National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

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	Merck Sharp & Dohme	Yes, MSD expect to receive positive CHMP opinion [redacted]; this will be followed by EMA market authorisation [redacted].	Comments noted. NICE can only begin to appraise a technology when it has been formally referred by the Secretary of State for Health. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Janssen-Cilag	Janssen believes this is an appropriate topic to refer to NICE for appraisal	Comments noted. No

Section	Consultee/ Commentator	Comments [sic]	Action
			action required.
	Public Health England	Yes, for consideration once a marketing authorisation in the UK is in place. It is a novel combination medicine which should be considered for patients with chronic HCV.	Comments noted. NICE can only begin to appraise a technology when it has been formally referred by the Secretary of State for Health. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	UK Clinical Pharmacy Association (UKCPA) Gastroenterology & Hepatology Group	We believe that this topic is of high importance.	Comments noted. No action required.
	UK Thalassaemia	The introduction of grazoprevir and elbasvir is appropriate	Comments noted. No action required.
Wording	Merck Sharp &	No comment	Comments noted. No

Section	Consultee/ Commentator	Comments [sic]	Action
	Dohme		action required.
	Janssen-Cilag	Janssen believes that the wording of the remit should reflect the anticipated licence	Comments noted. Grazoprevir-elbasvir will be appraised within its marketing authorisation for treating chronic hepatitis C.
	Public Health England	Yes, the cureent wording used is appropriate.	Comments noted. No action required.
	UK Thalassaemia	Yes	Comments noted. No action required.
Timing Issues	Merck Sharp & Dohme	We anticipate that the proposed appraisal should be scheduled to enable NICE to issue final guidance soon after regulatory approval expected [redacted]. Grazoprevir-elbasvir is intended for the treatment of patients with chronic hepatitis C GT 1, 4, and 6. Treatment can be initiated in patients described as treatment-naïve or experienced. The duration and combination (ie. the addition of ribavirin) of therapy varies according to patient group. There is a clear unmet need for patients with chronic hepatitis C diagnosed with severe renal disease (eGFR; <30mL/min/1.73m2) or end stage renal disease (ESRD), including patients on dialysis (including haemodialysis or peritoneal dialysis); there are currently limited treatment options available to this group. Furthermore, no dose adjustment is required for patients with mild, moderate, or severe renal impairment. There is no dose adjustment required	Comments noted. NICE can only begin to appraise a technology when it has been formally referred by the Secretary of State for Health. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.

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		for patients with ESRD who are on dialysis (haemodialysis or peritoneal dialysis). Grazoprevir-elbasvir in combination with sofosbuvir is intended for the treatment of chronic hepatitis C GT3 in patients described as treatment naïve. This combination provides an alternative to the limited existing interferon-free treatment regimens.	Grazoprevir-elbasvir will be appraised within its marketing authorisation for treating chronic hepatitis C.
	Janssen-Cilag	No comment	Comments noted. No action required.
	Public Health England	Urgent - when more drugs are available for this indication the current high prices will be driven down. This treatment may also fill gaps in patient groups that currently do not have direct acting antiviral options. A number of drug treatment options are available however securing availability will increase the likelihood of patient accessibility.	Comments noted. NICE can only begin to appraise a technology when it has been formally referred by the Secretary of State for Health. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
Additional comments on the draft remit	Janssen-Cilag	No comment	Comments noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Merck Sharp & Dohme	No comment	Comments noted. No action required.
	Janssen-Cilag	No comment	Comments noted. No action required.
	Public Health England	In the background, is says that: "More than half of people with chronic hepatitis C are unaware of their infection (3)" The guidance document that has been referenced is very out of date (2004); Suggestion consider deleting the second sentence in favour of saying "….As a result a significant number of people remain undiagnosed."	Comments noted. The background section has been updated.
	UK Thalassaemia	The information provided is minimal at this stage	Comments noted. The background is only intended to provide a brief overview of the condition and current treatment options. A more detailed description will be included in the company's submission.
The technology/ intervention	Merck Sharp & Dohme	Grazoprevir–elbasvir disrupts the biogenesis of components necessary for HCV replication by inhibiting key HCV proteins. It is orally administered as a fixed-dose combination. Grazoprevir-elbasvir is a film coated tablet containing 100mg grazoprevir and 50mg elbasvir. The recommended treatment dose is	Comments noted. Grazoprevir-elbasvir will be appraised within its marketing authorisation

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		one tablet once daily with or without food. Grazoprevir-elbasvir does not require dose adjustment in the elderly, patients with renal impairment (mild, moderate, or severe (eGFR <30mL/min/1.73m2), or patients with ESRD. Grazoprevir-elbasvir does not require dose adjustment in patients who are on dialysis (including haemodialysis or peritoneal dialysis) Grazoprevir–elbasvir has been studied in eight clinical trials in approximately 1,800 patients, including: randomised placebo controlled trials (GT 1, 4, and 6); open label comparative trials (GT 1, 4, and 6), and non-comparative (GT 3) clinical trials in combination with sofosbuvir.	for treating chronic hepatitis C. The company will have the opportunity to include additional information around the technology and the clinical evidence in its submission.
	Janssen-Cilag	No comment	Comments noted. No action required.
	Public Health England	The intervention is presumably Grazoprevir-Elbasvir and not in combination with any other agents, but this should be clarified ie that grazpprevir -elbasvir is a novel combination in its own right. The mechanism of antiviral action should be expanded further. "Grazoprevir–elbasvir (brand name unknown, Merck Sharp & Dohme) disrupts the biogenesis of components necessary for HCV replication by inhibiting key HCV proteins with grazoprevir inhibiting HCV NS3/4A protease and elbasvir the NS5A replication complex. It is orally administered as a once daily, fixed-dose single-tablet combination."	Comments noted. Grazoprevir-elbasvir will be appraised within its marketing authorisation for treating chronic hepatitis C. Please note that the technology section has been updated. The company will be expected to provide additional information

Section	Consultee/ Commentator	Comments [sic]	Action
			around the technology in its evidence submission.
	UK Thalassaemia	Yes	Comments noted. No action required.
Population	Merck Sharp & Dohme	MSD request further clarity relating to the eligible patient population, please see our recommendations below: Adults aged ≥18 years with chronic hepatitis C with or without HIV co-infection: • Who have not had treatment for chronic hepatitis C (treatment-naive) o Genotypes 1, 4, 6, including patients with severe renal disease (eGFR; <30mL/min/1.73m^2) or with ESRD, including patients on dialysis (including haemodialysis or peritoneal dialysis) o Genotype 3* in combination with sofosbuvir. **Genotype 3 does not include patients with severe renal impairment (eGFR, <30mL/min/1.73m^2) or ESRD. It should be noted that patients with GT3 infection received grazoprevir–elbasvir in combination with sofosbuvir.* • Who have had treatment for chronic hepatitis C (treatment-experienced) o Genotypes 1, 4, 6, including patients with severe renal disease (eGFR; <30mL/min/1.73m^2) or with ESRD, including patients on dialysis (including haemodialysis or peritoneal dialysis) o Treatment experienced defined as prior treatment with: ▪ Interferon containing regimen +/- ribavirin	Comments noted. Grazoprevir-elbasvir will be appraised within its marketing authorisation for treating chronic hepatitis C. During the scoping workshop, attendees agreed that the population was defined appropriately in the draft scope. No action required.

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		▪ Telaprevir/ simeprevir + Peg INF + RBV	
	Janssen-Cilag	No comment	Comments noted. No action required.
	Public Health England	PLEASE NOTE: The new drug approval with the United States Food and Drug Administration (FDA) is only for genotypes 1, 4 and 6 for treatment experienced as well as treatment naïve cirrhotics and non-cirrhotics, and for complex patients such as HIV co-infection, chronic kidney disease stage 4/5 etc. The population is defined appropriately.	Comments noted. Grazoprevir-elbasvir will be appraised within its marketing authorisation for treating chronic hepatitis C. No changes to the scope required.
	UK Clinical Pharmacy Association (UKCPA) Gastroenterology & Hepatology Group	End stage renal disease could be added as a population group	Comments noted. During the scoping workshop, attendees agreed that 'people with renal impairment' should be included as a subgroup. Please note that the 'other considerations' section of the scope has been updated.
	UK Thalassaemia	Yes; other important groups for consideration are those with renal impairment and patients with haemoglobinopathies, including thalassaemia major and sickle cell disease as well as people with injecting drug use.	Comments noted. During the scoping workshop, attendees

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			agreed that 'people with renal impairment' and 'people with haemoglobinopathies' should be included as subgroups. Attendees further agreed that 'people with injecting drug use' was not an appropriate subgroup. NICE noted that uptake of the guidance was not part of the Committee's considerations. Please note that the 'other considerations' section of the scope has been updated.
Comparators	Merck Sharp & Dohme	MSD also request that for those interventions listed as genotypes 1-6, this is amended for data relevant to genotypes 1, 3, 4, and 6 only. MSD will not be seeking a license in genotypes 2 and 5; therefore, this will not be considered within this submission. Further clarity is needed to define best supportive care (BSC) (watchful waiting); MSD recommend the wording: "no active drug treatment" as per	Comments noted. During the scoping workshop, attendees agreed that the comparators listed in the draft scope were

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		previous/ ongoing manufacturer submissions. Inclusion of comparators described as "subject to ongoing NICE appraisal" (ID766, ID742, ID 731) should be included within the draft/ final scope. However, if these appraisals do not receive a recommendation they will not be considered within our submission for the relevant licensed indications. [redacted]	appropriate. No changes to the scope required. NICE's guide to the methods of technology appraisal (2013) states that: "The Committee has to make judgements on the appropriateness and relevance of comparator technologies because this is crucial to the consideration of the clinical and cost-effectiveness evidence. When selecting the most appropriate comparator(s), the Committee will consider: • established NHS practice in England • the natural history of

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			the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status." of the comparator.
	Janssen-Cilag	Janssen suggests the description for simeprevir be changed to: Simeprevir in combination with peginterferon alfa and ribavirin for: o Patients who are genotype 1a Q80K negative and genotype 1b patients. o Genotype 4 patients.	Comments noted. During the scoping workshop, attendees agreed that the comparators listed in the draft scope were appropriate. No changes to the scope required.
	Public Health England	The list of comparators is comprehensive and contains the various options that could lend as 'best alternative care'. Sofosbuvir or other new direct acting antivirals are the best existing drugs for genotype 1; however, certain non-1 genotype patients may only be eligible for pegylated interferon and ribavirin, which would be the best alternative in these cases..	Comments noted. During the scoping workshop, attendees agreed that the comparators listed in the draft scope were appropriate. No changes to the scope

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			required.
	UK Clinical Pharmacy Association (UKCPA) Gastroenterology & Hepatology Group	It is unnecessary to compare to telaprevir and boceprevir.	Comments noted. During the scoping workshop, attendees noted that the use of boceprevir and telaprevir was likely to decline because of the availability of several all oral treatment options. However, attendees agreed that based on the guidance in NICE's methods guide (2013), the comparators listed in the draft scope were appropriate. No changes to the scope required.
	UK Thalassaemia	Yes; grazoprevir and elbasvir can be considered an alternate non sofosbuvir based regimen.	Comments noted. During the scoping workshop, attendees agreed that the comparators listed in the draft scope were

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			appropriate. No changes to the scope required.
Outcomes	Merck Sharp & Dohme	MSD request that sustained virological response (SVR) is considered at Weeks 12 and 24. As a point of accuracy, MSD request that the stated outcome "development of resistance to grazoprevir-elbasvir" is replaced with "treatment emergent resistance variants to grazoprevir-elbasvir". This reflects that patients do not develop resistance, but rather resistant isolates are selected for.	Comments noted. During the scoping workshop, attendees agreed that the outcomes listed in the draft scope were the most appropriate for chronic hepatitis C. It was acknowledged by attendees that the wording of 'development of resistance' outcome included consideration of 'treatment emergent resistant variants'. No changes to the scope required.
	Janssen-Cilag	No comment	Comments noted. No action required.
	Public Health	Outcomes should also include relapse rates	Comments noted. During the scoping

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	England		workshop, attendees agreed that because 'sustained virological response' was listed as an outcome, 'relapse rates' was not needed. No changes to the scope required.
	UK Thalassaemia	Yes	Comments noted. No action required.
Economic analysis	Merck Sharp & Dohme	No comment	Comments noted. No action required.
	Janssen-Cilag	No comment	Comments noted. No action required.
	Public Health England	Lifetime costs and QALYs should be considered due to the long incubation time before severe disease develops.	Comments noted. No action required.
	UK Thalassaemia	To be provided in more detail	Comments noted. The company will be expected to provide details around the economic analysis in its evidence submission.
Equality and	Merck Sharp &	No comment	Comments noted. No

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Diversity	Dohme		action required.
	Janssen-Cilag	No comment	Comments noted. No action required.
	Public Health England	There is no apparent discimination in the proposed remit against those inidividuals with protected characteristics as outlined in the Equality Act.	Comments noted. No action required.
	UK Thalassaemia	Important to consider groups with sickle cell disease (more prevalent in those with African ethnicity) and thalassaemia (southern mediterranean and Asian anccestry	Comments noted. Equality issues and any recommendations that may indirectly discriminate against any group will be considered by the Appraisal Committee in its decision-making. The company and other consultees are encouraged to provide any data that may support any potential equality issues in their evidence submission or supporting statements.
Innovation	Merck Sharp & Dohme	There is a clear unmet need for patients diagnosed with severe renal disease (eGFR; <30mL/min/1.73m2) or with end stage renal disease (ESRD),	Comments noted. The potential innovative

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		including patients on dialysis (including haemodialysis or peritoneal dialysis) who are also infected with chronic hepatitis C. Grazoprevir-elbasvir can be administered with no dose adjustment for patients with mild, moderate, or severe renal impairment. There is no dose adjustment required for patients with ESRD who are on dialysis (haemodialysis or peritoneal dialysis). There is no dose adjustment required for the elderly.	nature of the technology will be considered by the Appraisal Committee.
	Janssen-Cilag	No comment	Comments noted. No action required.
	Public Health England	Yes very possible to have a significant impact if accessible to patients. Possible to be effective in broad and diverse patient populations with chronic HCV.	Comments noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.
	UK Thalassaemia	Yes; will improve lives of those benefiting from an SVR; best opportunity to treat those on dialysis.	Comments noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.
Other considerations	Merck Sharp & Dohme	MSD request that: • When genotype is taken into consideration, this should be further	Comments noted. Grazoprevir-elbasvir will

Section	Consultee/ Commentator	Comments [sic]	Action
		discussed in relation to patients who are classified as either treatment naïve or treatment experienced. • The statement "People who have received treatment pre- and post-liver transplant" is removed from the draft scope, as this patient group will not be within our license. • "non-response" is updated to null-response or partial response, for consistency across the scoping document. • Patients with severe renal disease (eGFR; <30mL/min/1.73m2) or with ESRD, including patients on dialysis (including haemodialysis or peritoneal dialysis) with chronic hepatitis C infection GT 1, 4, and 6.	be appraised within its marketing authorisation for treating chronic hepatitis C. NICE will also offer the company an opportunity to discuss its evidence submission at a decision problem meeting. Please note that the 'other considerations' section of the scope has been updated.
	Janssen-Cilag	Janssen suggests that if evidence allows: • The patient groups should be split by level of fibrosis.	Comments noted. Grazoprevir-elbasvir will be appraised within its marketing authorisation for treating chronic hepatitis C. During the scoping workshop, attendees agreed that if evidence allows the following subgroups will be considered:

Section	Consultee/ Commentator	Comments [sic]	Action
			• people with and without cirrhosis • people with advanced liver disease Please note that the 'other considerations' section of the scope has been updated.
	Public Health England	Coinfection with hepatitis B should be considered as an important sub-group. There have been recent discussions as to whether there are alternatives to an "all or nothing" approach to treatment appraisal for HCV. In particular, mild disease stage patients who are at low risk of developing severe disease in the near future may be kept under watchful waiting and treated at a later stage - rather than either being treated immediately, or kept permanently under watchful waiting. This issue is likely to be beyond the scope of this appraisal, but should be considered.	Comments noted. During the scoping workshop, attendees agreed that 'coinfection with hepatitis B' was not an appropriate subgroup.
	UK Thalassaemia	Provision of treatment to patients on haemodialysis with hepatitis C	Comments noted. Please note that the 'other considerations' section of the scope has been updated.
NICE Pathways	Merck Sharp & Dohme	MSD expect that grazoprevir–elbasvir would represent a treatment option in patients with HCV infections 1, 3, 4, and 6 as per the license indication(s).	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Questions for consultation	Merck Sharp & Dohme	Have all relevant comparators for grazoprevir–elbasvir been included in the scope? Which treatments are considered to be established clinical practice in the NHS for chronic hepatitis C? • MSD believe that all relevant comparators have been included. • [redacted] 'How should best supportive care be defined?' • This is a topic for ongoing discussion, and MSD look to previous and ongoing submissions to best answer this question. It seems that BSC would be most accurately described as watchful-waiting (no treatment). This is the case for submissions: o ID766, daclatasvir o ID742, ledipasvir-sofosbuvir • Similarly, TA331 (simeprevir) included no treatment as a comparator when treating patients with HCV GT 1 and 4. • MSD recommend the wording "no active drug treatment" in the place of best supportive care. Have all relevant outcomes been included in the scope? • Yes, MSD do not believe there is anything missing. Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom grazoprevir–elbasvir is expected to be more clinically effective and cost effective or other groups that should be	Comments noted. During the scoping workshop, attendees agreed that based on the guidance in NICE's methods guide (2013), the comparators listed in the draft scope were appropriate. No changes to the scope required. Attendees agreed that

Section	Consultee/ Commentator	Comments [sic]	Action
		examined separately? • MSD anticipate that Grazoprevir-elbasvir will provide data specific to patients diagnosed with severe renal disease (eGFR; <30mL/min/1.73m2) or with end stage renal disease (ESRD), including patients on dialysis (including haemodialysis or peritoneal dialysis) who are also infected with chronic hepatitis C for whom there is an unmet need.	'people with renal impairment' should be included as a subgroup. Please note that the 'other considerations' section of the scope has been updated.
	Janssen-Cilag	No comment	Comments noted. No action required.
	Public Health England	Best supportive care is difficult to define in this context because watchful waiting is high risk in the marginalised groups that make up a significant proportion of the HCV patient population because these groups often become disengaged from long-term monitoring programmes thereby missing out on future treatment opportunities (thus widening health inequalities).	Comments noted. No action required.
	UK Thalassaemia	Grazoprevir elbasvir are an important addition to the treatment of hepatitis C; many patients including those without cirrhosis are now candidates for treatment. The application of IFN free regimens (coformulated as a single tablet) will widen care. The relevant outcomes have been included. NICE will exhaustively examine the effiacy and safety data derived from over 1600 patients, with genotype 1 and 4 infection including naïve and experienced patients, patients with our without cirrhosis, the optimal duration ribavirin requirement.	Comments noted. No action required.
Additional comments on the	Merck Sharp & Dohme	No comment	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
draft scope	Janssen-Cilag	No comment	Comments noted. No action required.
	UK Thalassaemia	Full details of the efficacy of the combination will be submitted via a large number of studies in a variety of patient groups to provide a full set of analysis.	Comments noted. No action required.

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

- Department of Health
- Roche Products
- Royal College of Nursing

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.	Add British Kidney Patient Association	Merck Sharp Dohme		Not included	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. The British Kidney Patient Association has not been included in the matrix of consultees and commentators.
2.	Add Haemophilia Society	Merck Sharp Dohme		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. The Haemophilia Society has been added to the matrix of consultees and commentators under 'patient' groups.

3.	Add Renal Association	Merck Sharp Dohme		Not included	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. The Renal Association has not been included in the matrix of consultees and commentators.
4.	Add United Kingdom Haemophilia Centre Doctors Association	Merck Sharp Dohme		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. United Kingdom Haemophilia Centre Doctors Association has been added to the matrix of consultees and commentators under 'professional' groups.

5.	Add British Society of Haematology	Merck Sharp Dohme		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. The British Society of Haemophilia has been added to the matrix of consultees and commentators under 'professional' groups.
6.	Add Scottish Viral Hepatology Group	Merck Sharp Dohme		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. The Scottish Viral Hepatology Group has been added to the matrix of consultees and commentators under 'general commentators'.

7.	Add STOP-HCV UK	Merck Sharp Dohme		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. STOP HCV UK has been added to the matrix of consultees and commentators under 'relevant research groups.
8.	Add HCV Research UK	Merck Sharp Dohme		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. HCV Research UK has been added to the matrix of consultees and commentators under 'relevant research groups.

9.	Add UK Thalassaemia Society	Clinical Expert - UK Thalassaemia Society		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. UK Thalassaemia Society has been added to the matrix of consultees and commentators under 'patient' groups.
10.	Remove British Association for the Study of the Liver Nurses Forum	NICE Secretariat		Removed	This organisation is a subgroup of the British Association for Study of the Liver (BASL) which is already on the matrix of consultee and commentators under 'professional groups'. British Association for the Study of the Liver Nurses Forum has been removed from the matrix of consultees and commentators.

11.	Add Haemophilia Nurses Association	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. Haemophilia Nurses Association has been added to the matrix of consultees and commentators under 'professional' groups.
12.	Add Hospital Information Services – Jehovah's Witnesses	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. Hospital Services – Jehovah's Witnesses has been added to the matrix of consultees and commentators under 'general commentator'.

13.	Add Haemophilia Alliance	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. Haemophilia Alliance has been added to the matrix of consultees and commentators under 'patient/carer groups'.
14.	Add Adfam	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal and meets the selection criteria to participate in this appraisal. Adfam has been added to the matrix of consultees and commentators under 'patient/carer groups'.