National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Zanubrutinib for treating Waldenström's macroglobulinaemia ID1427

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Beigene Ltd	Yes, the wording is appropriate.	Thank you for your comment. No change to scope.
	Janssen-Cilag Ltd	No comment	No change to scope.
Timing Issues	Beigene Ltd	BeiGene considers this appraisal to be urgent as zanubrutinib will offer patients and the NHS a new treatment choice for the treatment of Waldenström's macroglobulinaemia irrespective of MYD88 mutational status, with deep and durable responses (Trotman et al. 2020), clinically meaningful advantages in safety and tolerability (Tam et al. 2020), and notable improvements in quality of life from baseline compared with ibrutinib. As Waldenström's macroglobulinaemia is largely a disease of the elderly (Kastritis et al. 2018), there is a need for new treatment options that are well tolerated and suitable for those who are immunosuppressed or who have considerable comorbidities. References	Thank you for your comment. NICE has scheduled this topic into its work programme. No change to scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		Kastritis et al. Ann Oncol. 2018;29 (Suppl 4):41-50. Tam et al. [published online ahead of print, 30 Jul 2020]. Blood. 2020;blood.2020006844. Trotman et al. [published online ahead of print, 22 Jul 2020]. Blood. 2020;blood.2020006449.	
	Janssen-Cilag Ltd	No comment	No change to scope.
Additional comments on the draft remit	Beigene Ltd	No additional comments.	No change to scope.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Beigene Ltd	The information is accurate.	Thank you for your comment. No change to scope.
	Janssen-Cilag Ltd	No comment	No change to scope.
	British Society for Haematology	**IgM molecules are very large and can thicken the blood, reducing its flow through capillaries which can cause nerve damage in the hands and feet.[1,2] Symptoms are highly variable, but the most common ones include severe fatigue, night sweats, lack of concentration,**	Thank you for your comment. The scope has been updated.

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		frequent/persistent infections, breathlessness, sinus problems, and unexplained weight loss. SUGGESTED WORDING: IgM molecules cluster together in groups of five, and as the amount of IgM production rises this can lead to the clinical syndrome of hyperviscosity which may result in headaches. poor mentation, lack of concentration, breathlessness, poor circulation in the organs and limbs, risk of stroke. If the IgM has autoimmune properties, it may result in a range of inflammatory conditions such as neuropathy, autoimmune haemolytic anaemia. The IgM may have cryoglobulin properties which may cause kidney or nerve damage or ulceration of the skin or may form deposits of insoluble proteins resulting in AL-amyloidosis- resulting in neuropathies, heart failure and/or renal failure. Whilst these complications are individually rare, they collectively add up to a significant unmet need. Waldenstroms cells can also infiltrate the central nervous system (CNS) resulting in an entity called Bing-Neel syndrome (BNS). Treatment of this complication requires special consideration as not all chemotherapy treatments penetrate the blood brain barrier (BBB). *There is evidence that BTK inhibitors do penetrate the BBB (Castillo et al. Blood 2019 Jan 24;133(4):299-305. doi: 10.1182/blood-2018-10-879593. Epub 2018 Dec 6.)*	
The technology/ intervention	Beigene Ltd	The description of the technology is accurate, other than: • The brand name is 'Brukinsa®'. • 'It has been studied in a clinical trial in patients with Waldenström's macroglobulinaemia with or without MYD88 mutation, compared with ibrutinib' should read 'It has been studied in a randomised phase III clinical trial in patients with Waldenström's macroglobulinaemia with MYD88 mutation, compared with ibrutinib. Patients without a MYD88	Thank you for your comment. The brand name has been added to the scope. The description of the clinical trial has been updated.

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		mutation were enrolled in this trial in a separate uncontrolled cohort and treated with zanubrutinib'	
	Janssen-Cilag Ltd	No comment	No change to scope.
	British Society for Haematology	Brand name: Brukinsa™	Thank you for your comment. The brand name has been added to the scope.
Population	Beigene Ltd	The population(s) should be defined as: Adult patients with Waldenström's macroglobulinaemia: • who have received at least one previous treatment, or • who have not received previous treatment and are considered unsuitable candidates for chemo-immunotherapy	Thank you for your comment. The population has been updated.
	Janssen-Cilag Ltd	No comment	No change to scope.
	WMUK and Lymphoma Action	We suggest that the population should be adults with WM who are not suitable candidates for standard chemo-immunotherapy or who have relapsed or refractory disease after previous treatment (including ibrutinib). IgM-related conditions such as paraproteinaemic neuropathies, cryoglobulinaemia, secondary cold agglutinin disease and Bing-Neel syndrome are valid and important subgroups to be considered. These entities are often at the low disease burden end of the spectrum (MGUS), frequently possess the MYD88 L265P mutation and cause significant impact on health. They are an important group to consider for a more subtle but highly	Thank you for you comment. The population has been updated. A new subgroup has been added to the scope.

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		efficacious treatment like zanubrutinib. Whilst each subgroup is small in terms of numbers, they collectively add up to a significant total and comprise a definite constellation of unmet clinical need.	
	British Society for Haematology	Adults with WM *including* those with and without the MYD88 L265P mutation. *There is evidence of efficacy of zanubrutinib, in a selected group of patients with MYD88 wild type Waldenström Macroglobulinemia (in press).*	Thank you for your comment. The population has been kept broad to include people with and without MYD88 mutation-positive Waldenström's macroglobulinaemia. People with MYD88 mutation-positive Waldenström's macroglobulinaemia have been included as a subgroup of interest.
Comparators	Beigene Ltd	We agree with the selection of multiple comparators as this reflects the lack of an established standard of care for Waldenström's macroglobulinaemia in England. Data from the WMUK Rory Morrison Registry (a registry with a total 579 Waldenström's macroglobulinaemia patients registered from 19 hospitals across the UK) indicate that a wide range of treatments are prescribed for the treatment of Waldenström's macroglobulinaemia in the UK (WMUK, 2018). In first-line treatment of Waldenström's macroglobulinaemia, the two most common regimens in 2018 for patients considered fit enough to tolerate them were rituximab and bendamustine (BR) and dexamethasone, rituximab and cyclophosphamide (DRC).	Thank you for your comment. The list of comparators has been updated. Ibrutinib has been removed as a comparator as it is currently available through the Cancer Drugs Fund and therefore not considered established

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		In people who have had at least 1 prior therapy, registry data from 2018 indicate that BTK inhibitors are an emerging standard of care and the most frequently used treatment in clinical practice in approximately 18.2% of cases. The next most commonly used treatments were DRC (6.7%) and BR (6.1%). We suggest that comparisons are therefore focused on the most commonly used treatments i.e. ibrutinib, DRC and BR. It should be noted that data for many of the other listed comparator regimens, and in patients who are not eligible for chemo-immunotherapy, are very sparse and may limit the comparisons that can be made. Reference WMUK. The Rory Morrison Registry. 2018. https://www.wmuk.org.uk/research/rory-morrison-wmuk-registry	practice. Please see NICE's position statement on consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product.
	Janssen-Cilag Ltd	1) Ibrutinib is the only targeted product both licensed and approved by NICE for the treatment of patients with Waldenström's macroglobulinaemia (WM). All other treatment options are used off-label and are not approved by NICE for the indication in scope. 2) Ibrutinib is currently available to NHS patients via the Cancer Drugs Fund (CDF). As per NICE position statement, "products recommended for use in the CDF after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. Companies of new cancer products under appraisal should therefore not include treatments recommended for use in the CDF as comparators, or treatment sequence products in their economic modelling"[1]; therefore, ibrutinib cannot be deemed a comparator.	Thank you for your comment. Ibrutinib has been removed as a comparator.

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		1. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf	
	WMUK and Lymphoma Action	**Which treatments are considered to be established clinical practice in the NHS for WM?** *De facto* 'standard of care' consists of use and re-use of cytotoxic agents (typically bendamustine or cyclophosphamide) in conjunction with rituximab. Other chemo-immunotherapy combinations are available and in use, comprising agents that have alternative cytotoxic mechanisms such as purine analogues (cladribine and fludarabine) but their myelosuppressive and immunosuppressive effects are a pertinent concern, along with a risk of second malignancies and myelodysplasia. These concerns are significant in a chronic disease, in which sequential use of multiple lines of chemotherapy takes its toll and leads to a progressive degradation in performance status. We have seen this result in morbidity and mortality from the therapy rather than the disease itself, which is to be avoided. In terms of comparators in people who are eligible for chemotherapy, (R)-CHOP use is restricted to transformation of WM to high grade lymphoma. In some (younger, fitter) patients, other combinations may be used as 2nd and beyond line of therapy such as R-ESHAP or R-GDP- with a view to an autologous stem cell transplant (ASCT). For people not eligible for chemo-immunotherapy, the list of comparators is fair and representative. **Should alemtuxumab be included as a comparator?** No, despite proof-of-principle evidence of efficacy against the disease, the degree of immunosuppression is unjustifiable. **Should bortezomib be included as a comparator?**	Thank you for your comment. R-CHOP has been removed as a comparator. The description of best supportive care has also been updated.

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		In theory, yes as it is an effective agent. However, as it is not commissioned for WM in the UK and therefore not used in practice, it would be an unfair and inaccurate inclusion. **How should best supportive care be defined?** Support of bone marrow and immune system deficiencies due to disease or treatment, including blood product transfusions, use of granulocyte stimulating factors (G-CSF) to support neutrophils counts, plasma exchange for hyperviscosity, intravenous immunoglobulin infusions for hypogammaglobulinaemia secondary to prior chemoimmunotherapy, to manage recurrent severe infections.	
	British Society for Haematology	The use of purine analogues, Fludarabine and Cladribine is no longer recommended in the front line treatment of WM due to concerns regarding toxicity. *This will be reflected in the new BSH guidelines (in preparation)* and is in line with global clinical practice. These agents may be used in the relapse setting. CHOP is not used except for transformed disease. The effective standards of care are DRC or BR. Autologous stem cell transplantation and rarely allogeneic stem cell transplantation is used in younger/fitter patients who have relapsed. Alemtuzumab should not be included (too immunosuppressive to be justifiable). Bortezomib: currently no access in the NHS in the UK so not a fair comparator. Supportive care should include growth factors, blood transfusions, plasma exchange, IVIG if low antibody levels.	Thank you for your comment. The comparators have been updated.

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Outcomes	Beigene Ltd	Yes, the outcomes listed are appropriate and should capture the health-related benefits of zanubrutinib.	Thank you for your comment. No change to scope.
	Janssen-Cilag Ltd	No comment	No change to scope.
	WMUK and Lymphoma Action	Yes, however it is important to be aware of the difference between biochemical progression (rising paraprotein signifying disease progression) and the time to next treatment as many months can pass between these two timepoints - something that is appropriate in the setting of WM.	Thank you for your comment. Both progression-free survival and time to next treatment are included in the scope as outcomes. No change to scope.
	British Society for Haematology	Owing to the plasma cells in lymphoplasmacytic lymphoma, there can be a lag between the disease indicators: anaemia, fatigue, and paraprotein levels, so important to be mindful of assessment of response and progression events. *(Response Assessment in Waldenström's Macroglobulinaemia October 2017* *DOI: 10.1007/978-3-319-22584-5_18* *In book: Waldenström's Macroglobulinemia)*	Thank you for your comment. No change to scope.
Economic analysis	Beigene Ltd	The economic analysis suggested is appropriate.	Thank you for your comment. No change to scope.

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	Janssen-Cilag Ltd	No comment	No change to scope.
Equality and Diversity	Beigene Ltd	No equality issues identified.	Thank you for your comment. No change to scope.
	Janssen-Cilag Ltd	No comment	No change to scope.
Other considerations	Beigene Ltd	The final subgroup listed should read 'people who have not received prior therapy and are considered unsuitable candidates for chemo-immunotherapy'. The statement 'The availability and cost of biosimilars should be taken into account' should be removed as zanubrutinib is a small molecule so this is not applicable.	Thank you for your comment. This subgroup has been removed from the scope as it is covered in the differentiated populations included in the population section. Rituximab biosimilars are available in the UK, and therefore the statement remains relevant.
	Janssen-Cilag Ltd	No comment	No change to scope.
	British Society for Haematology	Would the Acalabrutinib experience be included?	Thank you for your comment. Acalabrutinib

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		Acalabrutinib monotherapy in patients with Waldenström macroglobulinemia: a single-arm, multicentre, phase 2 study *Roger G Owen, MD et al.* *DOI: https://doi.org/10.1016/S2352-3026(19)30210-8*	is not established treatment in UK practice for Waldenström macrogloulinemia and therefore is not included in the scope as a comparator.
Innovation	Beigene Ltd	Yes, zanubrutinib is innovative, and as a second-generation, BTK inhibitor with high potency and selectivity for BTK, represents a 'step-change' in its potential to impact health-related benefits and to improve current treatment options for the management of Waldenström's macroglobulinaemia. The mechanism of action and pharmacodynamics of zanubrutinib are specific and selective for BTK, with sustained BTK occupancy and minimal off-target inhibition of other kinases (Tam et al. 2018). Off-target effects of ibrutinib, a first generation BTK inhibitor, against TEC- and EGFR-family kinases are associated with adverse events including bleeding, rash, diarrhoea and atrial fibrillation (Wu et al. 2016). Due to the specificity of the mechanism of action, zanubrutinib has demonstrated a favourable safety and tolerability profile, with a lower incidence of these adverse events and a lower rate of discontinuation due to adverse events than ibrutinib, allowing consistent and continuous treatment and a greater improvement in quality of life from baseline. Furthermore, zanubrutinib has demonstrated clinically meaningful antitumor activity in patients with MYD88 wild type, with a major response rate of 50.0%, including a very good partial response (VGPR) rate of 26.9% (Garcia-Sanz et al. 2020). There is a particular unmet need in this patient population, where ibrutinib has been found to demonstrate a shorter median survival and a lower probability of response than in those with MYD88 (Treon et al. 2015).	Thank you for your comment. The extent to which the technology may be innovative will be considered in the appraisal. No change to scope.

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		References Garcia-Sanz et al. Journal of Clinical Oncology 2020;38(15):e20056. Tam et al. Future Oncology 2018;14(22):2229-2237. Treon et al. N Engl J Med 2015;372:1430-1440. Wu et al. J Hematol Oncol. 2016;9(1):80.	
	Janssen-Cilag Ltd	No comment	No change to scope.
	WMUK and Lymphoma Action	Yes - it raises the bar in the provision of BTK inhibition in WM with its effectiveness and excellent safety profile. Yes - the QALY is a useful measure of health outcomes, but it is a simplification in the cancer setting and more so in the era of novel therapies. Firstly, the QALY combines changes in morbidity (quality) and mortality (amount) in a single indicator. Secondly, although QALYs are easy to calculate via simple multiplication, the prior estimation of utilities associated with particular health states is a more complicated task. Finally, QALYs form an integral part of one particular type of economic analysis within healthcare, ie cost-utility analysis (CUA). BTK inhibitors are a sea- change in the treatment of Waldenström's macroglobulinaemia, offering the prospect of disease control and prolongation of life with continuous oral therapy. This is literally a new lease of life when prior immunochemotherapy has become less effective. Expressing these benefits in numerical terms is not possible. Based on the Aspen study (https://doi.org/10.1182/blood.2020006844) and the experience of investigators in the study, immeasurable benefits do occur. These provide personal and societal advantages as a result of a remission that enables patients to return to their lives as workers, family members and contributing members of society.	Thank you for your comment. The extent to which the technology may be innovative will be considered in the appraisal. If there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, the committee can take this into account in its decision making. No change to scope.

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	British Society for Haematology	Yes- the Aspen study has demonstrated efficacy and an excellent safety profile, possibly superior to Ibrutinib. Zanubrutinib may also offer an opportunity to overcome the adverse prognosis of wild-type MYD88 disease.	Thank you for your comment. No changes to scope.
Questions for consultation	Beigene Ltd	***Population*** **Is zanubrutinib intended to be offered to people who have not received previous treatment for Waldenström's macroglobulinaemia and are considered suitable candidates for standard chemo-immunotherapy?** No. Zanubrutinib is indicated for people with Waldenström's macroglobulinaemia who have received at least one previous treatment, or who have not received previous treatment and are considered unsuitable candidates for standard chemo-immunotherapy. ***Comparators*** **Have all relevant comparators for zanubrutinib been included in the scope? In particular,** • **Which treatments are considered to be established clinical practice in the NHS for Waldenström's macroglobulinaemia?** Yes – all relevant comparators have been included in the scope. As outlined above, BTK inhibitors are an emerging standard of care in the treatment of Waldenström's macroglobulinaemia. A review of registry data indicates that BTK inhibitors were the most commonly used treatment in clinical practice in the UK in 2018, for adults with Waldenström's macroglobulinaemia who have received at least one prior treatment (WMUK, 2018). The next most commonly used regimens were dexamethasone, rituximab and cyclophosphamide (DRC), and rituximab and bendamustine (BR).	Thank you for your comment. The population and the list of comparators have been updated. The subgroup you refer to has been removed from the scope as it is covered in the differentiated populations in the population section. No other changes to scope.

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		Due to the heterogenous disease, and as treatment is highly personalised based on patient characteristics, a wide range of treatment options can be used. Furthermore, as Waldenström's macroglobulinaemia is a rare disease, comparative data for many treatment options are sparse – due to the limited data available and the wide range of potential comparators, we suggest that the comparisons are focused on the most commonly used regimens in established clinical practice in the NHS (i.e. ibrutinib, DRC and BR). • **Should alemtuzumab included as a comparator?** No. Alemtuzumab is not licensed for the treatment of Waldenström's macroglobulinaemia, and BeiGene is not aware of any recommendations from NICE, or any registry data, that suggest it is used in clinical practice to treat Waldenström's macroglobulinaemia. • **Should bortezomib be included as a comparator?** No. Bortezomib is not licensed for the treatment of Waldenström's macroglobulinaemia. Furthermore, in August 2018, NHS England reviewed bortezomib for relapsed / refractory Waldenstrom's macroglobulinaemia and determined that there was not enough evidence to make the treatment available for routine commissioning (NHS England, 2018). • **How should best supportive care be defined?** The definition of best supportive care is not currently specified in published guidelines. **Are the outcomes listed appropriate?** **Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom zanubrutinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?**	

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		Outcomes The outcomes listed are appropriate (see above for further information). *Subgroups* As also indicated above, the final subgroup listed should read 'people who have not received prior therapy and are considered unsuitable candidates for chemo-immunotherapy'. **Where do you consider zanubrutinib will fit into the existing NICE pathway, Non-Hodgkin's lymphoma?** We expect zanubrutinib to fit alongside ibrutinib in the 'Waldenström's macroglobulinaemia' part of the pathway following 'Managing non-Hodgkin's lymphoma'. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** No. We do not anticipate any barriers. ***Cost comparison*** **Would it be appropriate to use the cost comparison methodology for this topic?** Yes. **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** Zanubrutinib has demonstrated similar clinical efficacy to ibrutinib but a more favourable safety and tolerability profile which may lead to a reduction in resource use associated with the management of adverse events associated with treatment.	

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		Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Yes. Zanubrutinib was studied in ASPEN, the largest phase 3 trial of BTK inhibitors in Waldenström's macroglobulinaemia and the first head-to-head comparison of BTK inhibitors in any disease (Tam et al. 2020). The outcomes measured in the trial included response, PFS and OS, which are widely regarded as appropriate and clinically relevant endpoints to assess the efficacy of anti-cancer therapies. **Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** We are not aware of any new evidence/important ongoing trials reporting in the next year. <u>Reference</u> NHS England (2018) Specialised Services clinical commissioning policy: Bortezomib for Relapsed/ Refractory Waldenstrom's Macroglobulinaemia. Consultation Tam et al. [published online ahead of print, 30 Jul 2020]. Blood. 2020;blood.2020006844. WMUK. The Rory Morrison Registry. 2018. https://www.wmuk.org.uk/research/rory-morrison-wmuk-registry	
	Janssen-Cilag Ltd	"*Should alemtuzumab be included as a comparator?"* While 2014 BCSH guidelines mention alemtuzumab as a potential treatment option in WM patients, there is little evidence of alemtuzumab use in these patients in clinical practice. Alemtuzumab European market authorisation was withdrawn in 2012[1] and the Rory Morrison Registry (RMR) report from 2018[2]	Thank you for your comment. No change to scope.

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		reports no use of alemtuzumab data across 473 UK patients diagnosed with WM. "*Should bortezomib be included as a comparator?"* While 2014 BCSH guidelines recommend bortezomib-containing regimens as suitable in the WM relapse setting, there is little evidence of bortezomib use in clinical practice. The 2018 RMR report[1] shows a very small percentage of WM patients received bortezomib in combination with dexamethasone and rituximab. *"How should best supportive care be defined?"* Best supportive care (BSC) refers to a non-interventional form of treatment (i.e. no active therapy) with the intent of symptom management. In clinical practice BSC primarily includes haematologist visits and management of hyperviscosity. 1. https://www.ema.europa.eu/en/medicines/human/EPAR/mabcampath 2. https://www.wmuk.org.uk/sites/default/files/2020-01/The%20Rory%20Morrison%20WM%20Registry%20Report%20%281%29%20-%20March%202018.pdf	
	WMUK and Lymphoma Action	**Where do you consider zanubrutinib will fit into the existing NICE pathway for Non-Hodgkin's lymphoma?** WM is a rare type of blood cancer with its own distinct characteristics that require specialist treatment and care. At the present time, the NICE guideline [NG52] https://www.nice.org.uk/guidance/ng52 does not include WM at all so it is not possible to comment.	Thank you for your comment. No change to scope.

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	British Society for Haematology	The NICE guideline NG52 does not cite WM at all, so not relevant here.	Thank you for your comment. The reference to NICE guideline 52 has been removed.
Additional comments on the draft scope	Beigene Ltd	No additional comments.	No change to scope.
	Janssen-Cilag Ltd	Leuka no longer exist (Relevant research groups). They have now amalgamated with Leukaemia UK.	Thank you for your comment. The stakeholder list has been updated.
	British Society for Haematology	British Society for Haematology- was not on the list and should be included in the future.	Thank you for your comment. The British Society for Haematology has been added to the list of consultees and commentators.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Leukaemia Care