radiologists won't report a response assessment unless there is a pre-treatment PET!	We thank you for this comment which succinctly expresses the problem with reporting PET scans in the UK. There is very little published evidence(with no good quality evidence) to support the assertion that a baseline PET-CT scan is required to interpret an end of treatment PET-CT scan, the key question on the end of treatment PET-CT scan being whether lymphoma is 'present or not' (not the quality of response). Good clinical practice mandates that equivocal abnormalities on an end of treatment PET-CT scan should be clinically investigated on merit (usually with interval repeat imaging and/ or biopsy). Due to the uncertainty and lack of evidence as to whether a baseline PET scan is actually required to interpret an end of treatment scan, we have proposed a research recommendation – "In people with Diffuse large B-cell lymphoma stage II or above, does a FDG-PET CT scan have any advantages over the availability of a baseline CT-scan in the correct interpretation of the end of treatment FDG-PET-CT scan".
56	Royal College of	Full	52	19	The RCR are concerned as the distribution of	Thank you for your comment. The guideline

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	Radiologists				anatomical sites treated with radiotherapy differs significantly in the FoRT study (reference below, comment 8). 25% of patients had inguinal nodes irradiated. Necks nodes , as mentioned, were also very common, but there are also extranodal sites which are not mentioned|: orbits, conjunctiva, parotids and scalps or skin	refers to first line therapy of localised FL whereas the FoRT study included patients receiving palliative therapy for local control of more advanced disease.
57	Royal College of Radiologists	Full	52	25	The RCR are concerned that this recommendation has not considered the evidence in the largest trial for low grade lymphoma: Hoskin PJ, Kirkwood AA, Popova B, Smith P, Robinson M, Gallop-Evans E, Coltart S, Illidge T, Madhavan K, Brammer C, Diez P, Jack A, Syndikus I. 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. Lancet Oncol. 2014 Apr;15(4):457-63	Thank you for your comment. The guideline refers to first line therapy of localised FL whereas the Fort study included patients receiving palliative therapy for local control of more advanced disease.
59	Royal College of Radiologists	Full	53	41	The RCR are concerned that this recommendation specifies IFRT to be used. There are now numerous consensuses and good practice publications which recommend ISRT or INRT should be used. References: -Hoskin PJ, Díez P, Williams M, Lucraft H, Bayne M; Participants of the Lymphoma Radiotherapy Group. Recommendations for the use of radiotherapy in nodal lymphoma. Clin Oncol (R Coll Radiol). 2013 Jan;25(1):49-58. doi: 10.1016/j.clon.2012.07.011. Epub 2012 Aug 11. -Specht L, Yahalom J, Illidge T, Berthelsen AK, Constine LS, Eich HT, Girinsky T, Hoppe RT, Mauch P, Mikhaeel NG, Ng A; ILROG. Modern radiation therapy forHodgkin lymphoma: field and dose guidelines from the international lymphoma	The question comparing IFRT and ISRT or INRT was not included within the scope of this guideline. We have amended the recommendations to read local radiotherapy.

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					radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys. 2014 Jul15;89(4):854-62. doi: 10.1016/j.ijrobp.2013.05.005. Epub 2013 Jun 18 -Verhappen MH, Poortmans PM, Raaijmakers E, Raemaekers JM. Reduction of the treated volume to involved node radiation therapy as part of combined modality treatment for early stage aggressive non-Hodgkin's lymphoma. Radiother Oncol. 2013 Oct;109(1):133-9. doi: 10.1016/j.radonc.2013.07.013. Epub 2013 Sep 7. -Campbell BA, Connors JM, Gascoyne RD, Morris WJ, Pickles T, Sehn LH. Limited-stage diffuse large B-cell lymphoma treated with abbreviated systemictherapy and consolidation radiotherapy: involved-field versus involved-node radiotherapy. Cancer. 2012 Sep 1;118(17):4156-65. doi: 10.1002/cncr.26687. Epub 2012 Jan 17.	
68	Royal College of Radiologists	Full	82	10	The RCR are concerned that this recommendation may imply that R-Bendamustine is not recommended as first line therapy; The RCR are concerned that the guideline omits offering Rituximab induction to patients with advanced stage asymptomatic stage 3/4 FL, based on limited data from 1 small trial (the UK W&W trial)	Thank you for your comment. We are aware of the data for R-bendamustine but we did not include it as an intervention in this topic as it is a regimen currently undergoing a NICE technology appraisal. We have added the following text in both the Short version of the guideline and in the LETR paragraph of the Full guideline to explain this omission: 'The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with follicular lymphoma , because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first line treatment of advanced indolent non-Hodgkin's lymphoma' was in development. This technology appraisal is

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						currently in development.
70	Royal College of Radiologists	Full	96	23	The RCR are concerned that this recommendation may imply that Rituximab monotherapy is not an option for patients unfit to receive chemotherapy and progress after eradication therapy.	Thank you for your comment. The Guideline Committee agreed that there are few patients who cannot tolerate a non-intensive chemotherapy regimen such as chlorambucil and the data for Rituximab monotherapy in Gastric Malt lymphomas is not convincing.
71	Royal College of Radiologists	Full	100	29	The RCR are concerned that this recommendation may imply that R-Bendamustine is not considered as treatment option for first line therapy	Thank you for your comment. We are aware of the data for R-bendamustine but we did not include it as an intervention in this topic as it is a regimen currently undergoing a NICE technology appraisal. We have added the following text in both the Short version of the guideline and in the LETR paragraph of the Full guideline to explain this omission: 'The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with follicular lymphoma , because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first line treatment of advanced indolent non-Hodgkin's lymphoma' was in development. This technology appraisal is currently in development.
78	Royal College of Radiologists	Full	116	9	The clinical and cost effectiveness of rituximab in patients with localised disease (Stage I) has not been established. It is recommended that rituximab be used in these circumstances only as part of ongoing or new clinical studies. The RCR are concerned as this recommendation completely contradicts the control arm of INCA, which is our current NCRI trial for patients unable	We agree that TA65 is no longer accepted as current practice and it has been removed from the guideline.

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					to have CHOP. Also, as most patients with early stage disease will have low IPI, they are probably most likely to benefit from Rituximab.	
79	Royal College of Radiologists	Full	118	44	The RCR are concerned that this recommendation as we would offer CNS prophylaxis to patients with disease encroaching the spinal canal	Thank you for your comment. The guideline committee reviewed data on a range of different lymphoma sites that confer an increased risk of progression in the central nervous system. There was insufficient evidence to support disease encroaching the spinal canal as representing an increased risk.
80	Royal College of Radiologists	Full	127	19	The RCR are concerned that this recommendation as patients with an early relapse <6mt and DLBCL may do better with RDHAP	Thank you for your comment. We are unaware of the data you refer to concerning relapse within 6 months.
81	Royal College of Radiologists	Full	131	42	The RCR are concerned that this recommendation recommends R-CODOX-M and not the combination R-CODOX-M/R-IVAC	Thank you for pointing out the error. This has now been amended.
104	Royal College of Radiologists	Short	4	19	PET-CT is currently used for staging all potential stages of DLBCL. The RCR have grave concerns of limiting this to just those patients that are stage I on CT. The reasons for this include: • Firstly, PET-CT has been demonstrated to be more sensitive for bone marrow involvement than bone marrow biopsy in aggressive NHL (Berthet et al, 2013; Khan et al, 2013). The study by Berthet et al demonstrated that FDG PET had a sensitivity of 94% for bone marrow involvement compared to 24% with bone marrow biopsy. PET-CT was also shown to have a higher negative predictive value than bone marrow biopsy as well as being more accurate (98% vs 81%). Khan et al showed that FDG PET demonstrated bone marrow involvement in over double the amount of patients when compared to bone marrow biopsy	Thank you for your comment about the detection of bone marrow involvement. The guideline committee accept that PET CT will pick up a small number of patients with bone marrow involvement not detected by bone marrow biopsy, (particularly if unilateral) but consider that bone marrow biopsy is still the gold standard for bone marrow detection. There is very little published evidence (with no good quality evidence) to support the assertion that a baseline PET-CT scan is required to interpret an end of treatment PET-CT scan, the key question on the end of treatment PET-CT scan being whether lymphoma is 'present or not' (not the quality of response). Good clinical practice mandates that equivocal abnormalities on an end of treatment PET-CT scan should be clinically

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					(33 vs 14 patients). The RCR fear that not being able to perform staging PET-CT in all patients that have DLBCL will lead to the understaging of a significant number of patients. This is especially important as bone marrow involvement in patients with DLBCL can lead to a significant change in management; as these patients often go on to receive CNS prophylaxis. Therefore, without staging FDG PET-CT in all DLBCL patients, a large percentage of patients will receive the incorrect treatment. • Secondly, the presence of a baseline scan improves the accuracy of subsequent response assessment and improves reporter agreement (Meignan et al, 2009). The availability of a baseline scan has been reported to affect the classification of metabolic response in up to 34% of lymphoma patients. (Quarles van Ufford et al, 2010). In this paper, Quarles Van Ufford et al analysed data for all malignant lymphoma but if the DLBCL patients alone are analysed, baseline PET altered interpretation of the post treatment PET in 39% of cases. • In addition, baseline PET is also important for planning radiotherapy, especially using newer techniques that treat smaller volumes than traditional involved-field radiotherapy. An example where PET is useful to help guide radiotherapy is in the treatment of extranodal skeletal disease in DLBCL where consolidative radiotherapy has been shown to improve event free survival (Held et al 2013). The paper analysed nine consecutive prospective trials of the German High-Grade Non-Hodgkin lymphoma Study Group and	investigated on merit (usually with interval repeat imaging and/ or biopsy). Due to the uncertainty and lack of evidence as to whether a baseline PET scan is actually required to interpret an end of treatment scan, we have proposed a research recommendation – "In people with Diffuse large B-cell lymphoma stage II or above, does a FDG-PET CT scan have any advantages over the availability of a baseline CT-scan in the correct interpretation of the end of treatment FDG-PET-CT scan". The Berthet (2013) and Khan (2013) studies were included. Schaefer (2007) was excluded because it included both HD and NHL, and results were not reported separately. Meignan (2009) was excluded because it did not use PET-CT. The cited Quarles van Ufford (2010) meta-analysis was excluded because it did not include any haematological cancer studies. The Held et al 2013 paper highlighted, whilst demonstrating a significant benefit in event free survival for those patients treated with consolidative radiotherapy in addition to a standard regime was not included in our evidence review for this question. This was because our review focused on the staging accuracy of baseline PET-CT, rather than subsequent treatment directed to sites

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					demonstrated a significant benefit in event free survival for those patients treated with consolidative radiotherapy in addition to a standard regime. As PET-CT is known to have a much higher sensitivity and specificity for bone disease in aggressive Non-Hodgkin's Lymphoma when compared to CT and bone marrow biopsy (Schaefer NG et al 2007; Berthet et al, 2013; Khan et al, 2013), omitting PET-CT from staging in this patient group has the potential to lead to under treatment. *-Schaefer NG, Strobel K, Taverna C, et al. (2007) Bone involvement in patients with lymphoma: the role of F-FDG-PET/CT. European Journal of Nuclear Medicine and Molecular Imaging; 34(1): 60-67* *-Berthet, L., Cochet, A., Kanoun, S et al. (2013) In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. Journal of Nuclear Medicine; 54: 1244–1250* *-Khan, A.B., Barrington, S.F., Mikhaeel, N.G. et al. (2013) PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood; 122: 61–67* *-Meignan, M., Itti, E., Bardet, S., Lumbroso, J. et al. (2009) Development and application of a realtime on-line blinded independent central review of interim PET scans to determine treatment allocation in lymphoma trials. Journal of Clinical Oncology; 27: 2739–2741.* *-Quarles van Ufford, H.M., van Tinteren, H.,*	identified. The concept, however, is consistent with our recommendation to consider baseline PET-CT if it will alter management.

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					Stroobants eta al. (2010) Added value of baseline 18F-FDG uptake in serial18F-FDG PET for evaluation of response of solid extracerebral tumors to systemic cytotoxic neoadjuvant treatment: a meta-analysis. Journal of Nuclear Medicine; 51: 1507–1516.	
107	Royal College of Radiologists	Short	5	9	PET-CT is also currently used at the end of treatment response assessment of all stages of follicular lymphoma. This is due to the higher predictive power of PET-CT when compared to CT alone (Trotman J et al 2011; Dupuis J et al 2012). In the latter study, end of treatment PET-CT was more proficient in predicting progression free survival, when compared to CT. This is likely to be due to the poor concordance demonstrated by CT when compared to PET-CT in those patients that had an unconfirmed complete response or partial response by International Workshop Criteria (IWC). PET positivity demonstrated additional discrimination in these groups, in 19 of 46 patients. In the Trotman et al paper PET response, but not conventional IWC response, with CT was also an independent predictive factor for lymphoma progression. This highlights the superior accuracy of PET-CT when compared to conventional techniques. The guidelines above are also in conflict with the recommendations made at the 12th International conference for malignant Lymphoma published in the Journal of Clinical Oncology in 2014 under the title Recommendations for initial evaluation, staging and response assessment of Hodgkin and Non Hodgkin Lymphoma: The Lugano Classification (Cheson BD et al. 2014). These are	With regard to end of treatment scans for Follicular lymphoma and MALT there is a lack of evidence but we are not suggesting that there are no circumstances in which a PET-CT scan should be performed. We have amended the recommendation to say that they should be carried out only if they change therapy. The recommendation now states,: 'For people with subtypes of non-Hodgkin's lymphoma not listed in the above recommendation (1.2.4), do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management'. We have also stressed in the LETR table that this is an evolving field and the situation could change as data emerges from recent and ongoing trials, particularly if there is a change of practice with regards to maintenance rituximab therapy.

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					currently classed as the gold standard guidance for PET-CT in lymphoma. For these reasons the RCR feel that in addition to the draft guidelines, PET-CT is also indicated and should be recommended in the staging of all patients with DLBCL and for the end of treatment response in follicular lymphoma. *-Cheson BD, Fisher RI, Barrington SF et al. (2014) Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. Journal of Clinical Oncology; 32: 3059-3068.* *-Dupuis J, Berriolo-Riedinger A, Julian A, et al. (2012) Impact of [(18)F]fluorodeoxyglucose positron emission tomography response evaluation in patients with high-tumor burden follicular lymphoma treated with immunochemotherapy: A prospective study from the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. Journal of Clinical Oncology; 30: 4317-4322,* *-Trotman J, Fournier M, Lamy T, et al. (2011) Positron emission tomography-computed tomography (PETCT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: Analysis of PET-CT in a subset of PRIMA trial participants. Journal of Clinical Oncology; 29:3194-3200.*	
95	Royal College of Surgeons	General	General	General	Unfortunately, the College will not be providing comments for this request.	Thank you.
30	South Wales Cancer Network	Full	41	32	**PET in Diffuse Large B-Cell Lymphoma** The NICE guidelines do not recommend doing a	The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of

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					PET scan at diagnosis for patients with a new diagnosis of DLBCL. However, they do recommend doing a PET at the end of therapy to confirm that a remission has been achieved. Although there are no published data to show that a baseline PET is helpful for radiologists when interpreting the end of treatment PET, it is the view of our specialist PET radiologists that a baseline PET is hugely helpful in interpreting response. It is the view of our lymphoma MDT that a lack of data to show the importance of the baseline scan is not the same as data to demonstrate a lack of benefit.	opinion and for this reason we have revised the recommendation to: 'For people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation, consider FDG-PET-CT imaging to confirm staging if the results will alter management'. The GC have amended the linking evidence to recommendations (LETR) paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area.
77	South Wales Cancer Network	Full	116	9	**Rituximab plus chemotherapy** The NICE guidelines are recommending that rituximab therapy is only used in combination with CVP or CHOP based therapy for patients with DLBCL. There are good data from the UK showing the benefit of using R-GCVP in elderly patients that are not fit for anthracycline based therapy. There is a NICE technology appraisal expected for the use of Bendamustine with rituximab for NHL as well. In addition there are data, again from the UK, showing the effectiveness of Rituximab in combination with CODOX-M / IVAC in patients with high risk DLBCL. We are aware that these recommendations are taken from NICE technology appraisal guidance 65 but we are concerned that this recommendation does not allow for the use of RGCVP, R-CODOX-M / R-	Thank you for your comments. It was our intention at scoping to include TA65 in the guideline but we have now agreed to omit it as it no longer reflects current practice.

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					IVAC or R Bendamustine, all of which are used in the UK for specific indications. Given the marked improvements in outcomes for patients with DLCBL in recent years due to the addition of rituximab to standard chemotherapy, it seems inconceivable that we would drop out rituximab for patients who require therapies other than CVP or CHOP. In relation to the use of R-Bendamustine, we feel that NICE they should wait for the technology appraisal.	
105	Southend University Hospital NHS Foundation Trust	Short	5	20	We are concerned you have omitted stage 1a follicular lymphoma as treatable with radiotherapy.	The topics included in the scope of this guideline were chosen principally because they address issues that are controversial or there is variation in practice within the UK. Treatment of stage Ia follicular lymphoma was not considered to be either controversial or has variable treatment and therefore no evaluation of radiotherapy for stage 1a disease was carried out. The heading in this section has been amended to reflect this.
106	Southend University Hospital NHS Foundation Trust	Short	5	26	? error – this should read: disease to people with stage IIB follicular lymphoma who are symptomatic	Thank you for your comment. No - We mean IIa who are symptomatic because asymptomatic IIa would be suitable for Rituximab or Watch and Wait
108	Southend University Hospital NHS Foundation Trust	Short	6	19	We are concerned that you have omitted the combination of Rituximab and Bendamustine – as an option for Rituximab + chemotherapy for advanced stage symptomatic follicular lymphoma. This is currently CDF funded and probably a majority choice first line therapy in the UK. The other chemo options currently used in the UK are CVP. CHOP and Chlorambucil. The options offered in para 1.3.7 are based on NICE approved combinations from 2007 and are out of date.	Thank you for your comment. We are aware of the data for R-bendamustine but we were unable to include it as an intervention in this topic as it is a regimen currently undergoing a NICE technology appraisal. We have added the following text in both the Short version of the guideline and in the LETR paragraph of the Full guideline to explain this omission: 'The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with

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						follicular lymphoma , because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first line treatment of advanced indolent non-Hodgkin's lymphoma' was in development. This technology appraisal is currently in development.
109	Southend University Hospital NHS Foundation Trust	Short	6	25	We would suggest including stage IIB with Stage IIIB and Stage IVB –as suitable for R-Chemo	Thank you for your comment. This wording has been taken from a technology appraisal and therefore cannot be changed.
88	The Royal Marsden Hospital	General	General	General	**Diagnosis** **Consider using FISH to identify a *MYC* rearrangement in all people newly presenting with histologically high-grade B-cell lymphoma. If a *MYC* rearrangement is found, use FISH to identify the immunoglobulin partner and the presence of *BCL2* and *BCL6* rearrangements.** • Presence of MYC/double/triple-hit rearrangement by FISH is a negative prognostic but not predictive biomarker in DLBCL. It is therefore unjustified to routinely recommend FISH testing for all patients with presenting with DLBCL, as there is insufficient evidence to alter management at present. • Standard MYC/double/triple-hit assessment would have significant cost and service implications without impact on clinical care.	The guideline committee discussed these recommendations at length and they represent the majority view of the committee. The Guideline Committee accept that in the absence of any high quality data decisions about FISH testing is a matter of opinion and for this reason we have not revised the recommendation.
89	The Royal Marsden Hospital	General	General	General	**Staging** **No routine baseline PET-CT for DLBCL stage ≥ II, FL stage ≥ III, MCL; no end-of-treatment**	Thank you for your comment. We acknowledge that some radiotherapy guidelines recommend baseline PET scanning

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					PET-CT for FL, MCL *Comments regarding baseline PET-CT:* • Improving accuracy of staging with baseline PET-CT is of significant relevance for FDG avid lymphomas other than stage I DLBCL and stage I/II FL, e.g.: - Baseline PET in DLBCL Stage II is essential for patients to be treated with limited course of chemotherapy and consolidation radiotherapy. Without PET information radiation fields would be significantly larger due to the increased uncertainties in target volume assessment. The international standard for radiotherapy is moving from involved field radiotherapy to involved site radiotherapy in keeping with both the International lymphoma radiation oncology group (ILROG) and UK recommendations (Spect et al 2014, Illidge et al 2015, Yaholom et al 2015, Hoskins et al 2013, Hoskin et al 2015). Limiting baseline (and end of treatment) PETs will hinder the UK's Clinical Oncologists' ability to keep up with international radiotherapy standards and increase late toxicity including second malignancies in a group of patients with long term survival and cure rates. - Essential for correct IPI and FLIPI group allocation of DLBCL and FL, respectively. This is important for correct prognostication and for translation of international trial data into clinical practice. • Response criteria for definition of PR and SD take into account difference of FDG avidity compared to baseline and therefore require	to facilitate radiotherapy planning. However this topic was not within the scope of the guideline. Therefore the evidence was not reviewed by the Guideline Committee and we are unable to make recommendations in this area. However we would point out that the International Radiation Oncology Group guidelines does not specify the need for baseline PET-CT scanning. The Guideline Committee accept that in the absence of any high quality data decisions about staging PET-CT scans are a matter of opinion and for this reason we have revised the recommendation to: 'Consider FDG-PET-CT imaging to confirm staging if the results will alter management for people diagnosed with subtypes or stages of non-Hodgkin lymphoma not listed in the above recommendation'. The GC have amended the LETR paragraph to explain the rationale behind this decision and they have also recommended that further research is carried out in this area. The guideline committee does not accept that FDG-PET is useful when identifying high grade transformation as non-transformed follicular lymphoma is typically FDG avid. Follicular lymphoma paradoxically demonstrates intense FDG uptake (with high SUVmax levels) on a PET-CT scan, high grade lymphomas also demonstrate intense FDG uptake, therefore high grade transformation of follicular lymphoma cannot be detected using PET SUVmax levels. We

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					both baseline and end-of-treatment assessments. • The committee states that the recommendations would result in fewer patients with false positive results on staging, but there are no data given on the relevance of this assumption. • The committee states that the recommendation (omission of baseline PET-CT) would allow making more appropriate management decisions, but there are no data provided supporting this. *Comments regarding end-of-treatment PET-CT:* • Baseline PET-CTs are crucial for interpreting end-of-treatment PET-CT scans. • Uncertainty about PET abnormalities at end-of-treatment could result in unnecessary biopsies and distress for patients. • End-of-treatment response by PET-CT has been demonstrated in different studies to be associated with PFS and OS in advanced stage FL. *General comments:* • PET-CT at baseline and end-of-treatment for FDG avid lymphomas is regarded standard of care in international guidelines for DLBCL (NCCN, Lugano consensus guidelines). • The recommendations may significantly disadvantage the position of the UK in international clinical trial participation. This would not only take away treatment options for refractory patients, but would also have negative implications for compassionate use programs and IITs and thus on the UK's general research potential.	would make the point that good practice is to biopsy in cases of suspected transformation based on clinical grounds, including biopsy as required of any disproportionate sites of disease volume increase or change in morphology of lesion/s on imaging. After reviewing the evidence the Guideline Committee concluded there was insufficient high quality data to make a recommendation for the use of interim PET-CT. With regard to end of treatment scans for Follicular lymphoma and MALT there is a lack of evidence but we are not suggesting that there are no circumstances in which a PET-CT scan should be performed. We have amended the recommendation to say that they should be carried out only if they change therapy. The recommendation now states,: 'Do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the findings of the FDG-PET-CT will alter therapy for people with: • follicular lymphoma • mantle cell lymphoma • MALT lymphoma'. We have also stressed in the LETR table that this is an evolving field and the situation could change as data emerges from recent and ongoing trials, particularly if there is a change of practice with regards to maintenance rituximab therapy.

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90	The Royal Marsden Hospital	General	General	General	**Management** **Follicular Lymphoma:** **Consolidation ASCT should be offered in second or subsequent remission (complete or partial) who have not already had a transplant and who are fit enough for transplantation. Consolidation with allogeneic transplant should be considered for patients who are fit enough, have a suitable donor and when ASCT is inappropriate.** • The data to assess effectiveness and cost-effectiveness of transplant are poor, mainly due to trials being non-randomised and only few data being from Rituximab era. In view of the poor quality of data, no recommendation stronger than "consider" should be given. • The probability of relapse for R-Chemo (vs ASCT and alloSCT) used in the cost effectiveness analysis was calculated from results of a study using CHOP only, without Rituximab induction and without Rituximab maintenance and thus significantly underestimates the cost benefit of R-Chemo. • Clinical factors like previous depth and duration of response, FLIPI or histology component of higher grade disease should primarily drive the decision whether to offer ASCT/allogeneic transplant as consolidation in second or subsequent remissions. • Particularly patients with chemo-sensitive disease, e.g. first relapse 5-10 years after initial R-Chemo treatment would have a very high chance of achieving a second long remission with R-Chemo. In view of the higher morbidity and mortality associated with	Thank you for your comments about the generally poor quality of data in the transplant field. Our recommendation to offer ASCT in second or subsequent remission is largely based on the economic analysis carried out for this topic. We accept that there will be some patients (long remissions) for whom this 'offer' recommendation will not be appropriate. Please note it is a 'consider' recommendation not an 'offer' recommendation for allogenenic transplantation. The word 'consider' was used for allogeneic transplantation as the evidence underpinning this recommendation was of low quality as determined by GRADE. The 'consider' recommendation gives flexibility to clinicians to take into account factors such as those that you mention.

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					transplant, a QoL and survival benefit of ASCT/allograft can certainly not be assumed for this chemo-sensitive patient population. • The committee states that the recommendations will likely increase the use of ASCT for FL. This could cause significant capacity issues with longer waiting times for patients with other haematological malignancies requiring transplant. **Offer rituximab induction therapy to asymptomatic patients with advanced stage FL** • Follow-up of the study of Ardeshna *et al.* is too short to justify any such recommendation. **Diffuse Large B-cell Lymphoma:** **Rituximab is recommended for use in combination with a regimen of CHOP for the first-line treatment of people with CD-20 positive DLBCL at clinical stage II, III or IV.** **Rituximab is not recommended for use when CHOP is contraindicated.** • In light of the results of the recently published UK phase II study of R-GCVP in the first-line treatment of patients with de novo DLBCL and cardiac co-morbidity (Fields et al, JCO 2014); the use of rituximab in the first-line treatment of DLBCL should not be limited to CHOP alone. **CNS prophylaxis in DLBCL:** **Explain to people with DLBCL that they may have an increased risk of central nervous system lymphoma if they have 2 or more of the following and that the level of risk increases with the number of factors involved:** • **Elevated LDH**	We agree that follow up is too short in the Ardeshna *et al*. (2014) study and have amended our recommendation to consider Thank you for your comments. It has been agreed with NICE that all references to TA65 can be removed from the guideline. We accept that the incidence of CNS disease in different risk groups seems to vary from trial to trial and country to country. This obviously impacts on the threshold for giving CNS prophylaxis and for this reason the recommendation is to 'consider' rather than 'offer'

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					• **Age >60 years** • **Poor performance status (ECOG score 2 or more)** • **More than 1 extranodal site involved** • **Stage III or IV disease** **Consider CNS-directed prophylactic therapy for people with DLBCL who have 2 or 3 factors that are associated that are associated with increased risk of CNS relapse** • The incidence of CNS relapse with R-CHOP is low, in the R-CHOP 14 v 21 prospective trial CNS relapse occurred in only 1.7% of patients. A similarly low incidence of CNS relapse (1.1%) was demonstrated in a retrospective study of 259 patients (Arkenau et al, Ann Oncology 2007). • Considering patients with 2-3 IPI risk factors will significantly increase the number of patients eligible for CNS prophylaxis in the UK, for example in the recent NCRI R-CHOP 14 v 21 trial 764/1080 (71%) patients had an IPI score of ≥2 (this is without taking account of the potential additional patients with IPI <2, with disease involvement of testis, breast and kidney/adrenal gland). • Patients with 4-5 IPI risk factors would have accounted for 16.5% (179/1,080) of the R-CHOP 14 v 21 cohort. • Consideration of CNS prophylaxis should be limited to patients with high-risk sites of disease as above and **considered** for patients with 4-5 IPI risk factors **at most**. • CNS prophylaxis is an invasive and potentially toxic treatment and the efficacy is unclear. Adoption of such a broad NICE recommendation for CNS prophylaxis will	

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					lead to a significant increase in the use of prophylaxis across the UK and overtreatment of patients with resultant additional impacts on health care services.	
91	The Royal Marsden Hospital	General	General	General	**Comments from:** [redacted] **On behalf of the Royal Marsden Hospital, London & Surrey**	
8	WMUK (Waldenström's Macroglobulinemia UK)	Full	General		We warmly welcome the publication of this very comprehensive survey of the treatment of NHL, but make the following comments. Due to the time in gestation, some of the content perhaps does not reflect developments in treatment over the last year, and likely transformation in some NHL's by the additional of small molecule compounds such as BTK and PI3K inhibitors.	Thank you for your comment. We note the exciting development in BCELL signalling inhibitors. However the assessment of these agents was outside the scope of the guideline. We are aware that some of the content perhaps does not reflect developments in treatment. NICE review published guidelines to assess if an update is necessary.
11	WMUK (Waldenström's Macroglobulinemia UK)	Full	22	1-2	Fig1 includes only ICD10 codes C82-85, thus excluding WM code C88.0 (and some other	Thank you for your comment. Waldenström's was excluded from the scope of the guideline.

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					NHLs). In the list of NHLs at line 15 table 6 WM would likely fit between mantle cell and marginal zone lymphomas.	
113	WMUK (Waldenström's Macroglobulinemia UK)	Appendix E	64	1-19 E 4.1	Appendix E lists NHL types included and excluded from the scope. Waldenström's Macroglobulinemia (WM) or LPL is not excluded nor specifically included. As there is considerable variation in clinical practice in this disease area, transformations and attitude to SCT in treatment ,it suggests that inclusion or at least mention would be beneficial. This cannot be on grounds of rarity: WM = 0.81/100,000 occurrence, other types mentioned:Burkitts 0.17, Mantle Cell 0.36, Splenic /MALT 0.36 (European Surveillance of Rare Cancers Data, RareCare 2011). Mention of WM does not appear anywhere in the main document, which is deeply disappointing.	Thank you for your comment. Waldenström's was excluded from the scope of the guideline.

Registered stakeholders