National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Pegaspargase for treating acute lymphoblastic leukaemia
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Royal College of Pathologists and British Society for Haematology (BSH)	Yes	Comment noted. No action required.
Wording	Baxalta UK	No. The indication states "without asparaginase", which is incorrect. Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients	Comment noted. The comment refers to description of population which has been updated accordingly.
Timing Issues	Leukaemia CARE	Although there is an overall survival rate of 80% in childhood cases (at five years) of ALL, the survival rate drops to 35% (at five years) for adults. It can be suggested then that there is an urgent need for alternative treatment options for adults. In particular, there is a clear need for more effective and more tolerable treatments for less fit patients that may not be able to tolerate aggressive treatments such as chemotherapy.	Comment noted. Once an appraisal topic has been referred from the Department of Health, NICE aims to provide guidance to the NHS

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		There is also no current NICE guidance for treating ALL as mentioned in the draft scope document. We would therefore suggest that there is an urgent need to assess the treatment options available to ALL patients.	within 6 months from the date when the marketing authorisation for a technology is granted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Baxalta UK	Baxalta wish to highlight the comment that there is currently no NICE-evaluated products in ALL, and that most treatment options are administered under trial conditions. They are also predominantly curative. As noted, ALL is most common in children, teenagers and young adults, with 65% of cases diagnosed in people under the age of 25. (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all#heading-Zero). Patients have various risk factors which will determine their stratification for treatment, including high vs. standard risk of disease, which determines the dosing regimen. Baxalta would, therefore, disagree with the overarching mention of "high vs low dose" asparaginase and chemotherapy, and would suggest the removal of the words "high dose" and "low dose". We would suggest this wording: asparaginase therapy plus standard chemotherapy is used for patients with an ALL diagnosis, in line with UK and internationally accepted treatment regimens	Comment noted. No action required. Comment noted. No action required. Comments noted. The reference to high dose asparaginase has been removed from the scope. Comment noted. The treatment pathway stated in the scope is in line with the suggestion. No action required.

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The technology/ intervention	Baxalta UK	Yes	Comment noted. No action required.
	National Cancer Research Institute (NCRI)/ Royal College of Physicians **(**RCP)/ Association of Cancer Physicians (ACP)	We agree that the polyethylene glycol conjugation of asparaginase is expected to extend its duration of activity. With regard to improved tolerability, this is accurate in that there would be fewer allergic and anaphylactic reactions. There is also an issue of so called 'silent inactivation' in which there is an immune reaction which inactivates the drug but produces no symptoms in the patient. It is given intramuscularly or intravenously.	Comments noted. The description of the technology has been updated to include that polyethylene glycol conjugation is also expected to improve bioavailability.
	Royal College of Pathologists and BSH	"expected to extend its duration of activity and improve tolerability" - this is true as far as their being fewer allergic and anaphylactic reactions. There is also a issue of so called 'silent inactivation' in which there is an immune reaction which inactivates the drug but produces no symptoms in the patient	Comments noted. The description of the technology has been updated to include that polyethylene glycol conjugation is also expected to improve bioavailability.
Population	Baxalta UK	Children, Adolescents and adults with acute lymphoblastic leukaemia	Comment noted. Attendees at the scoping workshop agreed that population as described in the scope covers children, adolescents and adults, therefore no change

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			had been made.
Comparators	Baxalta UK	Baxalta wish to clarify that most comparators listed are used in **conjunction with** asparaginase, and are therefore not comparators themselves, which is also the rationale for our comments on the Contributor matrix document. NICE's guidance states "A comparator technology is one that is currently used in the NHS and could be replaced by the intervention, if recommended." (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance). Baxalta wish to highlight that Pegaspargase IS the standard asparaginase treatment currently used in the NHS. This is demonstrated by the 2014 SACT data for ALL. If Pegaspargase were not available then the following 2 alternatives could potentially be used in conjunction with standard accepted concomitant chemotherapy combinations as listed in the comparator section : • L-asparaginase (E.coli) • Erwinia l-asparaginase Baxalta would like to highlight that there is currently no NICE–evaluated product for ALL, with treatment being based on clinician choice, mainly in a clinical trial setting. L-asparaginase (E.coli) is unlicensed in this indication and has not been evaluated by NICE.	Comment noted. The comparators in the scope have been updated to; Non-PEGylated form of • *Escherichia coli* derived L-asparaginase plus standard chemotherapy • *Erwinia chrysanthemi* derived L-asparaginase (crisantaspase) plus standard chemotherapy. Comment noted. The scope tends to be inclusive and lists all potentially relevant comparators. Technologies that do not have a marketing authorisation can still be considered comparators if they are

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			a part of established clinical practice (see Guide to the methods of technology appraisal, sections 6.2.1–4).
	NCRI/RCP/ACP	The comparators here are unclear as these are standard Acute Lymphoblastic Leukaemia (ALL) drugs used in combination. They are not comparators for asparaginase, but are used in conjunction with asparaginase. The description of 'high dose asparaginase' is also unclear as we are not aware of any high dose asparaginase regimens. Should this refer to high dose methotrexate instead?	Comment noted. The comparators in the scope have been updated to; Non-PEGylated form of • *Escherichia coli* derived L-asparaginase plus standard chemotherapy • *Erwinia chrysanthemi* derived L-asparaginase (crisantaspase) plus standard chemotherapy. The reference to 'high dose' asparaginase has been removed from the scope.
	Royal College of	These are standard ALL drugs used in combination – they are not	Comment noted. The

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	Pathologists and BSH	comparators for asparginases but used in conjunction with asparaginse "High dose asparaginase (for people without known hypersensitivity to asparginase)" Unsure what this means. I don't know of any high dose asparaginase regimens – do they mean high dose methotrexate?	comparators in the scope have been updated to; Non-PEGylated form of • *Escherichia coli derived* L-asparaginase plus standard chemotherapy • *Erwinia chrysanthemi* derived L-asparaginase (crisantaspase) plus standard chemotherapy. The reference to 'high dose' asparaginase has been removed from the scope.
	Leukaemia CARE	At present the treatment options available to ALL patients are extremely limited. As such, there is an urgent need for alternative treatment options. Pegaspargase appears to offer an innovative, effective alternative. The treatment options for patients are further reduced if they are hypersensitive to asparaginase (used in both induction and consolidation chemotherapy). For these patients, access for new treatment options is even more urgent. Additionally, could a stem cell transplant be considered as a relevant	Comment noted. Attendees heard that pegaspargase is already an established clinical practice and patients in the NHS have access to

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		comparator?	pegaspargase. Clinical experts at the scoping workshop considered that stem cell transplant is used for treating refractory or relapsed ALL and therefore is not an appropriate comparator for pegaspargase.
Outcomes	Baxalta UK	**Overall Survival & Progression Free Survival:** Baxalta agrees that it is appropriate to measure "Overall Survival", but, as this disease often leads to a cure, we would advise replacing "Progression Free Survival" with "Event Free Survival", as this is likely to be more representative in this disease area. **Treatment response rates (including cytogenetic and haematologic responses)** Baxalta would like to highlight that Cytogenetic responses are not used in the ALL disease area as a measure of response	Comment noted. The scope has been updated to include event free survival and to remove cytogenetic response.
	NCRI/RCP/ACP	It will be very difficult to assess these straightforwardly as asparaginase is used as part of a multi drug combination. 'Treatment response rates' and 'time to and duration of response' are not relevant to adult ALL. It is worth noting that asparaginase activity (and aspargine depletion) can be monitored and anti-asparginse antibodies can be quantified. This is not mentioned within the document but may be more realistic than the clinical endpoints, there is a lot of literature available on this.	Comments noted. The scope has been updated to include asparaginase activity and to remove 'time to and duration of response'. Clinical experts at the scoping workshop considered that treatment response

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			rate is an appropriate outcome.
	Royal College of Pathologists and BSH	A straight forward assessment of this will be very difficult as asparaginase is used as part of a multi drug combination. It's not mentioned at all that asparaginase activity (and aspargine depletion) can be monitored or that anti-asparginse antibodies can be quantified. These may be more realistic than the clinical endpoints and there is a lot of literature on them.	Comment noted. The scope has been updated to include asparaginase activity as an outcome.
Economic analysis	Baxalta UK	It is important to recognise the lack of data where non NICE appraised, unlicensed medicines are concerned, as stated in the Methods guide*: "Specifically when considering an 'unlicensed' medicine, the Appraisal Committee will have due regard for the extent and quality of evidence, particularly for safety and efficacy, for the unlicensed use".* NICE should also recognise that this will also add to the uncertainty. SACT data also highlights the high percentage of patients receiving treatment via clinical trials.	Comment noted. The uncertainties associated with the lack of robust data will be considered by the Appraisal Committee in due course. Comment noted. No action required.
Equality and Diversity	No comments received		
Innovation	Leukaemia CARE	As suggested in the draft scope, pegaspargase is a polyethylene glycol conjugation of asparaginase and is expected to extend its duration of activity and improve tolerability of the drug, making it a more effective treatment option for ALL patients. Therefore, we consider the technology to be innovative.	Comment noted. The innovative nature of pegaspargase will be considered during the course of the appraisal.
Other	Baxalta UK	**Is the subgroup suggested in 'other considerations' *(people with known hypersensitivity to asparaginase)* appropriate?**	Comments noted. The

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considerations		• No – these patients would not be eligible for any asparaginase products due to their hypersensitivity **Are there any other subgroups of people in whom pegaspargase is expected to be more clinically effective and cost effective, or other groups that should be examined separately?** • No	scope has been updated to remove the subgroups.
	NCRI/RCP/ACP	Peg asparaginase is considered potentially more effective and cost effective in every situation than standard non pegylated asparaginase by most ALL experts and is pretty much standard of care in pediatric ALL throughout the world. In the UK there is a large ongoing trial in adults UKALL14 one aim of which is to determine the toxicity and tolerability of peg-asp in a large patient population (N=760) The trial in paediatrics UKALL2011 employs peg asp as standard of care and did the previous paediatric trial UKALL2003. We would therefore advise that NICE should have relevant workshop attendees to cover this trial and the paediatric angle, in general. If pegasparginse was not available in the UK it would be really unfortunate and wrong on many levels including having a detrimental impact making on two large, ongoing national trials	Comments noted. No action required Comment noted. NICE aims to identify the widest range possible of relevant consultees and commentators who have an interest in the technology or disease area including patient and professional groups. NICE recognises the

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			importance of the clinical expertise into the development of the scope and values all specialist input from patient groups, NHS commissioners and healthcare professionals provided at consultation and during the workshop discussions. The Appraisal Committee will deliberate the impact of its recommendation on all aspect of the patient care including on-going clinical trials, in due process.
	Royal College of Pathologists and BSH	Pegasparaginase is considered potentially more effective and cost effective in every situation than standard non pegylated asparaginase by most ALL experts and is pretty much standard of care in paediatric ALL throughout the world. In the UK there is a large ongoing trial in adults UKALL14 one aim of which is to determine the toxicity and tolerability of peg-asp in a large patient	Comment noted. No action required. Comment noted. NICE

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		population (N=760). The trial in paediatrics UKALL2011 employs peg asp as standard of care and did the previous paediatric trial UKALL2003. It would be wise to consult [redacted] on this. If pegasparginse was not available in the UK it would be very unfortunate and risk causing harm to two large, ongoing national trials.	aims to identify the widest range possible of relevant consultees and commentators who have an interest in the technology or disease area that also include patient or professional groups. NICE recognises the importance of the clinical expertise into the development of the scope and values all specialist input from patient groups, NHS commissioners and healthcare professionals provided at consultation and during the workshop discussions. The Appraisal Committee will deliberate the impact of its recommendation on

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			all aspect of the patient care including on-going clinical trials, in due process.
NICE Pathways	Baxalta UK	**Place in treatment pathway**: • Pegaspargase is likely to be used in all treatment phases, as per the comparator section in the draft scope. **Where do you consider pegaspargase will fit into the existing NICE pathway, Blood and bone marrow cancers?** • At present, ALL is not included in this pathway, so would need to be included as a separate "arm"	Comment noted. The NICE pathway will be reviewed following publication of the guidance.
	NCRI/RCP/ACP	**Where do you consider pegaspargase will fit into the existing NICE pathway, Blood and bone marrow cancers?** There is currently nothing in the pathway for acute lymphoblastic leukaemia but if there was it would fit into 'person with leukaemia'.	Comment noted. The NICE pathway will be reviewed following publication of the guidance.
	Royal College of Pathologists and BSH	**Where do you consider pegaspargase will fit into the existing NICE pathway, Blood and bone marrow cancers?** There is currently nothing in the pathway for acute lymphoblastic leukaemia but if there was it would fit into "person with leukaemia"	Comment noted. The NICE pathway will be reviewed following publication of the guidance.
	Leukaemia CARE	**Where do you consider pegaspargase will fit into the existing NICE pathway, "Blood and bone marrow cancers?"** Due to the lack of NICE guidance on ALL, there is currently no provision in the NICE pathway for the treatment of ALL. As such, it is important that a	Comment noted. The NICE pathway will be reviewed following publication of the

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		pathway for the treatment of ALL is developed as soon as possible.	guidance.
Questions for consultation	Baxalta UK	**Have all relevant comparators for pegaspargase been included in the scope?** • Yes, the combinations of asparaginase with other drugs listed reflect current clinical practice **How is standard induction and consolidation chemotherapy for ALL defined?** • Standard induction and consolidation chemotherapy has been devised through systematic clinical trials incorporating different risk stratifications. **Which chemotherapies are used most often in clinical practice for induction and consolidation chemotherapy?** • These have been mentioned above **Would stem cell transplant be considered for this population in clinical practice?** • Stem cell transplantation is used; eligible patients could be treated with stem cell transplant, as defined by the appropriate clinical trial. **Are there any differences in how ALL is managed in adults compared with children and adolescents?** • Yes, treatment options differ, as reflected in the trial protocols.	Comments noted. No action required. Comment noted. Clinical experts at the scoping workshop considered that stem cell transplant is used for treating refractory or relapsed ALL and therefore is not an appropriate comparator for pegaspargase.

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	NCRI/RCP/ACP	**At which treatment phase is pegaspargase most likely to be used? For induction and/or consolidation treatment? Could it be used at other treatment phases?** It is also used during 'intensification' in conjunction with high dose methotrexate. However, these are every course of ALL therapy apart from maintenance, so it's not useful to characterise asparaginase as being anything other than a standard part of ALL treatment during all the intensive phases. There is no argument internationally, whether asparaginase should be part of standard therapy for ALL. Most regimens include it except hyperCVAD. The key issue here is whether the pegylated version should be used or any of the standard, non pegylated versions. Have all relevant comparators for pegaspargase been included in the scope? We wish to highlight concern that the comparators do not appear to be fully understood. The comparators are not standard chemotherapy drugs, they are non pegylated aspargainses, which have very different pharmacokinetics and pharmacodynamics properties. There is a large literature on the topic of comparisons between asparaginase preparations. It is not apparent that these have been taken into account and the document would benefit greatly from this. **How is standard induction and consolidation chemotherapy for ALL defined?**	Comment noted. Clinical experts at the scoping workshop agreed that hyper CVAD is rarely used for treating ALL in the UK. The comparators in the scope have been updated to; • *Escherichia coli* derived L-asparaginase plus standard chemotherapy • *Erwinia chrysanthemi* derived L-asparaginase (crisantaspase) plus standard chemotherapy. Comment noted. No

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		Induction simply means chemotherapy given at the start of therapy prior to remission induction in order to achieve remission. Consolidation is the name given to any therapy used to 'consolidate' remission. In reality it would not matter what these courses were called but by historical nomemclature, they are named induction and consolidation. In the USA a commonly used regimen, hyperCVAD is just named by course, but the courses have the same function. **Which chemotherapies are used most often in clinical practice for induction and consolidation chemotherapy?** In order to answer this question accurately it needs to be confirmed whether it is asking which individual drugs, or which protocols or regimens. **Would stem cell transplant be considered for this population in clinical practice?** Yes. This would be considered for adult patients with 'high risk' disease. **Are there any differences in how ALL is managed in adults compared with children and adolescents?** Yes. Therapy for young people is more intensive and stem cell transplant is much more uncommon.	action required. Comment noted. No action required. Comment noted Clinical experts at the scoping workshop considered that stem cell transplant is used for treating refractory or relapsed ALL and therefore is not an appropriate comparator for pegaspargase. Comment noted. No action required.
	Royal College of	**At which treatment phase is pegaspargase most likely to be used? For induction and/or consolidation treatment? Could it be used at other**	Comment noted.

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	Pathologists and BSH	**treatment phases?** These are the most likely – it is also used during "intensification" in conjunction with high dose methotrexate. However, these are pretty much every single course of ALL therapy apart from maintenance, so it's not useful to characterise asparaginase as being anything other than a standard part of ALL treatment during all the intensive phases. There is no argument internationally, whether asparaginase should be part of standard therapy for ALL – pretty much all regimens include it except hyperCVAD - the key issue here is should the pegylated version be used or any of the standard, non pegylated versions. **Have all relevant comparators for pegaspargase been included in the scope?** It is concerning that the comparators haven't been grasped at all – the comparators aren't standard chemotherapy drugs. They are non pegylated aspargainses – which have very different pharmacokinetics and pharmacodynamics properties There is a large amount of literature on the topic of comparisons between asparaginase preparations which does not appear to have been taken into account. **How is standard induction and consolidation chemotherapy for ALL defined?** Induction simply means chemotherapy given at the start of therapy prior to remission induction in order to achieve remission. Consolidation is the name given to any therapy used to 'consolidate' remission. In reality it would not matter if they were called courses 1, 2, 3 etc but by historical nomenclature,	Clinical experts at the scoping workshop agreed that hyper CVAD is rarely used for treating ALL in the UK. The comparators in the scope have been updated to; Non-PEGylated form of • *Escherichia coli* derived L-asparaginase plus standard chemotherapy • *Erwinia chrysanthemi* derived L-asparaginase (crisantaspase) plus standard chemotherapy. Comment noted. No action required.

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		they are named induction and consolidation. In the USA a commonly used regimen, hyperCVAD is just named by course, but the courses have the same function. **Which chemotherapies are used most often in clinical practice for induction and consolidation chemotherapy?** Do you mean which individual drugs or which protocols or regimens? **Would stem cell transplant be considered for this population in clinical practice?** Yes – for adult patients with 'high risk' disease **Are there any differences in how ALL is managed in adults compared with children and adolescents?** Yes – therapy for young people is more intensive and stem cell transplant is much more uncommon	Comment noted. No action required. Comments noted. Clinical experts at the scoping workshop considered that stem cell transplant is used for treating refractory or relapsed ALL and therefore is not an appropriate comparator for pegaspargase.
Additional comments on the draft scope	Baxalta UK	Pegaspargase has been used in UK clinical practice for many years and is currently the drug most predominantly used in the NHS for this patient population. NHS England has also endorsed its use with inclusion into routine commissioning. It is currently in use in active UK clinical trials.	Comments noted. No action required.

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	NCRI/RCP/ACP	We wish to emphasise the importance of accuracy in relation to pegaspargase. It is a highly valuable agent in routine use. As it is an enzyme (biological agent) it is quite different from many other chemotherapy agents. ALL therapy is complicated, making it difficult to assess one drug typically used in multiagent combination. It is therefore imperative that those involved in the scope have the appropropriate expertise. Our experts would have serious concerns if it is suggested this drug not be used as the ALL trials in the UK both adult and childhood would be compromised, as both use commercial stock. Asparaginase is one of the key drugs in childhood ALL. The Pegylated version is safer and better tolerated than the non-Pegylated version. In the UK, this is the main product used in children for the last 12 years and there is considerable data on pharmacokinetics, allergic responses, relationship to survival and MRD responses. We do not have this data or experience with the non-pegylated version as (1) the tools to study this in such great detail at that time (2) for a while UK used the alternative Asparaginase and not the E.coli derivative which has been pegylated. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial www.thelancet.com/oncology Vol 14 March 2013; authors: A Vora et al highlights this and shows some of the best results internationally. Our experts believe that PEG–Asnase played a significant part in this. Potentially, from 2017, the only source of non-PEG Asparaginase will be from unproven sources and, as yet, testing of these has failed to completely match the product currently used in the UK. There is insufficient PEG-Asnase available to meet demands in the overseas market and the cost is prohibitive. Therefore, if we opt out of PEG-ASNase, there is unlikely to be a reliable source of the native.	Comments noted. No action required.

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		The international ALL community believes very strongly that Pegylated ASNase is the way forward for children with ALL worldwide, which is why many of our experts have spent considerable time and effort over the last decade both evaluating the drug as well as working with the companies to continuously strive to have a stable supply. In conclusion, our experts believe that it is crucial that childhood ALL doctors are actively involved with this scoping and any appraisal thereafter. Pegaspargase is the standard of care for these clinicians and has been for many years.	

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.	Anthony Nolan	NICE Secretariat	1.	Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore Anthony Nolan have been added to the matrix under 'patient/carer' groups.
2.	Delete Blood Cancer	NICE Secretariat	2.	Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore Delete Blood Cancer have been added to the matrix under 'patient/carer' groups.

3.	African Caribbean Leukaemia Trust	NICE Secretariat	3.	Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore African Caribbean Leukaemia Trust have been added to the matrix under 'patient/carer' groups.
4.	National Children's Bureau	PIP	4.	Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore National Children's Bureau have been added to the matrix under 'patient/carer' groups.