Establishing UK Consensus in Clinical Standard of Care in Haemophilia and Inhibitors – Round 2

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 care only
- ○ Care of children and adolescents only
- ○ All questions 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:

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)].

October 2018
RCUKEMIC00134

Establishing UK Consensus in Clinical Standard of Care in Haemophilia and Inhibitors – Round 2

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.

* Please rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree)

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

If you have any additional comments related to clinical goals, please add them to this text box:

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.

* Please rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
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)	○	○	○	○	○	○	○	○

* Please rank the following recommendations in terms of their importance when offering a further round of ITI to patients who inadequately respond to their first round of ITI at the full dose of 200 IU/kg/day (1=most important; 3=least important; Slide 13):

	Only treatment with plasma-derived FVIII (pdFVIII) should be introduced	Treatment with immunosuppression should be introduced without pdFVIII	Treatment combining both pdFVIII and immunosuppression should be introduced
1 (Most important)	○	○	○
2 (Second most important)	○	○	○
3 (Least important)	○	○	○
Insufficient expertise	○	○	○
Do not wish to answer	○	○	○

If you have any additional comments related to ITI, please add them to this text box:

Section 3. Bypassing Agents

To see the results for the Round 1 questions from this section, please see the 'Results: Bypassing Agents' 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 rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
Infusion requirements (both volume and frequency) must be considered when selecting a therapy (Slide 15)	○	○	○	○	○	○	○	○
Anamnesis is an important consideration when selecting a therapy prior to ITI or during ITI (Slide 16)	○	○	○	○	○	○	○	○
Anamnesis is an important consideration when selecting a therapy for a patient who has failed ITI (Slide 16)	○	○	○	○	○	○	○	○

If you have any additional comments related to bypassing agents, please add them to this text box:

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 rate your level of agreement with the following statement (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
High dose factor prophylaxis is justified in **adults** who are partially tolerised to ITI (Slide 18)	○	○	○	○	○	○	○	○

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 can justify prophylaxis)	1–3 bleeds per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to answer
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 can justify prophylaxis)	1–3 bleeds per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to answer
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?

	<30%	30–60%	>60%	Insufficient expertise	Do not wish to answer
In adults (Slide 22)	○	○	○	○	○
In children and adolescents (Slide 22)	○	○	○	○	○

* What **number of joint bleeds per year (any severity)** justifies prophylaxis?

	0 bleeds (any bleed can justify prophylaxis)	1–3 bleeds per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to answer
In adults (Slide 23)	○	○	○	○	○	○
In children and adolescents (Slide 23)	○	○	○	○	○	○

* Based on your response to the previous question, what **percentage reduction in joint bleeds per year (any severity)** on prophylaxis would you then consider to be a clinically significant improvement?

	<30%	30–60%	>60%	Insufficient expertise	Do not wish to answer
In adults (Slide 24)	○	○	○	○	○
In children and adolescents (Slide 24)	○	○	○	○	○

* Based on your response to the previous questions, what **percentage reduction in bleeds per year (any severity)** on prophylaxis would you then consider to be a clinically significant improvement?

	<30%	30–60%	>60%	Insufficient expertise	Do not wish to answer
In adults (Slide 25)	○	○	○	○	○
In children and adolescents (Slide 25)	○	○	○	○	○

* Based on your response to the previous question(s), if you do not observe what you would consider to be an improvement with prophylaxis, what would you be most likely to offer next?

Please select one answer per row

	Increase dose alone	Increase frequency of prophylactic treatment alone	Increase both dose and frequency of prophylactic treatment	Switch to an alternative treatment	Other (please specify below)	Insufficient expertise	Do not wish to answer
In adults (Slide 19)	○	○	○	○	○	○	○
In children and adolescents (Slide 19)	○	○	○	○	○	○	○

If you answered 'Other' for adults and/or children and adolescents, please explain below:

If you have any additional comments related to prophylaxis, please add them to this text box:

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.

* Please rate your level of agreement with the following statement (1=strongly disagree; 6=strongly agree)

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
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)	○	○	○	○	○	○	○	○

* Based on your responses to the previous questions, please rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
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)	○	○	○	○	○	○	○	○
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)	○	○	○	○	○	○	○	○
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)	○	○	○	○	○	○	○	○
Eradicating inhibitors is a priority in mild or moderate haemophilia patients with inhibitors (Slide 28)	○	○	○	○	○	○	○	○

* 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

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 wish to answer
○	○	○	○	○	○	○

If you have any additional comments related to mild or moderate patients, please add them to this text box:

Final Comments

If you have any additional comments relating to the topics raised in 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 make any further changes.

- ○ Yes
- ○ No

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)].

This study is initiated and jointly funded by Roche Products Ltd and Chugai Pharma UK Ltd.
October 2018
RCUKEMIC00134

Establishing UK Consensus in Clinical Standard of Care in Haemophilia and Inhibitors – Round 2

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.

* Please rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree)

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

If you have any additional comments related to clinical goals, please add them to this text box:

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.

* Please rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
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)	○	○	○	○	○	○	○	○

* Please rank the following recommendations in terms of their importance when offering a further round of ITI to patients who inadequately respond to their first round of ITI at the full dose of 200 IU/kg/day (1=most important; 3=least important; Slide 12):

	Only treatment with plasma-derived FVIII (pdFVIII) should be introduced	Only treatment with immunosuppression should be introduced	Treatment combining both pdFVIII and immunosuppression should be introduced
1 (Most important)	○	○	○
2 (Second most important)	○	○	○
3 (Least important)	○	○	○
Insufficient expertise	○	○	○
Do not wish to answer	○	○	○

If you have any additional comments related to ITI, please add them to this text box:

Section 3. Bypassing Agents

To see the results for the Round 1 questions from this section, please see the 'Results: Bypassing Agents' 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 rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
Infusion requirements (both volume and frequency) must be considered when selecting a therapy (Slide 14)	○	○	○	○	○	○	○	○
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 therapy for a patient who has failed ITI (Slide 15)	○	○	○	○	○	○	○	○

If you have any additional comments related to bypassing agents, please add them to this text box:

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 rate your level of agreement with the following statement (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
High dose factor prophylaxis is justified in **adults** who are partially tolerised to ITI (Slide 17)	○	○	○	○	○	○	○	○

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 justify prophylaxis)	1–3 bleeds per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to answer
○	○	○	○	○	○

* What **number of major bleeds per year (joint or muscle)** justifies prophylaxis in **adults**? (Slide 20)

0 bleeds (any bleed can justify prophylaxis)	1–3 bleeds per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to 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)

<30%	30–60%	>60%	Insufficient expertise	Do not wish to answer
○	○	○	○	○

* What **number of joint bleeds per year (any severity)** justifies prophylaxis in **adults**? (Slide 22)

0 bleeds (any bleed can justify prophylaxis)	1–3 bleeds per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to answer
○	○	○	○	○	○

* Based on your response to the previous question, what **percentage reduction in joint bleeds per year (any severity)** on prophylaxis would you then consider to be a clinically significant improvement in **adults**? (Slide 23)

<30%	30–60%	>60%	Insufficient expertise	Do not wish to answer
○	○	○	○	○

* Based on your response to the previous questions, what **percentage reduction in bleeds per year (any severity)** on prophylaxis would you then consider to be a clinically significant improvement in **adults**? (Slide 24)

<30%	30–60%	>60%	Insufficient expertise	Do not wish to answer
○	○	○	○	○

* Based on your response to the previous question(s), if you do not observe what you would consider to be an improvement with prophylaxis, what would you be most likely to offer next to **adults**? (Slide 18)

Please select one answer

Increase dose alone (Slide 18)	Increase frequency of prophylactic treatment alone	Increase both dose and frequency of prophylactic treatment	Switch to an alternative treatment	Other (please specify below)	Insufficient expertise	Do not wish to answer
○	○	○	○	○	○	○

If you answered 'Other', please explain below:

If you have any additional comments related to prophylaxis, please add them to this text box:

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.

* Please rate your level of agreement with the following statement (1=strongly disagree; 6=strongly agree)

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
Mild haemophilia patients with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 26)	○	○	○	○	○	○	○	○
Moderate haemophilia patients with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 26)	○	○	○	○	○	○	○	○
Adults with haemophilia A and inhibitors should be treated with ITI to eradicate their inhibitors, regardless of severity (New)	○	○	○	○	○	○	○	○

* Based on your responses to the previous questions, please rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
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)	○	○	○	○	○	○	○	○

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
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 27)	○	○	○	○	○	○	○	○
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 27)	○	○	○	○	○	○	○	○
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 27)	○	○	○	○	○	○	○	○
Eradicating inhibitors is a priority in mild or moderate haemophilia patients with inhibitors (Slide 27)	○	○	○	○	○	○	○	○

* 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

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 wish to answer
○	○	○	○	○	○	○

If you have any additional comments related to mild or moderate patients, please add them to this text box:

Final Comments

If you have any additional comments relating to the topics raised in 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 make any further changes.

- ○ Yes
- ○ No

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)].

This study is initiated and jointly funded by Roche Products Ltd and Chugai Pharma UK Ltd.
October 2018
RCUKEMIC00134

Establishing UK Consensus in Clinical Standard of Care in Haemophilia and Inhibitors – Round 2

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.

* Please rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree)

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

If you have any additional comments related to clinical goals, please add them to this text box:

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.

* Please rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
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)	○	○	○	○	○	○	○	○
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)	○	○	○	○	○	○	○	○
For patients who inadequately respond to ITI, ITI should be terminated (Slide 9)	○	○	○	○	○	○	○	○

* Please rank the following recommendations in terms of their importance when offering a further round of ITI to patients who inadequately respond to their first round of ITI at the full dose of 200 IU/kg/day (1=most important; 3=least important; Slide 9):

	Only treatment with plasma-derived FVIII (pdFVIII) should be introduced	Only treatment with immunosuppression should be introduced	Treatment combining both pdFVIII and immunosuppression should be introduced
1 (Most important)	○	○	○
2 (Second most important)	○	○	○
3 (Least important)	○	○	○
Insufficient expertise	○	○	○
Do not wish to answer	○	○	○

If you have any additional comments related to ITI, please add them to this text box:

Section 3. Bypassing Agents

To see the results for the Round 1 questions from this section, please see the 'Results: Bypassing Agents' 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 rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
Infusion requirements (both volume and frequency) must be considered when selecting a therapy (Slide 11)	○	○	○	○	○	○	○	○
Anamnesis is an important consideration when selecting a therapy prior to ITI or during ITI (Slide 12)	○	○	○	○	○	○	○	○
Anamnesis is an important consideration when selecting a therapy for a patient who has failed ITI (Slide 12)	○	○	○	○	○	○	○	○

If you have any additional comments related to bypassing agents, please add them to this text box:

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’.

* What **annual bleed rate** do you feel justifies prophylaxis **in children and adolescents**? (Slide 15)

0 bleeds (any bleed can justify prophylaxis)	1–3 bleeds per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to answer
○	○	○	○	○	○

* What **number of major bleeds per year (joint or muscle)** justifies prophylaxis in **children and adolescents**? (Slide 16)

0 bleeds (any bleed can justify prophylaxis)	1–3 bleeds per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to 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 **children and adolescents**? (Slide 17)

<30%	30–60%	>60%	Insufficient expertise	Do not wish to answer
○	○	○	○	○

* What **number of joint bleeds per year (any severity)** justifies prophylaxis in **children and adolescents**? (Slide 18)

0 bleeds (any bleed can justify prophylaxis)	1–3 bleeds per year	4–6 bleeds per year	7+ bleeds per year	Insufficient expertise	Do not wish to answer
○	○	○	○	○	○

* Based on your response to the previous question, what **percentage reduction in joint bleeds per year (any severity)** on prophylaxis would you then consider to be a clinically significant improvement in **children and adolescents**? (Slide 19)

<30%	30–60%	>60%	Insufficient expertise	Do not wish to answer
○	○	○	○	○

* Based on your response to the previous questions, what **percentage reduction in bleeds per year (any severity)** on prophylaxis would you then consider to be a clinically significant improvement in **children and adolescents**? (Slide 20)

<30%	30–60%	>60%	Insufficient expertise	Do not wish to answer
○	○	○	○	○

* Based on your response to the previous question(s), if you do not observe what you would consider to be an improvement with prophylaxis, what would you be most likely to offer next to **children and adolescents**? (Slide 14)

Please select one answer

Increase dose alone	Increase frequency of prophylactic treatment alone	Increase both dose and frequency of prophylactic treatment	Switch to an alternative treatment	Other (please specify below)	Insufficient expertise	Do not wish to answer
○	○	○	○	○	○	○

If you answered 'Other', please explain below:

If you have any additional comments related to prophylaxis, please add them to this text box:

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.

* Please rate your level of agreement with the following statement (1=strongly disagree; 6=strongly agree)

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
Mild haemophilia patients with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 22)	○	○	○	○	○	○	○	○
Moderate haemophilia patients with inhibitors should not be routinely offered prophylaxis with bypassing agents (Slide 22)	○	○	○	○	○	○	○	○
Children and adolescents with haemophilia A and inhibitors should be treated with ITI to eradicate their inhibitors, regardless of severity (New)	○	○	○	○	○	○	○	○

* Based on your responses to the previous questions, please rate your level of agreement with the following statements (1=strongly disagree; 6=strongly agree):

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
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 23)	○	○	○	○	○	○	○	○
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 23)	○	○	○	○	○	○	○	○

	1 (Strongly disagree)	2	3	4	5	6 (Strongly agree)	Insufficient expertise	Do not wish to answer
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 23)	○	○	○	○	○	○	○	○
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 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

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 wish to answer
○	○	○	○	○	○	○

If you have any additional comments related to mild or moderate patients, please add them to this text box:

Final Comments

If you have any additional comments relating to the topics raised in 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 make any further changes.

- ○ Yes
- ○ No

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)].

This study is initiated and jointly funded by Roche Products Ltd and Chugai Pharma UK Ltd.
October 2018
RCUKEMIC00134

Establishing UK Consensus in Clinical Standard of Care in Haemophilia and Inhibitors – Round 2

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

Establishing UK Consensus in Clinical Standard of Care in Haemophilia and Inhibitors – Round 2

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

Establishing UK Consensus in Clinical Standard of Care in Haemophilia and Inhibitors - Round 2

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.

This study is initiated and jointly funded by Roche Products Ltd and Chugai Pharma UK Ltd.
October 2018
RCUKEMIC00 134

Done