National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Bristol-Myers Squibb Pharmaceuticals	This is an appropriate topic for NICE to consider.	Comment noted. No actions required.
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	Yes, assuming nivolumab is licensed in line with the NICE proposed single technology appraisal	Comment noted. Following the positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications.

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			Therefore the scope for the non-squamous indication has been amended to reflect this and focus on this population.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	Yes, the referral is appropriate	Comment noted. No actions required.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.

Section	Consultee/ Commentator	Comments	Action
Wording	Bristol-Myers Squibb Pharmaceuticals	The draft remit is appropriate and aligned with the proposed market authorisation sought for nivolumab.	Comment noted. Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. Therefore the scope for the non-squamous indication has been amended to reflect this and focus on this population.
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	Yes	Comment noted. No actions required.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	Yes; assuming that this is the licensed indication; the drug is not yet licensed (Dec 2014)	Comment noted. Following the positive opinion from the CHMP, for the squamous indication, it was

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			decided to go forward with two separate appraisals for the squamous and non-squamous indications. Therefore the scope for the non-squamous indication has been amended to reflect this and focus on this population.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.
Timing Issues	Bristol-Myers Squibb Pharmaceuticals	It is important for NICE to provide a recommendation for the use of nivolumab within the NHS as close to marketing authorisation as possible given the limited treatment options currently available for patients with non-small cell lung cancer (NSCLC).	Comment noted. NICE aims to provide guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted.
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic	Given the paucity of effective treatment options for the therapy area, there is	Comment noted. NICE

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	Oncology Group	a relative urgency to the proposed appraisal	aims to provide guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	This is a highly active drug for some patients and is eagerly anticipated by the cancer community and patients alike. It is important the drug is reviewed as soon as licensed.	Comment noted. NICE aims to provide guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.
Additional comments on the draft remit	Bristol-Myers Squibb Pharmaceuticals	The wording of the remit reflects the proposed marketing authorisation.	Comment noted. Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward

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			with two separate appraisals for the squamous and non-squamous indications. Therefore the scope for the non-squamous indication has been amended to reflect this and focus on this population.
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	No comments	Comment noted.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	No comments	Comment noted.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	Complete and accurate	Comment noted. No actions required.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	No mention of ALK+ NSCLC is given. These patients are a distinct category of NSCLC. Although NICE did not support crizotinib (TA296), crizotinib is standard of care clinically for these patients and is available on the CDF for English patients.	Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. Therefore the scope for the non-squamous indication has been amended to reflect this and focus on this population.

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		Background Paragraph 3: "NICE recommends docetaxel monotherapy afatinib and erlotinib as options…" a word is missing, as this sentence doesn't quite make sense	Thank you for this comment. The scope has been updated.
		"non-targeted chemotherapy" is a meaningless term, since all chemotherapy is non-targeted by definition.	Thank you for the comment. The scope has been updated for clarity.
		The background does not clarify that EGFR mutation positive untreated patients are generally treated with gefitinib (TA192), erlotinib (TA258), or afatinib (TA310).	The remit of this scope includes only previously treated locally advanced or metastatic non-squamous non-small cell lung cancer. The background information therefore focuses on treatments for previously treated disease.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.
The technology/ intervention	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	Yes	Comment noted. No actions required.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	Yes	Comment noted. No actions required.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.
Population	Bristol-Myers Squibb Pharmaceuticals	We recommend the wording in this section be amended as follows: [redacted]	Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. Therefore the scope has been amended to focus on non-squamous cancers, reflecting the

Section	Consultee/ Commentator	Comments	Action
			anticipated marketing authorisation.
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	Yes	Comment noted. Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. Therefore the scope has been amended to focus on non-squamous cancers, reflecting the anticipated marketing authorisation.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	Yes, assuming this is the licensed indication	Comment noted. Following the positive opinion from the CHMP, for the squamous

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			indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. Therefore the scope has been amended to focus on non-squamous cancers, reflecting the anticipated marketing authorisation.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.
Comparators	Bristol-Myers Squibb Pharmaceuticals	The comparators listed in the draft scope are representative the standard treatments used in the NHS. However, they are not all relevant comparators for nivolumab and we suggest the following amendments to the draft scope: <u>Non-squamous EGFR-TK mutation positive tumours:</u> After one prior therapy: • The clinical trials for nivolumab recruited patients who had received prior therapy and specifically, were required to have received a platinum containing doublet chemotherapy treatment before they could be enrolled. Therefore, platinum therapy in this section of the scope is not an appropriate comparator	Thank you for your comments. Attendees at the scoping workshop extensively discussed the list of comparators and the scope has been updated to reflect the treatment options currently used in UK clinical practice.

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		for nivolumab. • Afatinib - In the situation where a patient is eligible for an EGFR-TKI therapy due to delayed confirmation of mutation status (note, erlotinib and gefitinib are also approved therapies in this setting), a patient would typically receive this targeted therapy. Therefore patients who are prescribed afatinib (gefitinib or erlotinib) after one prior therapy are not appropriate comparators for nivolumab at this time. After two prior therapies (an EGFR-TKI and one other therapy): • There is no existing NICE guidance for treatment after two prior therapies. However, both docetaxel and best supportive care are likely to be options used in routine clinical practice. <u>Non-squamous EGFR-TK mutation negative tumours:</u> After one prior therapy: • No comments After two prior therapies: • There is no existing NICE guidance for treatment after two prior therapies. However, the treatment options listed are likely to be the options used in routine clinical practice. <u>Squamous tumours:</u> After one prior therapy: • No comments After two prior therapies: • No comments Please note that while the comparators discussed above may represent	Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. The comparators have been amended to include only treatments for non-squamous cancers, consistent with the anticipated marketing authorisation.

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		treatments used in the NHS, it is currently unclear whether comparative evidence will be available to compare all of these treatments in the different settings discussed with nivolumab.	
	Boehringer Ingelheim	Nintedanib is listed as a comparator for Non-squamous EGFR-TK mutation positive tumours as well as for for Non-squamous EGFR-TK mutation negative tumours. This is only the case for patients with tumours of adenocarconoma histology and having received 1st line chemotherapy (as stated in the marketing authorisation for nintedanib).	Comment noted. Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. The comparators have been amended to include only treatments for non-squamous cancers, consistent with the anticipated marketing authorisation.
	British Thoracic Oncology Group	For Squamous tumours after one prior therapy, Erlotinib should be included as a comparator as well as Docetaxel monotherapy. I do not think TA162 excludes squamous cancers.	This table focuses on the non-squamous indication only. Regarding the update of the scope for the squamous indication, please refer to the response table for consultation for the

Section	Consultee/ Commentator	Comments	Action
			squamous indication.
		Crizotinib and ceritinib should be included as comparators for ALK+ patients without additional treatment options.	Comment noted. Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. The comparators have been amended to include only treatments for non-squamous cancers, consistent with the anticipated marketing authorisation.
	Eli Lilly	Pemetrexed in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology. Pemetrexed is also indicated as monotherapy for the second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology. Pemetrexed is therefore not licensed as a combination therapy in a previously treated patient population. Since NICE TA181 was published it has become the first line standard of care in accordance with the NICE recommendation. It has also not been included in any other recent or ongoing NSCLC technology	Thank you for your comments. Attendees at the scoping workshop extensively discussed the list of comparators and the scope has been updated to reflect the treatment options currently used in UK clinical practice.

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		appraisals in the second line setting. The relevance and use in clinical practice of pemetrexed plus platinum in the proposed patient population is unsubstantiated and not in keeping with its marketing authorisation.	Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. The comparators have been amended to include only treatments for non-squamous cancers, consistent with the anticipated marketing authorisation.
	NCRI/RCP/RCR /ACP	The grouping of Non-squamous EGFR-TK mutation positive tumours, Non-squamous EGFR-TK mutation negative tumours, Squamous tumours is not appropriate. This takes no account of EGFR unknown results (molecular failures/samples unsuitable for molecular analyses) and the small numbers of squamous NSCLC that are EGFR mutation positive The correct classifications should be EGFR mutation positive, EGFR mutation negative/unknown squamous NSCLC, EGFR mutation negative/unknown non-squamous NSCLC. Non-squamous EGFR-TK mutation positive tumours: it is unclear why afatinib is singled out as a comparator, when erlotinib is also used, if patient is EGFR-TKI naïve and progressed after chemotherapy. Nintedanib should be referenced as nintedanib-docetaxel as the drug is	Thank you for your comments. Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. The comparators have been amended to include only treatments

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		licensed to be given in combination.	for non-squamous cancers, consistent with the anticipated marketing authorisation.
		Squamous tumours: after one and two prior therapies, erlotinib is indicated and licensed.	Thank you for your comments. Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. This table focuses on the non-squamous indication only. Regarding the update of the scope for the squamous indication, please refer to the response table for

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			consultation for the squamous indication.
		Non-squamous EGFR-TK mutation negative tumours: pemetrexed is a second-line comparator (available on CDF and licensed) for patients that did not receive 1st line pemetrexed (eg relapsing early after chemo-radiotherapy or adjuvant post surgical chemotherapy).	Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. The comparators have been amended to include only treatments for non-squamous cancers, consistent with the anticipated marketing authorisation.
	Royal College of Pathologists	No comments	Comment noted.

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	Roche Products	If best supportive care is to be considered as a comparator it should be considered in every line as a large proportion of patients still receive best supportive care rather than active treatment. Nintedanib is stated as a montherapy however according to the final scope it should be considered as a combination therapy with docetaxel. It also seems logical that wherever docetaxel monotheapy is stated as an option nintedanib plus docetaxel should also be stated. For patients with non-squamous EGFR-TK mutation positive tumours Erlotinib should be included as a comparator in second line treatment (see TA162). In this same subgroup Eroltinib should also be considered as a treatment option in third line.	Thank you for your comments. Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. The comparators have been amended to include only treatments for non-squamous cancers, consistent with the anticipated marketing authorisation for nivolumab. Best supportive care is included as a comparator.
Outcomes *Will these outcome measures capture the most*	Bristol-Myers Squibb Pharmaceuticals	The outcomes included in the draft scope are appropriate.	Comment noted. No actions required.
	Boehringer Ingelheim	No comments	Comment noted.

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important health related benefits (and harms) of the technology?	British Thoracic Oncology Group	Yes	Comment noted. No actions required.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	Yes	Comment noted. No actions required.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.
Economic analysis	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	No comments	Comment noted.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	No comments	Comment noted.
	Royal College of	No comments	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	Pathologists		
	Roche Products	No comments	Comment noted.
Equality and Diversity	Bristol-Myers Squibb Pharmaceuticals	No equality issues have been identified.	Comment noted. No actions required.
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	No comments	Comment noted.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	No comments	Comment noted.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.
Innovation	Bristol-Myers Squibb Pharmaceuticals	Nivolumab is a fully human monoclonal immunoglobulin (IgG4) antibody that specifically binds to PD-1 receptor on the surface of immune cells and restores T-cell activity by blocking the binding of the PDL1 and PD-L2 ligands found at the tumour site to PD-1 receptors on immune cells. This approach, enabling the body's own immune system to target cancer, is novel in NSCLC. Preliminary data from phase I and II studies in pre-treated patients suggests a	Comment noted. No changes to the scope required.

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		potentially clinically significant overall survival benefit. Furthermore, the clinical development programme is designed to demonstrate a benefit of this approach regardless of histology (squamous or non-squamous) and PD-L1 status in the pre-treated setting. Nivolumab therefore represents a 'step change' in terms of mechanism of action and potential clinical efficacy, in an area of unmet clinical need.	
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	This is a novel treatment strategy with promising trial data for a disease with a high unmet therapeutic need. It has the potential to be a step change in the way advanced non-small cell lung cancer is managed.	Comment noted. No changes to the scope required.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	Yes: this is first in class for lung cancer and a potential step-change in the management of these patients	Comment noted. No changes to the scope required.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.
Other considerations	Bristol-Myers Squibb Pharmaceuticals	Please note unlike EGFR-TK and ALK, PD-L1 is not a genetic marker, it is an immunologic marker.	Comment noted. The scope has been updated to reflect this.

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	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	No comments	Comment noted.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	No comments	Comment noted.
	Royal College of Pathologists	The Royal College of Pathologists is pleased to see the inclusion of biomarker testing in the remit. The expected cost of identifying suitable patients and the cost and timescale of the infrastructure needed to introduce routine PDL1 testing should be taken into account.	Comment noted.
	Roche Products	No comments	Comment noted.
Questions for consultation	Bristol-Myers Squibb Pharmaceuticals	Nivolumab would be used to treat both squamous and non-squamous tumours.	Comment noted. No actions required.
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	No comments	Comment noted.

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	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	**Which treatments are considered to be established clinical practice in the NHS for locally advanced or metastatic NSCLC that has progressed after prior chemotherapy?** as described in "comparators" section: EGFR Mutation positive patients are treated with platinum-doublet chemotherapy (cisplatin/carboplatin+ usually pemetrexed) after relapse on EGFR kinase inhibitor, and thereafter mono-chemotherapy (usually doectaxel) EGFR wild-type/unknown non-squamous patients are usually treated after relapse from chemotherapy either with erlotinib or docetaxel. Best supportive care is always an option for patients unsuitable for anti-cancer systemic therapy. **Should crizotinib and ceritinib for previously treated anaplastic lymphoma kinase (ALK) positive NSCLC be included as comparators?** Yes **How should best supportive care be defined?** There is no standard definition though generally it would exclude systemic anti-cancer treatment but include radiotherapy and palliative surgical procedures and palliative therapies eg analgesics.	Thank you for your comments. Attendees at the scoping workshop extensively discussed the list of comparators and the scope has been updated to reflect the treatment options currently used in UK clinical practice. Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications. The comparators have been amended to include only treatments for non-squamous cancers, consistent with the anticipated marketing authorisation for nivolumab. Best

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			supportive care is included as a comparator.

Section	Consultee/ Commentator	Comments	Action
		Would nivolumab be used to treat squamous or non-squamous tumours? Or both? Both	Thank you for your comment. Following the positive opinion from the CHMP, for the squamous indication, it was decided to go forward with two separate appraisals for the squamous and non-squamous indications.. The scope has been amended to reflect the anticipated marketing authorisation for non-squamous tumours.
		Are the subgroups suggested in 'other considerations' appropriate? **and** **Are there any other subgroups of people in whom nivolumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No, not currently, but perhaps more data will emerge during the regulatory submission.	Comment noted. No actions required.
		Should any other genetic markers be considered? No	Comment noted. No actions required.
		Where do you consider nivolumab will fit into the existing NICE	Comment noted. No

Section	Consultee/ Commentator	Comments	Action
		pathway, Lung cancer? This depends on the regulatory submission, but it is anticipated to be indicated in patients with relapsed NSCLC regardless of molecular status unsuitable for or declining further anti-cancer systemic therapy. There are no obvious equality issues	actions required.
		Do you consider nivolumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes, nivolumab is a first-in class therapy for NSCLC and is a game-changer. It would be classified as a step-change in the management of NSCLC	Comment noted. No actions required.
		Do you consider that the use of nivolumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No	Comment noted. No actions required.
		Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. N/A	Comment noted. No actions required.
		NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)	Comment noted. No actions required.

Section	Consultee/ Commentator	Comments	Action
		STA is appropriate	
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	Regarding the appropriateness of the subgroups PD-1/PDL-1 positivity should be considered on both tumour and tumour-infiltrating lymphocyte.	Comment noted. No actions required.
Additional comments on the draft scope	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	Boehringer Ingelheim	No comments	Comment noted.
	British Thoracic Oncology Group	No comments	Comment noted.
	Eli Lilly	No comments	Comment noted.
	NCRI/RCP/RCR /ACP	This submission should be suitable to be judged by end-of-life criteria	Comment noted. No actions required.
	Royal College of Pathologists	No comments	Comment noted.
	Roche Products	No comments	Comment noted.

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

Department of Health

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Afiya Trust	NICE Secretariat		Removed	This organisation is no longer active/engaging with NICE therefore Afiya Trust been removed from the matrix under 'patient/carer groups'
2.	Equalities National Council	NICE Secretariat		Removed	This organisation has narrowed it remit and therefore Equalities National Council been removed from the matrix under 'patient/carer groups'