### Introduction to the Delphi Panel

This study is initiated and jointly funded by Roche Products Ltd and Chugai Pharma UK Ltd. Thank you for participating and for taking the time to complete this Round 1 questionnaire.

#### **Delphi Panel Methodology**

The Delphi method is a technique often used to gather consensus on specific issues from a group of experts in a field, by conducting a series of questionnaires. At each stage, results from the previous round are reported to participants, to provide them with an opportunity to reassess their initial judgements on the information in question. The Delphi method is characterised by multiple iterations of questionnaires, participant anonymity and the controlled feedback process. Responses are assessed based on whether they reach the pre-defined consensus threshold, which has been set at 70% agreement or disagreement in this study.

#### **Questionnaire Development**

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**

The questionnaire will begin with questions designed to understand your role and experience in treating haemophilia patients with inhibitors. In this section, you will also 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.

You will also 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. Following your selection 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. The 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 feel that you do not have sufficient expertise to answer an individual question, please select 'Do not wish to answer'. 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.

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.

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.

| * Participants in this Delphi Panel should have experience of treating at least one haemophilia patient with inhibitors. Please specify the number of haemophilia patients with inhibitors you are currently treating and/or have treated in the past 5 years: Selecting '0' or 'Do not wish to answer' will disqualify you from the questionnaire.   |
|---|
| ○ 0 ○ 1–2 ○ 3–5 ○ More than 5 ○ Do not wish to answer   |
| 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 <a href="mailto:annabel.griffiths@costellomedical.com">annabel.griffiths@costellomedical.com</a> .  |
| * Please tick the box to confirm that you wish to proceed with completing this questionnaire.   |
| I wish to proceed with completing this questionnaire  |
| 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: <a href="https://www.ehc.eu/wp-content/uploads/EHC-Report-Round-Table-2016-02-Inhibitors-in-Haemophilia-A.pdf">https://www.ehc.eu/wp-content/uploads/EHC-Report-Round-Table-2016-02-Inhibitors-in-Haemophilia-A.pdf</a> (Last accessed 25.04.18)].  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: <a href="http://www.ukhcdo.org/wp-content/uploads/2017/01/ITI-protocol-2017.pdf">http://www.ukhcdo.org/wp-content/uploads/2017/01/ITI-protocol-2017.pdf</a> (Last accessed 25.04.18)].  Zinc code: RCUKEMIC00060f; Date of Preparation: May 2018 |
|   |

We are sorry, the questionnaire has ended as you are ineligible to participate. This is likely to have happened if you stated:

- You have not treated any inhibitor patients in the previous 5 years
- 'Do not wish to answer' when asked about your experience treating inhibitor patients

To be eligible for the Delphi Panel, you must have treated at least one inhibitor patient in the previous 5 years, and be willing to state the number of patients treated. You have a final opportunity to update your response to the disqualification question below.

\* Please confirm the number of haemophilia patients with inhibitors you are currently treating and/or have treated in the past 5 years:

Selecting '0' or 'Do not wish to answer' will disqualify you from the questionnaire. You will have no further opportunities to return and complete the questionnaire.

| $\bigcirc$ 0 $\bigcirc$ 1–2 $\bigcirc$ 3–5 $\bigcirc$ More than 5 $\bigcirc$ Do not wish |
|--|
|--|

### **Background Questions**

| * Please specify your role:         |  |
|-------------------------------------|--|
| Consultant Haematologist            |  |
| Consultant Paediatric Haematologist |  |
| Haemophilia Physiotherapist         |  |
| Haemophilia Nurse                   |  |
| On not wish to answer               |  |
| Other (please specify below):       |  |
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| Please specify the UK region you practice in:  |  |
|--|--|
| East of England  |  |
| Cast Midlands  |  |
| Condon   |  |
| O North East of England & Cumbria  |  |
| O Northern Ireland   |  |
| O North West of England  |  |
| ○ Scotland   |  |
| O South East of England  |  |
| O South West of England  |  |
| ○ Wales  |  |
| ○ West Midlands  |  |
| ○ Yorkshire  |  |
| On not wish to answer  |  |
| Other (please specify below):  |  |
|  |  |
| This questionnaire contains general questions relating to all p participants are invited to respond to. In addition, some questi adult care (patients over the age of 16), while others relate to adolescents (patients who are 16 years old or younger). Pleasyou wish to respond to: | ions specifically relate to care of children and |
| Adult care only  |  |
| Care of children and adolescents only  |  |
| All questions related to both adult care and care of children a  | and adolescents                                  |
|  |  |

| This study is initiated and jointly fun<br>Ltd.<br>Zinc code: RCUKEMIC00060f; Date |  | , nama or |
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### **Round 1 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

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

|  | 1<br>(Strongly<br>disagree) | 2          | 3          | 4          | 5          | 6<br>(Strongly<br>agree) | Do not wish to answer |
|--|-----------------------------|------------|------------|------------|------------|--------------------------|-----------------------|
| The aims of treatment in haemophilia patients with inhibitors are considerably different from the aims of treatment in haemophilia patients without inhibitors |                             |            |            |            |            | 0                        | 0                     |
| Restoring/maintaining an <b>adult's</b> independence should be the main priority   | $\bigcirc$                  | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$               | $\circ$               |
| Restoring/maintaining a child's or an adolescent's lifestyle, in terms of their everyday activities, should be the main priority                               | 0                           |            |            |            |            | 0                        | 0                     |
| A key aim of treatment in <b>adults</b> with inhibitors is to eradicate the inhibitor  | $\circ$                     | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\circ$                  | 0                     |
| A key aim of treatment in <b>children and adolescents</b> with inhibitors is to eradicate the inhibitor  | 0                           |            |            |            |            | 0                        | 0                     |

|   | 1<br>(Strongly<br>disagree) | 2          | 3          | 4          | 5          | 6<br>(Strongly<br>agree) | Do not wish to answer |
|---|-----------------------------|------------|------------|------------|------------|--------------------------|-----------------------|
| Joint health should be regularly measured in routine comprehensive care visits by a suitably trained physiotherapist using a validated tool     |                             | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$               | $\bigcirc$            |
| Quality of life should be regularly measured in routine comprehensive care visits using a validated tool  | 0                           | 0          | 0          | 0          | 0          | 0                        |                       |
| Pain in <b>adults</b> should be regularly measured in routine comprehensive care visits using a validated tool                                  | $\circ$                     | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | 0                        | $\bigcirc$            |
| Adults with long-standing inhibitors who are unresponsive to immune tolerance induction (ITI) should not experience more than 6 bleeds per year | 0                           |            | 0          | 0          |            | 0                        | 0                     |
| <b>Children and adolescents</b> with inhibitors on ITI should not have any bleeds   | $\bigcirc$                  | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\circ$                  | $\bigcirc$            |
| f you have any additional comments related ext box:   | to clinical                 | goal       | s, ple     | ease       | add        | I them to t              | his                   |
| ection 2. Role of Immune  | Γolera                      | nc         | e I        | ndı        | uct        | tion (I                  | TI)                   |
|   |                             |            |            |            |            |                          |                       |
|   |                             |            |            |            |            |                          |                       |
|   |                             |            |            |            |            |                          |                       |

|   | 1<br>(Strongly<br>disagree) | 2          | 3      | 4          | 5          | 6<br>(Strongly<br>agree) |                 |
|---|-----------------------------|------------|--------|------------|------------|--------------------------|-----------------|
| Tolerance to factor therapy is demonstrated in <b>adults</b> when an inhibitor is no longer detected (negative Bethesda assay)  | 0                           | 0          | 0      | 0          | 0          |                          | (               |
| Tolerance to factor therapy is demonstrated in <b>adults</b> when a half-life of >7 hours is observed   | $\bigcirc$                  | $\bigcirc$ | 0      | $\bigcirc$ | $\bigcirc$ | $\bigcirc$               | (               |
| 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   | 0                           |            |        | 0          | 0          | 0                        | (               |
| If inadequate response to ITI is observed   |                             |            |        |            |            |                          |                 |
| naemophilia patients who inadequately resp  |                             |            |        |            |            |                          |                 |
| should be increased to this level  Please rank the following recommendations naemophilia patients who inadequately resp   | oond to ITI a               | at the     | e full | dose       | e of 2     | 200 IU/kg                |                 |
| should be increased to this level  Please rank the following recommendations naemophilia patients who inadequately resp (1=most important; 4=least important):  Treatment with plasma-derived | oond to ITI a               | at the     | e full | VF c       | onten      | 200 IU/kg                | /day            |
| Please rank the following recommendations naemophilia patients who inadequately respondent important; 4=least important):  Treatment with plasma-derived FVIII) should be introduced          | oond to ITI a               | at the     | e full | VF c       | onten      | 200 IU/kg                | □ C not wis ans |
| Please rank the following recommendations haemophilia patients who inadequately resp (1=most important; 4=least important):  Treatment with plasma-derived FVIII) should be introduced        | d FVIII with                | a hi       | gh vV  | VF co      | onten      | 200 IU/kg                | □ C not wis ans |

| 6=strongly agree):   | 1<br>(Strongly<br>disagree) | 2          | 3       | 4      | 5          | 6<br>(Strongly<br>agree) | Do not<br>wish to<br>answer |
|--|-----------------------------|------------|---------|--------|------------|--------------------------|-----------------------------|
| Infusion requirements (volume and frequency) are key factors which should be considered when selecting a therapy |                             | $\bigcirc$ | 0       | 0      |            |                          |                             |
| The avoidance of allergic reactions is a key factor which should be considered when selecting a therapy          | $\circ$                     | $\bigcirc$ | 0       | 0      | $\bigcirc$ | $\bigcirc$               | 0                           |
| Anamnesis is a key factor which should be considered when selecting a therapy                                    |                             | $\bigcirc$ | $\circ$ | 0      | $\bigcirc$ |                          | 0                           |
| If you have any additional comments related this text box:  ection 4. Prophylaxis                                | to bypassi                  | ing a      | igent   | ts, pl | ease       | e add ther               | n to                        |

|  | 1<br>(Strongly<br>disagree) | 2          | 3          | 4          | 5          | 6<br>(Strongly<br>agree) | Do<br>wis<br>ans |
|--|-----------------------------|------------|------------|------------|------------|--------------------------|------------------|
| In <b>adults</b> who have failed ITI, prophylaxis with bypassing therapy should be offered, if not already initiated   | 0                           | 0          | 0          | 0          |            |                          |                  |
| In <b>children and adolescents</b> who have failed ITI, prophylaxis with bypassing therapy should be offered, if not already initiated   | 0                           | $\bigcirc$ | 0          | $\bigcirc$ | 0          | 0                        |                  |
| Prophylaxis with bypassing agents is justified in <b>adults</b> who have had a single lifethreatening bleed  | 0                           | 0          | 0          | 0          | 0          |                          |                  |
| Prophylaxis with bypassing agents is justified in <b>children and adolescents</b> who have had a single life-threatening bleed   | $\bigcirc$                  | $\bigcirc$ | 0          | 0          | $\bigcirc$ | $\circ$                  |                  |
| Prophylaxis with bypassing agents is justified in <b>adults</b> who require joint preservation   | $\bigcirc$                  | $\bigcirc$ | $\bigcirc$ | $\circ$    | $\bigcirc$ | $\circ$                  |                  |
| Prophylaxis with bypassing agents is justified in <b>children and adolescents</b> who require joint protection   | 0                           | 0          | $\bigcirc$ | $\bigcirc$ | 0          | 0                        |                  |
| High dose factor prophylaxis is justified in adults who are partially tolerised to ITI   | 0                           | $\bigcirc$ | 0          | 0          | $\bigcirc$ | $\circ$                  |                  |
| High dose factor prophylaxis is justified in <b>children and adolescents</b> who are partially tolerised to ITI  | $\bigcirc$                  | 0          | $\bigcirc$ | 0          | $\bigcirc$ | $\bigcirc$               |                  |
| ease respond to the following questions with one se questions, please consider prophylaxis with answer these questions, please respond with what annual bleed rate do you feel justifies in adults | th bypass<br>NA:            | ing a      |            |            |            |                          | sh               |
| n children and   |                             |            |            |            |            |                          |                  |
|  |                             |            |            |            |            |                          |                  |

| In adults                         |   |
|-----------------------------------|---|
| In children and                   |   |
| adolescents                       |   |
| major bleeds (j                   | esponse to the previous question, what <b>percentage reduction in oint or muscle)</b> on prophylaxis would you then consider to be a ant improvement? |
| In adults                         |   |
| In children and adolescents       |   |
| What <b>number o</b>              | f joint bleeds (any severity) justifies prophylaxis?  |
| In adults                         |   |
| In children and adolescents       |   |
| significant impro In adults       | vement?   |
| In children and adolescents       |   |
|                                   | esponse to the previous questions, what <b>percentage reduction in</b> verity) on prophylaxis would you then consider to be a clinically              |
| bleeds (any sex significant impro |   |
| bleeds (any sev                   |   |
| bleeds (any sex significant impro |   |

|  | Please select one | Increase<br>dose alone | Increase frequency of prophylactic treatment alone | Increase<br>both dose<br>and<br>frequency<br>of<br>prophylactic<br>treatment | Stop<br>prophylaxis | Other<br>(please<br>specify<br>below) | Do not<br>wish to<br>answer           |
|--|-------------------|------------------------|--|--|---------------------|---------------------------------------|---------------------------------------|
| 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  Please rate your level of agreement with the following statement (1=strongly disagree; 6=strongly agree)  1 6 Do not (Strongly (Strongly wishted disagree) 2 3 4 5 agree) answer  Mild or moderate haemophilia patients with inhibitors should be considered for |                   |                        |  |  |                     |                                       | 0                                     |
| 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  Please rate your level of agreement with the following statement (1=strongly disagree; 6=strongly agree)  1 6 Do not (Strongly (Strongly wishted disagree) 2 3 4 5 agree) answer  Mild or moderate haemophilia patients with inhibitors should be considered for |                   | $\bigcirc$             | $\bigcirc$   |  | $\bigcirc$          | $\bigcirc$                            | $\bigcirc$                            |
| 1 (Strongly disagree) 2 3 4 5 agree) answer Mild or moderate haemophilia patients with inhibitors should be considered for   |                   | dditional con          | nments relate                                      | ed to prophyl  | laxis, please       | add them                              | to this text                          |
| (Strongly disagree) 2 3 4 5 agree) answer Mild or moderate haemophilia patients with inhibitors should be considered for   | ection 5: N       | <b>Mild or N</b>       | Moderat  | te Patie   | nts                 |                                       |                                       |
| Mild or moderate haemophilia patients with inhibitors should be considered for   | ection 5: N       | <b>Mild or N</b>       | Moderat  | te Patie   | nts                 | =strongly c                           | lisagree;                             |
|  | ection 5: N       | <b>Mild or N</b>       | Moderat  | te Patie ne following s  | nts<br>statement (1 | =strongly o                           | lisagree;<br>S Do not<br>engly wishto |

|                         | ase select at least one answer (multiple options can be selected)   |
|-------------------------|---|
|                         | Number of bleeds (any type)   |
|                         | Number of joint bleeds only   |
| I                       | nfusion requirements  |
| [                       | Do not wish to answer   |
|                         | Other (please state)  |
|                         |   |
|                         | should mild/moderate haemophilia A patients with inhibitors be treated to eradication inhibitors?   |
| Plea                    | ase provide your answer in the text box below:  |
| 7 700                   | do provido your unever in the text bex below.   |
| 7 700                   | de previde year anewer in the text sex selew.   |
|                         |   |
| If yo                   |   |
| If yo                   | u have any additional comments related to mild or moderate patients, please add   |
| If yo                   | u have any additional comments related to mild or moderate patients, please add   |
| If yo then              | u have any additional comments related to mild or moderate patients, please add n to this text box:  al Comments  |
| If yo then              | u have any additional comments related to mild or moderate patients, please add n to this text box:   |
| If yo then              | u have any additional comments related to mild or moderate patients, please add to this text box:  al Comments u have any additional comments relating to the topics raised in this Round 1   |
| If yo then              | u have any additional comments related to mild or moderate patients, please add to this text box:  al Comments u have any additional comments relating to the topics raised in this Round 1   |
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| If you then If you que: | u have any additional comments related to mild or moderate patients, please add not to this text box:  al Comments u have any additional comments relating to the topics raised in this Round 1 stionnaire, please add them to this text box: |

#### 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: <a href="https://www.ehc.eu/wp-content/uploads/EHC-Report-Round-Table-2016-02-Inhibitors-in-Haemophilia-A.pdf">https://www.ehc.eu/wp-content/uploads/EHC-Report-Round-Table-2016-02-Inhibitors-in-Haemophilia-A.pdf</a> (Last accessed 25.04.18)].
- 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: <a href="http://www.ukhcdo.org/wp-content/uploads/2017/01/ITI-protocol-2017.pdf">http://www.ukhcdo.org/wp-content/uploads/2017/01/ITI-protocol-2017.pdf</a> (Last accessed 25.04.18)].

### **Round 1 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

|  | 1<br>(Strongly<br>disagree) | 2          | 3          | 4          | 5          | 6<br>(Strongly<br>agree) |            |
|--|-----------------------------|------------|------------|------------|------------|--------------------------|------------|
| The aims of treatment in haemophilia patients with inhibitors are considerably different from the aims of treatment in haemophilia patients without inhibitors | 0                           | 0          | 0          | 0          | 0          | 0                        | 0          |
| Restoring/maintaining an <b>adult's</b> independence should be the main priority   | $\circ$                     | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\circ$                  | $\bigcirc$ |
| A key aim of treatment in <b>adults</b> with inhibitors is to eradicate the inhibitor  | 0                           | 0          | 0          | 0          | $\bigcirc$ | $\circ$                  |            |
| Joint health should be regularly measured in routine comprehensive care visits by a suitably trained physiotherapist using a validated tool                    | $\circ$                     | 0          | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\circ$                  | 0          |
| Quality of life should be regularly measured in routine comprehensive care visits using a validated tool   | 0                           |            | 0          | 0          | 0          | 0                        |            |
| Pain in <b>adults</b> should be regularly measured in routine comprehensive care visits using a validated tool   | $\bigcirc$                  | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | 0                        | $\bigcirc$ |
| Adults with long-standing inhibitors who are unresponsive to immune tolerance induction (ITI) should not experience more than 6 bleeds per year                | 0                           | 0          | 0          | 0          | 0          | 0                        | 0          |
| f you have any additional comments related ext box:  | to clinical                 | goal       | s, pl      | ease       | ado        | I them to t              | :his       |
|  |                             |            |            |            |            |                          |            |

Section 2. Role of immune Tolerance induction (111)

|   | 1<br>(Strongly<br>disagree) | 2          | 3          | 4          | 5          | 6<br>(Strongly<br>agree) |                        |
|---|-----------------------------|------------|------------|------------|------------|--------------------------|------------------------|
| Tolerance to factor therapy is demonstrated in <b>adults</b> when an inhibitor is no longer detected (negative Bethesda assay)  | 0                           | 0          | 0          | 0          | 0          |                          | (                      |
| Tolerance to factor therapy is demonstrated in <b>adults</b> when a half-life of >7 hours is observed   | $\bigcirc$                  | $\bigcirc$ | 0          | $\bigcirc$ | $\bigcirc$ | $\circ$                  | (                      |
| 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   | 0                           |            | 0          | 0          | 0          | 0                        |                        |
| If inadequate response to ITI is observed with a dose of <200 IU/kg/day, the dose   |                             | $\circ$    | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$               | (                      |
| naemophilia patients who inadequately resp  |                             |            |            |            |            |                          |                        |
| Please rank the following recommendations naemophilia patients who inadequately resp  | oond to ITI a               | at the     | e full     | dose       | e of 2     | 200 IU/kg                | □ D not wish           |
| Please rank the following recommendations naemophilia patients who inadequately response (1=most important; 4=least important):  Treatment with plasma-derive                             | oond to ITI a               | at the     | e full     | VF co      | onter      | 200 IU/kg                | not wish not wish wish |
| Please rank the following recommendations haemophilia patients who inadequately response (1=most important; 4=least important):  Treatment with plasma-derive FVIII) should be introduced | ed FVIII with               | a hi       | gh vV      | VF co      | onter      | 200 IU/kg                | □ C not wis ans        |

| S=strongly agree):   | 1<br>(Strongly<br>disagree) | 2          | 3     | 4          | 5          | 6<br>(Strongly<br>agree) | Do no wish to answe |
|--|-----------------------------|------------|-------|------------|------------|--------------------------|---------------------|
| Infusion requirements (volume and frequency) are key factors which should be considered when selecting a therapy |                             |            |       |            | 0          |                          | 0                   |
| The avoidance of allergic reactions is a key factor which should be considered when selecting a therapy          | 0                           | $\bigcirc$ | 0     | $\bigcirc$ | $\bigcirc$ | 0                        | $\bigcirc$          |
| Anamnesis is a key factor which should be considered when selecting a therapy                                    | $\circ$                     | 0          | 0     | 0          | $\bigcirc$ | $\circ$                  |                     |
| f you have any additional comments related his text box:   | I to bypassi                | ng a       | igent | s, pl      | ease       | e add ther               | n to                |

|   | Please rate your level of agreement with the 6=strongly agree):   | following s                 | state      | men        | ts (1      | =stro      | ongly disa               | gree;                      |
|---|---|-----------------------------|------------|------------|------------|------------|--------------------------|----------------------------|
|   |   | 1<br>(Strongly<br>disagree) | 2          | 3          | 4          | 5          | 6<br>(Strongly<br>agree) | Do not<br>wishto<br>answer |
|   | In <b>adults</b> who have failed ITI, prophylaxis with bypassing therapy should be offered, if not already initiated                  | $\circ$                     | 0          | 0          | 0          | 0          |                          |                            |
|   | Prophylaxis with bypassing agents is justified in <b>adults</b> who have had a single lifethreatening bleed                           | $\bigcirc$                  | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$               | $\bigcirc$                 |
|   | Prophylaxis with bypassing agents is justified in <b>adults</b> who require joint preservation  | $\circ$                     | 0          | 0          | $\bigcirc$ | $\bigcirc$ |                          |                            |
|   | High dose factor prophylaxis is justified in adults who are partially tolerised to ITI  | $\circ$                     | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$               | $\bigcirc$                 |
| * | What annual bleed rate do you feel justifies  What number of major bleeds (joint or mu  | prophylax                   |            |            |            | kis in     | adults?                  |                            |
|   | Based on your response to the previous quest major bleeds (joint or muscle) on prophyla clinically significant improvement in adults? |                             |            |            |            |            |                          |                            |
| * | What <b>number of joint bleeds (any severity</b>  | ) justifies p               | oropl      | hylax      | kis in     | adu        | ilts?                    |                            |
|   | Based on your response to the previous quest bleeds (any severity) on prophylaxis would significant improvement in adults?            |                             |            |            |            |            |                          | joint                      |

| significant impr  | rovement in ad   | phylaxis would jults?                                      | you then c                    | onsid | ier to d         | e a clir | nically                               |                   |
|---|--|--|-------------------------------|-------|------------------|----------|---------------------------------------|-------------------|
|   | to be an impro   | e previous ques  |                               |       |                  |          |                                       |                   |
| Increase dose<br>alone  | Increase<br>frequency of<br>prophylactic<br>treatment<br>alone | Increase both dose and frequency of prophylactic treatment | Stop<br>prophyla:             | xis   | Other of specify |          | e Do not<br>) ans                     | : wish to<br>swer |
|   |  |  |                               |       | (                |          | (                                     |                   |
| box:  |  | nments related   |                               |       |                  |          |                                       |                   |
| ection 5: Please rate you   | ur level of agre   | Moderate   |                               |       | nent (1:         | =stron(  | gly disag                             | gree;             |
| ection 5:   | ur level of agre   |  |                               | tatem | nent (1:         |          | gly disag<br>6<br>(Strongly<br>agree) | Do not            |
| ection 5:  Please rate you 6=strongly agree  Mild or modera inhibitors should | ur level of agre   | ement with the same a patients with ed for                 | following s<br>1<br>(Strongly | tatem |                  | (        | 6<br>(Strongly                        | Do not            |

|                 | sed on your response to the previous question, please select which criteria should be<br>sidered when deciding whether to offer prophylaxis with bypassing agents to a mile   |
|-----------------|---|
|                 | noderate haemophilia patient with inhibitors:   |
| Ple             | ase select at least one answer (multiple options can be selected)   |
|                 | Number of bleeds (any type)   |
|                 | Number of joint bleeds only   |
|                 | Infusion requirements   |
|                 | Do not wish to answer   |
|                 | Other (please state)  |
|                 |   |
| thei            | v should mild/moderate haemophilia A patients with inhibitors be treated to eradicar inhibitors?  |
| Ple             | ase provide your answer in the text box below:  |
|                 |   |
|                 |   |
| 14              |   |
|                 | ou have any additional comments related to mild or moderate patients, please add m to this text box:  |
|                 |   |
| ther            | m to this text box:   |
| Final If you    |   |
| Final If you    | al Comments ou have any additional comments relating to the topics raised in this Round 1   |
| Find If you que | al Comments ou have any additional comments relating to the topics raised in this Round 1   |
| Fin. If you que | al Comments ou have any additional comments relating to the topics raised in this Round 1 estionnaire, please add them to this text box:  |
| Find If you que | al Comments ou have any additional comments relating to the topics raised in this Round 1 estionnaire, please add them to this text box:  Infirm that I have responded to all questions, and do not wish to make any further nges.      |
| Find If you que | al Comments ou have any additional comments relating to the topics raised in this Round 1 estionnaire, please add them to this text box:  Infirm that I have responded to all questions, and do not wish to make any further nges.  Yes |
| Find If you que | al Comments ou have any additional comments relating to the topics raised in this Round 1 estionnaire, please add them to this text box:  Infirm that I have responded to all questions, and do not wish to make any further nges.  Yes |

#### References

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- 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.
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- 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: <a href="http://www.ukhcdo.org/wp-content/uploads/2017/01/ITI-protocol-2017.pdf">http://www.ukhcdo.org/wp-content/uploads/2017/01/ITI-protocol-2017.pdf</a> (Last accessed 25.04.18)].

### **Round 1 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

| Please rate your level of agreement with the S=strongly agree)   | ioliowing s                 | otate      | men        | ເວ (1      | =5110      | origiy disa              | igree;              |
|--|-----------------------------|------------|------------|------------|------------|--------------------------|---------------------|
|  | 1<br>(Strongly<br>disagree) | 2          | 3          | 4          | 5          | 6<br>(Strongly<br>agree) | Do no wish to answe |
| The aims of treatment in haemophilia patients with inhibitors are considerably different from the aims of treatment in haemophilia patients without inhibitors | 0                           |            |            |            |            | 0                        |                     |
| Restoring/maintaining a child or an adolescent's lifestyle, in terms of their everyday activities, should be the main priority                                 | $\bigcirc$                  | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ |            | $\bigcirc$               | $\bigcirc$          |
| A key aim of treatment in <b>children and adolescents</b> with inhibitors is to eradicate the inhibitor  | 0                           | 0          | 0          | 0          | 0          | 0                        | 0                   |
| Joint health should be regularly measured in routine comprehensive care visits by a suitably trained physiotherapist using a validated tool                    | $\bigcirc$                  | 0          | 0          | $\bigcirc$ | $\bigcirc$ | 0                        | 0                   |
| Quality of life should be regularly measured in routine comprehensive care visits using a validated tool   | 0                           | 0          | 0          | 0          | 0          | 0                        | 0                   |
| Children and adolescents with inhibitors on TI should not have any bleeds  | $\circ$                     | $\bigcirc$ | $\bigcirc$ | 0          | $\bigcirc$ | $\circ$                  | $\circ$             |
| you have any additional comments related ext box:  | to clinical                 | goal       | s, pl      | ease       | ado        | d them to t              | this                |
|  |                             |            |            |            |            |                          |                     |
| ection 2. Role of Immune   | Tolera                      | nc         | e I        | nd         | uci        | tion (l                  | TI)                 |
|  | , 0101a                     |            |            |            |            | (1                       | ,                   |
|  |                             |            |            |            |            |                          |                     |

| Please rate your level of agreement with the 6=strongly agree):   | e following s               | state | men   | ts (1: | =stro      | ongly disa               | gree;                           |
|---|-----------------------------|-------|-------|--------|------------|--------------------------|---------------------------------|
|   | 1<br>(Strongly<br>disagree) | 2     | 3     | 4      | 5          | 6<br>(Strongly<br>agree) | Do no wishto                    |
| 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 | 0                           | 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                           | $\bigcirc$                  | 0     | 0     | 0      | $\bigcirc$ | $\bigcirc$               | $\bigcirc$                      |
| Please rank the following recommendations haemophilia patients who inadequately responder (1=most important; 4=least important):              |                             |       |       |        |            |                          |                                 |
| Treatment with plasma-derive FVIII) should be introduced  | ed FVIII with               | a hi  | gh vV | VF c   | ontei      | nt (pd                   | ☐ Do<br>not<br>wish to<br>answe |
|   | ession shou                 | ld be | intro | oduce  | ed         |                          | ☐ Do<br>not<br>wish to<br>answe |
| Treatment combining both pd be introduced   | FVIII and in                | nmui  | nosu  | opres  | ssior      | should                   | □ Do<br>not<br>wish to<br>answe |
| # ITI should be terminated  |                             |       |       |        |            |                          | □ Do<br>not<br>wish to<br>answe |
| If you have any additional comments related   | d to ITI, plea              | ase a | add t | hem    | to th      | nis text bo              | X:                              |
|   |                             |       |       |        |            |                          |                                 |
| ection 3. Bypassing Agen  | ts                          |       |       |        |            |                          |                                 |

| 6=strongly agree):   |                             |            |            |            |            |                          |   |
|--|-----------------------------|------------|------------|------------|------------|--------------------------|---|
|  | 1<br>(Strongly<br>disagree) | 2          | 3          | 4          | 5          | 6<br>(Strongly<br>agree) |   |
| Infusion requirements (volume and frequency) are key factors which should be considered when selecting a therapy | 0                           |            | 0          |            | 0          | 0                        |   |
| The avoidance of allergic reactions is a key factor which should be considered when selecting a therapy          | 0                           | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | $\bigcirc$ | 0                        | 0 |
| Anamnesis is a key factor which should be considered when selecting a therapy                                    | 0                           | 0          | 0          | 0          | $\bigcirc$ | $\circ$                  | 0 |
| ection 4. Prophylaxis  |                             |            |            |            |            |                          |   |
| ection 4. Prophylaxis  |                             |            |            |            |            |                          |   |

| Please rate your level of agreement with the 6=strongly agree):  | following s                 | state      | men   | ts (1  | =stro   | ongly disa               | gree;                 |
|--|-----------------------------|------------|-------|--------|---------|--------------------------|-----------------------|
|  | 1<br>(Strongly<br>disagree) | 2          | 3     | 4      | 5       | 6<br>(Strongly<br>agree) | Do not wish to answer |
| In <b>children and adolescents</b> who have failed ITI, prophylaxis with bypassing therapy should be offered, if not already initiated | 0                           | 0          | 0     | 0      | 0       | 0                        | 0                     |
| Prophylaxis with bypassing agents is justified in <b>children and adolescents</b> who have had a single life-threatening bleed         | $\circ$                     | $\bigcirc$ | 0     | 0      | 0       | 0                        | $\circ$               |
| Prophylaxis with bypassing agents is justified in <b>children and adolescents</b> who require joint protection                         | 0                           | 0          | 0     | 0      | 0       | 0                        | 0                     |
| High dose factor prophylaxis is justified in <b>children and adolescents</b> who are partially tolerised to ITI                        | 0                           | $\bigcirc$ | 0     | 0      | $\circ$ | 0                        | $\circ$               |
| What <b>annual bleed rate</b> do you feel justifies  |                             |            |       |        |         |                          |                       |
| What number of major bleeds (joint or mu adolescents?  | scie) justii                | ies        | oropi | пунах  | as in   | children                 | and                   |
| Based on your response to the previous quest major bleeds (joint or muscle) on prophyla clinically significant improvement in children | xis would                   | you        | then  | cons   |         |                          |                       |
| What number of joint bleeds (any severity adolescents?   | <b>)</b> justifies p        | oropl      | hylax | kis in | chi     | dren and                 | I                     |
|  |                             |            |       |        |         |                          |                       |

| * Based on your of bleeds (any se significant impro      | verity) on prop  | phylaxis would   | you then co                 |     |            | uction in joint<br>linically            |
|--|--|--|-----------------------------|-----|------------|---|
| * Based on your bleeds (any se significant impro         | verity) on prop  | phylaxis would   | you then co                 | •   |            |   |
| * Based on your would consider offer next to <b>ch</b> i | to be an impro   | ovement with pr  |                             |     |            | ve what you<br>be most likely to        |
| Increase dose<br>alone                                   | Increase<br>frequency of<br>prophylactic<br>treatment<br>alone | Increase both dose and frequency of prophylactic treatment | Stop<br>prophylax           |     | her (pleas | se Do not wish to<br>w) answer          |
|  |  |  |                             |     |            |   |
| box:   |  |  |                             |     | ase add t  | them to this text                       |
| Section 5:   |  | Moderate ement with the                                    |                             |     | nt (1=stro | ngly disagree;                          |
| •  | e)   |  |                             |     |            |   |
| 6=strongly agre  | ee)  |  | 1<br>(Strongly<br>disagree) | 2 3 | 4 5        | 6 Do not (Strongly wishto agree) answer |

| Plea             | ase select at least one answer (multiple options can be selected)   |
|------------------|---|
|                  | Number of bleeds (any type)   |
|                  | Number of joint bleeds only   |
|                  | Infusion requirements   |
|                  | Do not wish to answer   |
|                  | Other (please state)  |
|                  |   |
| thei             | v should mild/moderate haemophilia A patients with inhibitors be treated to eradical rinhibitors?   |
| Plea             | ase provide your answer in the text box below:  |
|                  |   |
|                  |   |
|                  |   |
|                  | ou have any additional comments related to mild or moderate patients, please add in to this text box:   |
|                  |   |
| ther             | n to this text box:   |
| ther<br>Fina     |   |
| Final If you     | n to this text box:   |
| Final If you     | al Comments ou have any additional comments relating to the topics raised in this Round 1   |
| Final If you     | al Comments ou have any additional comments relating to the topics raised in this Round 1   |
| Fina If you      | al Comments ou have any additional comments relating to the topics raised in this Round 1   |
| Final If you que | al Comments but have any additional comments relating to the topics raised in this Round 1 stionnaire, please add them to this text box:  Infirm that I have responded to all questions, and do not wish to make any further      |
| Fina If you que  | al Comments ou have any additional comments relating to the topics raised in this Round 1 stionnaire, please add them to this text box:  Infirm that I have responded to all questions, and do not wish to make any further nges. |

#### References

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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)   |  |  |
| <ul> <li>No - I wish to update my responses (all questions related to both adult care and care of<br/>children and adolescents)</li> </ul>  |  |  |
| 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.  Zinc code: RCUKEMIC00060f; Date of Preparation: May 2018  |  |  |
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| Thank you for completing this Round 1 questionnaire. We will be in touch with you again shortly with the results of Round 1 as well as the questionnaire for Round 2.   |
|---|
| In the meantime, if you have any comments or queries, please do not hesitate to contact Annabel Griffiths at <a href="mailto:annabel.griffiths@costellomedical.com">annabel.griffiths@costellomedical.com</a> . |
| This study is initiated and jointly funded by Roche Products Ltd and Chugai Pharma UK Ltd.  Zinc code: RCUKEMIC00060f; Date of Preparation: May 2018  |
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We are sorry, the questionnaire has ended. This is likely to have happened if you stated that:

- You have not treated any inhibitor patients
- 'Do not wish to answer' when asked about your experience treating inhibitor patients
- 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.

Zinc code: RCUKEMIC00060f; Date of Preparation: May 2018

Done

1 of 1