Introduction to the Delphi Panel

This study is initiated and jointly funded by Roche Products Ltd and Chugai Pharma UK Ltd. Thank you for completing Round 1 of the Delphi panel, and for taking the time to complete this Round 2 questionnaire.

Round 2 Questionnaire Development

Any questions which achieved consensus in Round 1 have not been included in Round 2. Questions which did not achieve consensus at Round 1 have been asked again in this Round 2 questionnaire. These questions have been restated, rephrased or split into multiple related questions in light of the Round 1 free-text comments received from panellists. In response to Round 1 free text comments specifically in the Mild and Moderate Patients section, one new Adult Care and one new Care of Children and Adolescents question have also been included in this section.

The development of this questionnaire has been directed by a Steering Committee of clinical experts, consisting of Dr Elizabeth Chalmers, Dr Pratima Chowdary, Dr Gerry Dolan, Thuvia Flannery and Dr Kate Khair.

Questionnaire Structure and Data Sharing

At the start of this questionnaire, you will be asked to select whether you wish to respond to specific questions related to adult care only, care of children and adolescents only, or both adult care and care of children and adolescents; please select the questions you responded to in the Round 1 survey. You will then be asked to provide your email address; please note this will only be used by Costello Medical, the Delphi Panel facilitators, for the purposes of sharing a summary of your responses and the Delphi Panel's overall feedback with you in the next round.

Based on your choice of questions, you will be directed to the appropriate section of the survey and asked to provide your opinion on a series of points related to the standard of care in haemophilia patients with inhibitors. As was the case for Round 1, this questionnaire is structured around five main sections:

- 1. Clinical Goals
- 2. Role of Immune Tolerance Induction (ITI)
- 3. Bypassing Agents
- 4. Prophylaxis
- 5. Mild or Moderate Patients

If you would like to provide justification for your answers, or have any additional comments, please complete the available text boxes at the end of each section. For each question that you do not wish to respond to for any reason, you will be able to select one of the options described below:

- If you feel that you do not have sufficient experience or expertise to answer an individual question, please select `Insufficient expertise'
- If you do not wish to answer a question for any other reason, please select '**Do not** wish to answer'

The responses and comments you provide throughout this questionnaire will be shared anonymously with the Steering Committee and used to inform subsequent rounds of the Delphi Panel. In this Round 2 questionnaire we refer to slides included in the Round 1 Results Summary slideset, which is attached to your Round 2 invitation email.

Therefore, we recommend that you review this slideset while completing the Round 2 questionnaire.

Please note the questionnaire should take approximately 10–30 minutes to complete, and your responses will remain anonymous to the Steering Committee and the wider Delphi Panel.

Adverse Event Reporting

Should you raise an adverse event and/or product complaint associated with the use of a Roche or Chugai medicinal product, we will need to report this, even if it has already been reported by you directly to the company or the regulatory authorities using the MHRA's 'Yellow Card' system. In such a situation you will be contacted to ask whether or not you are willing to waive the confidentiality specifically in relation to that adverse event and/or product complaint. Everything else you contribute during the course of the project will continue to remain confidential, unless stated otherwise in the text above.

* This questionnaire contains general questions relating to all patients, which all participants are invited to respond to. In addition, some questions specifically relate to adult care (patients over the age of 16), while others relate to care of children and adolescents (patients who are 16 years old or younger). Please select which of these you wish to respond to:

Please select the same option that you chose in Round 1.

Adult car	e only
O Care of c	children and adolescents only
O All questi	ons related to both adult care and care of children and adolescents

* Please provide your email address Please note, this will only be used by Costello Medical for the purposes of sharing future iterations of the questionnaire, along with your results from the previous round.
* Please tick the box to confirm that you wish to proceed with completing this questionnaire.
I wish to proceed with completing this questionnaire
If you have any additional questions or comments relating to this questionnaire, or the Delphi Panel in general, please do not hesitate to contact Annabel Griffiths at annabel.griffiths@costellomedical.com .
References The content of questions and statements has been informed by the Steering Committee, as well as the following literature:
 Collins PW et al. Diagnosis and Treatment of Factor VIII and IX Inhibitors in Congenital Haemophilia: (4th Edition). British Journal of Haemophilia. 2013; 160(2): 153–170. Event Report: EHC Round Table of Stakeholders on 'Inhibitors in Haemophilia A'. EHC. 2016. [Available at: https://www.ehc.eu/wp-content/uploads/EHC-Report-Round-Table-2016-02-Inhibitors-in-
Haemophilia-A.pdf (Last accessed 08.10.18)]. 3. López-Fernández MF et al. Spanish Consensus Guidelines on Prophylaxis with Bypassing Agents in Patients with Haemophilia and Inhibitors. Thrombosis and Haemostasis. 2016; 115(5): 872–895. 4. Srivastava A et al. Guidelines for the Management of Hemophilia. Haemophilia. 2013; 19(1): e1–47. 5. UKHCDO Protocol for First Line Immune Tolerance Induction for Children with Severe Haemophilia A: A Protocol from the UKHCDO Inhibitor and Paediatric Working Parties (1st February 2017). UKHCDO. 2017. [Available at: http://www.ukhcdo.org/wp-content/uploads/2017/01/ITI-protocol-2017.pdf (Last accessed 08.10.18)].
October 2018 RCUKEMIC00134

Round 2 Delphi Questions

All questions (relating to general care, adult care and care of children and adolescents)

When answering the following questions, please consider both haemophilia A and B patients, unless otherwise specified, with current clinically relevant inhibitors (i.e. who are eligible for bypass therapy).

If you would like to make any suggestions for changes to the statements, or have any other comments, please write these in the 'Additional Comments' boxes provided.

Section 1. Clinical Goals

To see the results for the Round 1 questions from this section, please see the 'Results: Clinical Goals' section of the Round 1 Results Summary slideset attached to your Round 2 invitation email. At the end of each question in this Round 2 questionnaire, the relevant slide is shown in brackets.

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
The aims of treatment in haemophilia patients with inhibitors are completely different from the aims of treatment in haemophilia patients without inhibitors (Slide 4)			0	0	0	0		
When treating adults with long- standing inhibitors, the priority is not to eradicate the inhibitors (Slide 5)	\bigcirc	\bigcirc	\bigcirc		\bigcirc	\bigcirc	\bigcirc	0
When treating adults with newly-developed inhibitors, the priority is to eradicate the inhibitors (Slide 5)	0		0	0		0	0	
When treating adults with long- standing inhibitors who are unresponsive to ITI, the aim is for them to not have any bleeds (Slide 6)	0	0	0	0	0	0	0	
When treating children and adolescents with inhibitors on ITI, the aim is for them to not have any bleeds (Slide 7)						0		

Section 2. Role of Immune Tolerance Induction (ITI)

To see the results for the Round 1 questions from this section, please see the 'Results: Role of Immune Tolerance Induction (ITI)' section of the Round 1 Results Summary slideset attached to your Round 2 invitation email. At the end of each question in this Round 2 questionnaire, the relevant slide is shown in brackets.

If an inhibitor is no longer detected in adults (negative Bethesda assay), this indicates a positive response to ITI (Slide 9) Tolerance to factor therapy can be demonstrated in adults when a half-life of >7 hours is observed (Slide 10) Inadequate response to ITI should be defined as an upward trend in inhibitor titre or <20% reduction in inhibitor titre over a 6-month period (Slide 11) If inadequate response to ITI is observed with a dose of <200 IU/kg/day, the dose should be increased to this level (Slide 12) For patients who inadequately respond to ITI, ITI should be terminated (Slide 13)		1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
be demonstrated in adults when a half-life of >7 hours is observed (Slide 10) Inadequate response to ITI should be defined as an upward trend in inhibitor titre or <20% reduction in inhibitor titre over a 6-month period (Slide 11) If inadequate response to ITI is observed with a dose of <200 IU/kg/day, the dose should be increased to this level (Slide 12) For patients who inadequately respond to ITI, ITI should be	detected in adults (negative Bethesda assay), this indicates a			0		0	0	0	C
should be defined as an upward trend in inhibitor titre or <20%	be demonstrated in adults when a half-life of >7 hours is observed	0	\bigcirc	0	0	0	0	0	C
observed with a dose of <200 IU/kg/day, the dose should be increased to this level (Slide 12) For patients who inadequately respond to ITI, ITI should be	should be defined as an upward trend in inhibitor titre or <20% reduction in inhibitor titre over a		0	0	0	0	0		C
respond to ITI, ITI should be	observed with a dose of <200 IU/kg/day, the dose should be	0	\bigcirc	0	0	\bigcirc	0	0	C
	respond to ITI, ITI should be	0	0	0	0	0	0	0	C

full dose of 200 IU		ant; 3=least important; S Treatment with	irst round of ITI at the lide 13): Treatment combining
	plasma-derived FVIII (pdFVIII) should be introduced	immunosuppression should be introduced without pdFVIII	both pdFVIII and immunosuppression should be introduce
1 (Most important)	0	0	0
2 (Second most important)	\bigcirc		\bigcirc
3 (Least important)	\circ	\circ	0
Insufficient expertise	0	0	0
Do not wish to answer	\circ	\circ	
			em to this text box:
ection 3. B	ypassing Age		
see the results for passing Agents' se	r the Round 1 questions ection of the Round 1 Re mail. At the end of each		e see the 'Results: attached to your
see the results for passing Agents' se und 2 invitation en	r the Round 1 questions ection of the Round 1 Re mail. At the end of each	nts from this section, pleases	e see the 'Results: attached to your

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
Infusion requirements (both volume and frequency) must be considered when selecting a therapy (Slide 15)	0		0			0	0	(
Anamnesis is an important consideration when selecting a therapy prior to ITI or during ITI (Slide 16)		\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc		(
Anamnesis is an important consideration when selecting a therapy for a patient who has		\circ	\bigcirc	0	\bigcirc	0		(
failed ITI (Slide 16) f you have any additional comments text box:	ents related	to b	ypas	ssing	g age	ents, plea	se add ther	n tc
failed ITI (Slide 16) f you have any additional comments text box: ection 4. Prophylaxione the results for the Round 1 quantum description.	S uestions fro	om tl	his s	ectic	on, p	lease see	the 'Result	ts:
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failed ITI (Slide 16) f you have any additional comments text box: ection 4. Prophylaxi see the results for the Round 1 quelent appropriate of the Round 1 are text to mail. At the end of each evant slide is shown in brackets. Please rate your level of agreements	S uestions fro Results Su n question i	om thi	his s ary s	ectic slides ound	on, pi set a 2 qu	lease see ttached to restionnal	the 'Resuli your Rour ire, the	ts: nd Do wis

Please respond to the following questions by selecting only one option per question. When answering these questions, please consider prophylaxis with bypassing agents. If you feel that you do not have sufficient experience or expertise to answer an individual question, please select 'Insufficient expertise'; if you do not wish to answer a question for any other reason, please select 'Do not wish to answer'. * What **annual bleed rate** do you feel justifies prophylaxis? 0 bleeds (any bleed Do not can justify 1-3 bleeds 4-6 bleeds 7+ bleeds Insufficient wish to prophylaxis) per year expertise answer per year per year In adults (Slide 20) In children and adolescents (Slide 20) * What **number of major bleeds per year (joint or muscle)** justifies prophylaxis? 0 bleeds (any bleed Do not justify 1-3 bleeds 4-6 bleeds 7+ bleeds Insufficient wish to prophylaxis) per year expertise answer per year per year In adults (Slide 21) In children and adolescents (Slide 21) * Based on your response to the previous question, what percentage reduction in major bleeds per year (joint or muscle) on prophylaxis would you then consider to be a clinically significant improvement? Insufficient Do not wish <30% 30-60% >60% expertise to answer In adults (Slide 22) In children and adolescents (Slide 22)

What number of	joint bleeds	per year (a	ny severity)	justifies pr	ophylaxis'	?
	0 bleeds (any bleed can justify prophylaxis)	1–3 bleeds per year	4–6 bleeds per year	7+ bleeds per year	Insufficie expertis	
In adults (Slide 23)	0	\circ	\circ			0
In children and adolescents (Slide 23)	\bigcirc	\bigcirc		\bigcirc		\bigcirc
Based on your resoleeds per year (any severity	on prophy			_	_
	<30%	30–60%	% >60		sufficient kpertise	Do not wish to answer
In adults (Slide 24)	0	0)		0
In children and adolescents (Slide 24)	\circ	0	C)	\bigcirc	0
Based on your resoleeds per year (any severity	on prophy		you then co	nsider to	be a
	<30%	30–60%	% >60		sufficient kpertise	Do not wish to answer
In adults (Slide 25)	0	\circ)	\circ	\circ
In children and adolescents (Slide 25)	\bigcirc	\circ)	\bigcirc	\circ

Please select of		Increase frequency of prophylactic	Increase both dose and frequency of	Switch to an	Other (please		Do not
	dose alone	treatment alone	prophylactic treatment	alternative treatment	specify below)	Insufficient expertise	wish to answer
In adults (Slide 19)		0	0	0	0	0	
In children and adolescents (Slide 19)	\bigcirc			\bigcirc	\bigcirc	\circ	\bigcirc
If you answered	l 'Other' for	adults and/o	r children an	d adolescer	its, pleas	e explain be	low:
If you have any box:	/ additiona	I comments	related to pr	ophylaxis, p	olease ad	dd them to tl	nis text

To see the results for the Round 1 questions from this section, please see the 'Results: Mild or Moderate Patients' section of the Round 1 Results Summary slideset attached to your Round 2 invitation email. At the end of each question in this Round 2 questionnaire, the relevant slide is shown in brackets. In light of Round 1 free text comments, two new questions have also been included in this section; these are denoted with 'New' in brackets.

Mild haemophilia patients with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 27) Moderate haemophilia patients with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 27) Adults with haemophilia A and inhibitors should be treated with ITI to eradicate their inhibitors, regardless of severity (New) Children and adolescents with haemophilia A and inhibitors should be treated with ITI to eradicate their inhibitors, regardless of severity (New)		1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 27) Adults with haemophilia A and inhibitors should be treated with ITI to eradicate their inhibitors, regardless of severity (New) Children and adolescents with haemophilia A and inhibitors should be treated with ITI to eradicate their inhibitors, regardless of severity (New)	inhibitors should not be routinely offered prophylaxis with			0	0	0	0		0
inhibitors should be treated with ITI to eradicate their inhibitors, regardless of severity (New) Children and adolescents with haemophilia A and inhibitors should be treated with ITI to eradicate their inhibitors,	with inhibitors should not be routinely offered prophylaxis with	0	\bigcirc	0	0	\bigcirc	0	0	0
haemophilia A and inhibitors should be treated with ITI to	inhibitors should be treated with ITI to eradicate their inhibitors,						\circ		
	haemophilia A and inhibitors should be treated with ITI to eradicate their inhibitors,								

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
The number of joint bleeds should be specifically considered when deciding whether to offer prophylaxis with bypassing agents to a mild or moderate haemophilia patients with inhibitors (Slide 28)				0				(
The number of major bleeds should be specifically considered when deciding whether to offer prophylaxis with bypassing agents to a mild or moderate haemophilia patients with inhibitors (Slide 28)		0	0	0	0			(
Infusion requirements should be specifically considered when deciding whether to offer prophylaxis with bypassing agents to a mild or moderate haemophilia patients with inhibitors (Slide 28)								(
Baseline factor activity levels should be specifically considered when deciding whether to offer prophylaxis with bypassing agents to a mild or moderate haemophilia patients with inhibitors (Slide 28)		0	0	0	0	0	0	(
Eradicating inhibitors is a priority in mild or moderate haemophilia patients with inhibitors (Slide 28)	\circ	0	0	0	0	0	0	(

Number or severity of bleeds	Nature of the inhibitor	Length of time with the inhibitor	Quality of life	Haemophilia Joint Health Score (HJHS)	Insufficient experience	Do not w
		\circ		\circ		
Final Comn	nents					
If you have a	any additional	I comments red them to this	_	e topics raised	in this Rour	nd 1
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References

The content of questions and statements has been informed by the Steering Committee, as well as the following literature:

- 1. Collins PW et al. Diagnosis and Treatment of Factor VIII and IX Inhibitors in Congenital Haemophilia: (4th Edition). British Journal of Haemophilia. 2013; 160(2): 153–170.
- 2. Event Report: EHC Round Table of Stakeholders on 'Inhibitors in Haemophilia A'. EHC. 2016. [Available at: https://www.ehc.eu/wp-content/uploads/EHC-Report-Round-Table-2016-02-Inhibitors-in-Haemophilia-A.pdf (Last accessed 08.10.18)].
- 3. López-Fernández MF et al. Spanish Consensus Guidelines on Prophylaxis with Bypassing Agents in Patients with Haemophilia and Inhibitors. Thrombosis and Haemostasis. 2016; 115(5): 872–895.
- 4. Srivastava A et al. Guidelines for the Management of Hemophilia. Haemophilia. 2013; 19(1): e1–47.
- 5. UKHCDO Protocol for First Line Immune Tolerance Induction for Children with Severe Haemophilia
- A: A Protocol from the UKHCDO Inhibitor and Paediatric Working Parties (1st February 2017). UKHCDO. 2017. [Available at: http://www.ukhcdo.org/wp-content/uploads/2017/01/ITI-protocol-2017.pdf (Last accessed 08.10.18)].

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Round 2 Delphi Questions

Questions relating to general care and adult care only

When answering the following questions, please consider both haemophilia A and B patients, unless otherwise specified, with current clinically relevant inhibitors (i.e. who are eligible for bypass therapy).

If you would like to make any suggestions for changes to the statements, or have any other comments, please write these in the 'Additional Comments' boxes provided.

Section 1. Clinical Goals

To see the results for the Round 1 questions from this section, please see the 'Results: Clinical Goals' section of the Round 1 Results Summary slideset attached to your Round 2 invitation email. At the end of each question in this Round 2 questionnaire, the relevant slide is shown in brackets.

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
The aims of treatment in naemophilia patients with whibitors are completely different from the aims of treatment in naemophilia patients without within the complete statement in the complete statement		0	0	0	0			0
When treating adults with long- standing inhibitors, the priority is not to eradicate the inhibitors (Slide 5)	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc
When treating adults with newly-developed inhibitors, the priority s to eradicate the inhibitors (Slide 5)	0		0	0	0	0	0	0
When treating adults with long- tanding inhibitors who are nresponsive to ITI, the aim is for nem to not have any bleeds Slide 6)	0	0	0	0	0	0	0	0
you have any additional comme	nts related	to c	linica	al go	als,	please a	dd them to t	this
ection 2. Role of Imr	mune	То	ler	an	се	Indu	ction (I	TI)
see the results for the Round 1 que of Immune Tolerance Induction	(ITI)' secti	ion c	of the	Roi	und	1 Results	Summary	
eset attached to your Round 2 inv and 2 questionnaire, the relevant						each que	estion in this	8

If an inhibitor is no longer detected in adults (negative Bethesda assay), this indicates a positive response to ITI (Slide 8) Tolerance to factor therapy can be demonstrated in adults when a half-life of >7 hours is observed (Slide 9) Inadequate response to ITI should be defined as an upward trend in inhibitor titre or <20% reduction in inhibitor titre over a 6-month period (Slide 10) If inadequate response to ITI is observed with a dose of <200 IU/kg/day, the dose should be increased to this level (Slide 11) For patients who inadequately respond to ITI, ITI should be terminated (Slide 12)		1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
be demonstrated in adults when a half-life of >7 hours is observed (Slide 9) Inadequate response to ITI should be defined as an upward trend in inhibitor titre or <20% reduction in inhibitor titre over a 6-month period (Slide 10) If inadequate response to ITI is observed with a dose of <200 IU/kg/day, the dose should be increased to this level (Slide 11) For patients who inadequately respond to ITI, ITI should be	detected in adults (negative Bethesda assay), this indicates a	0		0	0	0	0	0	C
should be defined as an upward trend in inhibitor titre or <20%	be demonstrated in adults when a half-life of >7 hours is observed	0	0	0	0	\bigcirc	0	0	C
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		0		0	0	0	0	0	C

	Only treatment with plasma-derived FVIII (pdFVIII) should be introduced	Only treatment with immunosuppression should be introduced	Treatment combini both pdFVIII and immunosuppression should be introduced.
1 (Most important)	\circ	\circ	
2 (Second most important)			
3 (Least important)	\circ	0	
Insufficient expertise	\bigcirc	\bigcirc	\bigcirc
Do not wish to answer	0	0	\circ
you have any ad	ditional comments relate	ed to ITI, please add the	em to this text box:
	ditional comments relate		em to this text box:
ection 3. Bosee the results for eassing Agents' se	ypassing Agel the Round 1 questions ection of the Round 1 Re nail. At the end of each		e see the 'Results: t attached to your

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
Infusion requirements (both volume and frequency) must be considered when selecting a therapy (Slide 14)	0		0			0	0	(
Anamnesis is an important consideration when selecting a therapy prior to ITI or during ITI (Slide 15)	•	•	•	•	•	•	•	
Anamnesis is an important consideration when selecting a			0	0	0	0	0	(
therapy for a patient who has failed ITI (Slide 15) f you have any additional comments text box:	ents related	to b	ypas	ssing	g age	ents, plea	se add ther	n to
failed ITI (Slide 15) f you have any additional comments text box: ection 4. Prophylaxion see the results for the Round 1 querylaxis' section of the Round 1	S uestions fro Results Su	om ti	his s ary s	ectic slides	on, pi	lease see ttached to	the 'Result your Rour	ts:
failed ITI (Slide 15) f you have any additional comments text box: ection 4. Prophylaxi see the results for the Round 1 quelling phylaxis' section of the Round 1 avitation email. At the end of each evant slide is shown in brackets. Please rate your level of agreements	S uestions fro Results Su n question i	om ti immi	his s ary s is Ro	ectic slides ound	on, pa set a 2 qu	lease see ttached to uestionna	the 'Result your Rour ire, the	ts: nd
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Please respond to the following questions by selecting only one option per question. When answering these questions, please consider prophylaxis with bypassing agents. If you feel that you do not have sufficient experience or expertise to answer an individual question, please select 'Insufficient expertise'; if you do not wish to answer a question for any other reason, please select 'Do not wish to answer'. * What **annual bleed rate** do you feel justifies prophylaxis in **adults**? (Slide 19) 0 bleeds (any bleed can 1-3 bleeds 4-6 bleeds 7+ bleeds per Insufficient Do not wish to iustify prophylaxis) expertise answer per year per year year * What **number of major bleeds per year (joint or muscle)** justifies prophylaxis in adults? (Slide 20) 0 bleeds (any bleed can justify 1–3 bleeds 4-6 bleeds 7+ bleeds per Insufficient Do not wish to prophylaxis) expertise per year per year year answer * Based on your response to the previous question, what percentage reduction in major bleeds per year (joint or muscle) on prophylaxis would you then consider to be a clinically significant improvement in **adults**? (Slide 21) Insufficient Do not wish to <30% 30-60% >60% expertise answer * What **number of joint bleeds per year (any severity)** justifies prophylaxis in **adults**? (Slide 22) 0 bleeds (any bleed can 1-3 bleeds 4-6 bleeds 7+ bleeds per Insufficient Do not wish to justify prophylaxis) per year per year expertise answer year

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<30%	30	-60%	>60%	Insuffic exper		not wish to answer
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Based on your bleeds per year clinically signification	ar (any sev	verity) on pro	ophylaxis woul	d you then o	consider to b	e a
<30%	30-	-60%	>60%	exper		not wish to answer
		\bigcirc)	
•	ophylactic treatment	frequency of prophylactic	alternative	(please specify	Insufficient	Do not wish
dose alone t (Slide 18)	alone	treatment	treatment	below)	expertise	to answer
	alone	treatment	treatment	below)	expertise	to answer
	Ol 'Other', ple	ease explain l	pelow:			

Section 5. Mild or Moderate Patients

To see the results for the Round 1 questions from this section, please see the 'Results: Mild or Moderate Patients' section of the Round 1 Results Summary slideset attached to your Round 2 invitation email. At the end of each question in this Round 2 questionnaire, the relevant slide is shown in brackets. In light of Round 1 free text comments, two new questions have also been included in this section; these are denoted with 'New' in brackets.

mments, two new questions have noted with 'New' in brackets.	also been	inclu	ıded	in th	nis s	ection; the	ese are	
Please rate your level of agreeme 6=strongly agree)	nt with the	follo	owing	g sta	teme	ent (1=str	ongly disag	ree;
	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
Mild haemophilia patients with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 26)						0		
Moderate haemophilia patients with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 26)	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc
Adults with haemophilia A and inhibitors should be treated with ITI to eradicate their inhibitors, regardless of severity (New)	0					0	0	
Based on your responses to the p with the following statements (1=s							evel of agre	ement
(· · · · · · · · · · · · · · · · · · ·	1 (Strongly disagree)		3	4	5	6	Insufficient expertise	
The number of joint bleeds should be specifically considered when deciding whether to offer prophylaxis with bypassing agents to a mild or moderate haemophilia patients with inhibitors (Slide 27)								0

			1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
should be s when decidi prophylaxis agents to a	r of major blee pecifically con ing whether to with bypassin mild or model a patients with dide 27)	osidered o offer og rate	0							0
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should be s when decidi prophylaxis agents to a	ctor activity levelopecifically coning whether to with bypassin mild or moder patients with bilide 27)	osidered o offer og rate	0	0	0	0	0			0
in mild or m	inhibitors is a noderate haen n inhibitors (S	nophilia	0	0	0	\bigcirc	\bigcirc	0	0	0
Please selec	`	portant fa						licate the		
Please select Number or severity of	Nature of	Length time wi		ılity c	J	loint	ophi Heal ore	th	icient Do r	not wis

	patients, please add
them to this text box:	
Final Comments	
If you have any additional comments relating to the topics raised i	n this Round 1
questionnaire, please add them to this text box:	
* I confirm that I have responded to all questions, and do not wish to changes.	o make any further
○ Yes	
○ No	
References	
	Stooring
The content of questions and statements has been informed by the	Steering
Committee, as well as the following literature:	
. Collins PW et al. Diagnosis and Treatment of Factor VIII and IX Inhibitors in Co	ongenital Haemonhilia
4th Edition). British Journal of Haemophilia. 2013; 160(2): 153–170.	origorina ria orrio prima.
t. Event Report: EHC Round Table of Stakeholders on 'Inhibitors in Haemophi	lia A' FHC 2016
Available at: https://www.ehc.eu/wp-content/uploads/EHC-Report-Round-Table-2	
Haemophilia-A.pdf (Last accessed 08.10.18)].	
B. López-Fernández MF et al. Spanish Consensus Guidelines on Prophylaxis wi	th Bypassing Agents in
Patients with Haemophilia and Inhibitors. Thrombosis and Haemostasis. 2016;	
. Srivastava A et al. Guidelines for the Management of Hemophilia. Haemophil	lia. 2013; 19(1): e1–47.
. UKHCDO Protocol for First Line Immune Tolerance Induction for Children w	ith Severe Haemophilia
a: A Protocol from the UKHCDO Inhibitor and Paediatric Working Parties (1st	February 2017).
IKHCDO. 2017. [Available at: http://www.ukhcdo.org/wp-content/uploads/2017/0	
Last accessed 08.10.18)].	
the analysis is initial and analysis to the fermilian beaution D. H. D. H. (1991) 1991	
This study is initiated and jointly funded by Roche Products Ltd and Ch	ugai Pharma UK Ltd.
This study is initiated and jointly funded by Roche Products Ltd and Ch October 2018 RCUKEMIC00134	ugai Pharma UK Ltd.

Round 2 Delphi Questions

Questions relating to general care and care of children and adolescents only

When answering the following questions, please consider both haemophilia A and B patients, unless otherwise specified, with current clinically relevant inhibitors (i.e. who are eligible for bypass therapy).

If you would like to make any suggestions for changes to the statements, or have any other comments, please write these in the 'Additional Comments' boxes provided.

Section 1. Clinical Goals

To see the results for the Round 1 questions from this section, please see the 'Results: Clinical Goals' section of the Round 1 Results Summary slideset attached to your Round 2 invitation email. At the end of each question in this Round 2 questionnaire, the relevant slide is shown in brackets.

6=strongly agree)	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
The aims of treatment in haemophilia patients with inhibitors are completely different from the aims of treatment in haemophilia patients without inhibitors (Slide 4)		0	0	0	0			0
When treating children and adolescents with inhibitors on ITI, the aim is for them to not have any bleeds (Slide 5)	0	0	0	0	0	0		0

So To Ro slice	ection 2. Role of Im see the results for the Round 1 que of Immune Tolerance Induction deset attached to your Round 2 in	mune in the street of the stre	Toom toon to	ler his s of the	an ectic Rot e en	Ce on, p und d of	Induc lease see 1 Results	ction (l e the 'Resul Summary	TI) ts:
*	und 2 questionnaire, the relevant Please rate your level of agreeme 6=strongly agree):		follo				6	rongly disa Insufficient expertise	Do not wish to
	Inadequate response to ITI should be defined as an upward trend in inhibitor titre or <20% reduction in inhibitor titre over a 6-month period (Slide 7)		0	0	0		0		0
	If inadequate response to ITI is observed with a dose of <200 IU/kg/day, the dose should be increased to this level (Slide 8)	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	0	0	0
	For patients who inadequately respond to ITI, ITI should be terminated (Slide 9)	0	0	0	0	0	0	0	0

	Only treatment with plasma-derived FVIII (pdFVIII) should be introduced	Only treatment with immunosuppression should be introduced	Treatment combini both pdFVIII and immunosuppression should be introduced.
1 (Most important)	\circ	\circ	\circ
2 (Second most important)	\bigcirc	\bigcirc	
3 (Least important)	0	0	0
Insufficient expertise	\bigcirc	\bigcirc	\bigcirc
Do not wish to answer	0	0	0
f you have any ad	ditional comments relate	ed to ITI, please add the	em to this text box:
	ypassing Age		em to this text box:

* Please rate your level of agreem 6=strongly agree):	ent with the	follo	owing	g sta	tem	ents (1=s	trongly disa	gree;
	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
Infusion requirements (both volume and frequency) must be considered when selecting a therapy (Slide 11)	0					0	<u> </u>	0
Anamnesis is an important consideration when selecting a therapy prior to ITI or during ITI (Slide 12)	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc
Anamnesis is an important consideration when selecting a therapy for a patient who has failed ITI (Slide 12)	0					0	0	0
If you have any additional commethis text box:	ents related	to b	ура	ssing	g age	ents, plea	se add ther	n to

Section 4. Prophylaxis

To see the results for the Round 1 questions from this section, please see the 'Results: Prophylaxis' section of the Round 1 Results Summary slideset attached to your Round 2 invitation email. At the end of each question in this Round 2 questionnaire, the relevant slide is shown in brackets.

Please respond to the following questions by selecting only one option per question. When answering these questions, please consider prophylaxis with bypassing agents. If you feel that you do not have sufficient experience or expertise to answer an individual question, please select `Insufficient expertise'; if you do not wish to answer a question for any other reason, please select 'Do not wish to answer'.

(Slide 15)	al bleed rate do	you feel justifies	s propnylaxis in (children and	adolescents?
0 bleeds (a	1	4.011			
justify prophylaxis	1–3 bleeds s) per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to answer
					\circ
	•		oint or muscle)	ustifies proph	ylaxis in
justify prophylaxis	1–3 bleeds s) per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to answer
ргорпутахк	o) per year	per year	your	CAPCITIGO	answer
major bleed	our response to t ds per year (joir significant improv	nt or muscle) o	n prophylaxis wo	ould you then one ents? (Slide of	consider to be
<30%	30–60	10/.	000/	_	
	30-00	J /0 >	60% ex	xpertise	answer
	0	J/0 >	60% e	xpertise	answer
and adoles 0 bleeds (and bleed candidate) justify	per of joint bleed cents? (Slide 18 my 1—3 bleeds	is per year (and) 4–6 bleeds	y severity) justif 7+ bleeds per	ies prophylaxi	es in children Do not wish to
and adoles 0 bleeds (a	per of joint bleed cents? (Slide 18 my 1—3 bleeds	ls per year (an	y severity) justif	ies prophylaxi	s in children
and adoles 0 bleeds (and bleed candidate) justify	per of joint bleed cents? (Slide 18 my 1—3 bleeds	is per year (and) 4–6 bleeds	y severity) justif 7+ bleeds per	ies prophylaxi	es in children Do not wish to
and adoles 0 bleeds (and bleed cand justify prophylaxis * Based on your bleeds per	per of joint bleed cents? (Slide 18 my 1—3 bleeds	ds per year (and) 4–6 bleeds per year he previous que ity) on prophyla	7+ bleeds per year estion, what percexis would you the and adolescent	Insufficient expertise centage reduction consider to the consideration to the consider	Do not wish to answer ction in joint to be a
and adoles 0 bleeds (and bleed cand justify prophylaxis * Based on your bleeds per	per of joint bleed cents? (Slide 18 my 1–3 bleeds s) per year cour response to the year (any sever unificant improver	desper year (and and and and and and and and and and	7+ bleeds per year estion, what percents would you the and adolescents.	Insufficient expertise centage reduction consider to the consideration to the consider	Do not wish to answer ction in joint to be a
and adoles 0 bleeds (and bleed cand justify prophylaxis * Based on your bleeds per clinically significant signif	per of joint bleed cents? (Slide 18 my 1–3 bleeds s) per year cour response to the year (any sever unificant improver	desper year (and and and and and and and and and and	7+ bleeds per year estion, what percents would you the and adolescents.	Insufficient expertise centage reduction consider to the consideration to the conside	Do not wish to answer ction in joint to be a) Do not wish to

year (any sev	verity) on pro	phylaxis woul	ld you then	consider to b	
30	–60%	>60%			not wish to answer
	\bigcirc				\bigcirc
ider to be an i	mprovement v	with prophylax			
Increase frequency of	Increase both dose and		Other		
			(please	Insufficient	Do not wish
	treatment	treatment	below)	expertise	to answer
					\bigcirc
	·				. An Abin Anua
any additional	comments re	elated to prop	hylaxis, plea	ase add them	to this text
	year (any segnificant improduced one answer frequency of prophylactic treatment alone ered 'Other', ple	year (any severity) on prognificant improvement in characteristics and adolescent oct one answer Increase Increase both dose frequency of and prophylactic frequency of treatment prophylactic alone treatment ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the prophylactic frequency of the prophylactic ered 'Other', please explain to the	year (any severity) on prophylaxis would gnificant improvement in children and according to the previous question (s) ider to be an improvement with prophylaxis of children and adolescents? (Slide 14) for the contract of the previous question (s) ider to be an improvement with prophylaxic children and adolescents? (Slide 14) for the contract of the previous question (s) ider to be an improvement with prophylaxic children and adolescents? (Slide 14) for the contract of the previous question (s) ider to be an improvement with prophylaxic children and adolescents? (Slide 14) for the contract of the previous question (s) ider to be an improvement with prophylaxic children and adolescents? (Slide 14) for the contract of the previous question (s) ider to be an improvement with prophylaxic children and adolescents? (Slide 14) for the contract of the previous question (s) ider to be an improvement with prophylaxic children and adolescents? (Slide 14) for the contract of the previous question (s) ider to be an improvement with prophylaxic children and adolescents? (Slide 14) for the contract of the previous question (s) ider to be an improvement with prophylaxic children and adolescents? (Slide 14) for the contract of t	year (any severity) on prophylaxis would you then gnificant improvement in children and adolescents? Insufficial improvement in children and adolescents? Our response to the previous question(s), if you do not ider to be an improvement with prophylaxis, what would be children and adolescents? (Slide 14) Outcome answer Increase Increase Increase both dose Increase both dose Increase both dose Increase increase both dose Increase increase both dose Increase increas	our response to the previous question(s), if you do not observe we ider to be an improvement with prophylaxis, what would you be more children and adolescents? (Slide 14) extractione answer Increase Increase both dose frequency of and Other prophylactic frequency of Switch to an (please treatment prophylactic alternative specify Insufficient alone treatment treatment below) expertise

Section 5. Mild or Moderate Patients

To see the results for the Round 1 questions from this section, please see the 'Results: Mild or Moderate Patients' section of the Round 1 Results Summary slideset attached to your Round 2 invitation email. At the end of each question in this Round 2 questionnaire, the relevant slide is shown in brackets. In light of Round 1 free text comments, two new questions have also been included in this section; these are denoted with 'New' in brackets.

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	
Mild haemophilia patients with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 22)	0		0	0	0	0	0	
Moderate haemophilia patients with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 22)	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	
Children and adolescents with haemophilia A and inhibitors should be treated with ITI to eradicate their inhibitors,						\bigcirc	0	
regardless of severity (New)		4:				4		
				•		agree):	evel of agre Insufficient expertise	D ₀
regardless of severity (New) Based on your responses to the p	trongly dis 1 (Strongly disagree)	agre	ee; 6	estro	ongly	agree): 6 (Strongly	Insufficient	D w

	agree) expertise an	(Strongly agree)	5	4	3	2	1 rongly agree)	•		
should be specifically considered when deciding whether to offer prophylaxis with bypassing agents to a mild or moderate haemophilia patients with inhibitors (Slide 23) Eradicating inhibitors is a priority in mild or moderate haemophilia patients with inhibitors (Slide 23) Please select the most important factor to consider when treating mild/moderate haemophilia A patients with inhibitors, when the aim is to eradicate their inhibitors (New): Please select one answer only Haemophilia Number or Length of Soore Insufficient Do not			0	0			0	nen ig rate	considered whether to offer with bypassin mild or moder patients with	specifically deciding who prophylaxis agents to a haemophilia
patients with inhibitors (Slide 23) Please select the most important factor to consider when treating mild/moderate haemophilia A patients with inhibitors, when the aim is to eradicate their inhibitors (New): Please select one answer only Haemophilia Number or Length of Joint Health severity of Nature of time with Quality of Score Insufficient Do not			0	0	0		\bigcirc	osidered o offer og rate	pecifically con ing whether to with bypassin mild or moder a patients with	should be s when decidi prophylaxis agents to a haemophilia
haemophilia A patients with inhibitors, when the aim is to eradicate their inhibitors (New): Please select one answer only Haemophilia Number or Length of Joint Health severity of Nature of time with Quality of Score Insufficient Do not			\bigcirc	0	\bigcirc	\bigcirc	0	nophilia	noderate haen	in mild or m
bieeds the inhibitor the inhibitor line (HJHS) experience to al	cate their inhibitors a h Insufficient Do not	licate the	erad ophi Heal	is to laem	aim i	the		th inhibitors,	A patients wi	aemophilia New): Please seled
	experience to ans				'1	-		time with		•

questionna	re, please add them to this text box:
* 1	
changes.	at I have responded to all questions, and do not wish to make any further
O Yes	
O No	
References	
	f questions and statements has been informed by the Steering
Committee, a	s well as the following literature:
1. Collins PW et	al. Diagnosis and Treatment of Factor VIII and IX Inhibitors in Congenital Haemophilia
4th Edition). Br	tish Journal of Haemophilia. 2013; 160(2): 153–170.
•	EHC Round Table of Stakeholders on 'Inhibitors in Haemophilia A'. EHC. 2016.
	s://www.ehc.eu/wp-content/uploads/EHC-Report-Round-Table-2016-02-Inhibitors-in-
	o <u>df</u> (Last accessed 08.10.18)]. Idez MF et al. Spanish Consensus Guidelines on Prophylaxis with Bypassing Agents in
•	emophilia and Inhibitors. Thrombosis and Haemostasis. 2016; 115(5): 872–895.
	et al. Guidelines for the Management of Hemophilia. Haemophilia. 2013; 19(1): e1–47
5. UKHCDO Pr	tocol for First Line Immune Tolerance Induction for Children with Severe Haemophil
	m the UKHCDO Inhibitor and Paediatric Working Parties (1st February 2017).
	[Available at: http://www.ukhcdo.org/wp-content/uploads/2017/01/ITI-protocol-2017.pdf
Last accessed	08.10.18)].
This study is i	itiated and jointly funded by Roche Products Ltd and Chugai Pharma UK Ltd
October 2018	
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We are sorry, the questionnaire has ended. This is likely to have happened if you stated that you did not confirm that you have responded to all questions and do not wish to make any further changes. You have a final opportunity to update your response to this question below.
* I confirm that I have responded to all questions, and do not wish to make any further changes. Selecting 'No - Disqualify and do not count my responses in results' will disqualify you from the questionnaire. You will have no further opportunities to return and complete the questionnaire.
○ Yes - I have no further changes
No - I wish to update my responses (adult care)
No - I wish to update my responses (care of children and adolescents)
 No - I wish to update my responses (all questions related to both adult care and care of children and adolescents)
No - Disqualify and do not count my responses in results
This study is initiated and jointly funded by Roche Products Ltd and Chugai Pharma UK Ltd. October 2018 RCUKEMIC00134
October 2018

Thank you for completing this Round 2 questionnaire. We will be in touch with you again shortly with the results of Round 2 as well as the questionnaire for Round 3.
In the meantime, if you have any comments or queries, please do not hesitate to contact Annabel Griffiths at annabel.griffiths@costellomedical.com .
This study is initiated and jointly funded by Roche Products Ltd and Chugai Pharma UK Ltd. October 2018 RCUKEMIC00134

We are sorry, the questionnaire has ended. This is likely to have happened if you did not confirm that you have responded to all questions and do not wish to make any further changes.

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Pharma UK Ltd.
October 2018
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Done

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