ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

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Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Hanny
2. Surname (Last Name): Al-Samkari
3. Date: 20-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Agios	☑	☑	☐	☐	Consultancy, research funding to institution
Dova	☑	☑	☐	☐	Consultancy, research funding to institution
Amgen	☑	☐	☐	☐	Research funding to institution

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Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Al-Samkari reports grants and personal fees from Agios, grants and personal fees from Dova, grants from Amgen, outside the submitted work; .

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Elisabetta
2. Surname (Last Name): Buscarini
3. Date: 03-August-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name:

5. Manuscript Title: International Guidelines for the diagnosis and Management of hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Dr. Buscarini has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Murali
2. Surname (Last Name): Chakinala
3. Date: 28-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Cure HHT Foundation	☑	☐	☐	☐	Participated in multi-center clinical trial in HHT sponsored by the Foundation. Monies went to my institution.
Glaxo-Smith-Klein	☑	☐	☐	☐	Participated in multi-center clincial trial for HHT-related bleeding. Monies went to my institution.

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Dr. Chakinala reports grants from Cure HHT Foundation, grants from Glaxo-Smith-Klein, during the conduct of the study; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Mark
2. Surname (Last Name): Chesnutt
3. Date: 19-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it):

Section 2. The Work Under Consideration for Publication

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Dr. Chesnutt has nothing to disclose.

Evaluation and Feedback

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

1. Given Name (First Name) Marianne

2. Surname (Last Name) Clancy

3. Date July 21, 2020

4. Are you the corresponding author? [X] Yes [ ] No

5. Manuscript Title

"International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia"

6. Manuscript Identifying Number (if you know it)

M20-1443

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? [ ] Yes [X] No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Miles
2. Surname (Last Name): Conrad
3. Date: 18-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: Second International Guidelines for the Diagnosis and Management of HHT

6. Manuscript Identifying Number (if you know it):

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 6. Disclosure Statement

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Dr. Conrad has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Daniel
2. Surname (Last Name): Cortes
3. Date: 06-June-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name:

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Mr. Cortes has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Claudia
2. Surname (Last Name): Crocione
3. Date: 29-July-2020

4. Are you the corresponding author? [✓] Yes [ ] No

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? [ ] Yes [✓] No

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Are there any relevant conflicts of interest? [ ] Yes [✓] No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? [ ] Yes [✓] No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jama
2. Surname (Last Name): Darling
3. Date: 29-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Els
2. Surname (Last Name): de Gussem
3. Date: 19-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr Faughnan

5. Manuscript Title: "International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia"

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

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Dr. de Gussem has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Carol
2. Surname (Last Name): Derksen
3. Date: 28-July-2020

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.

Other: Anything not covered under the previous three boxes

Pending: The patent has been filed but not issued

Issued: The patent has been issued by the agency

Licensed: The patent has been licensed to an entity, whether earning royalties or not

Royalties: Funds are coming in to you or your institution due to your patent

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SAVE

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name)

2. Surname (Last Name)

3. Date

4. Are you the corresponding author? ☒ Yes ☐ No

5. Manuscript Title

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ No

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Section 6. Disclosure Statement

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Sophie
2. Surname (Last Name): Dupuis-Girod
3. Date: 21-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr. M.E. Faughnan

5. Manuscript Title: Second International Guidelines for the Diagnosis and Management of HHT

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

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Dr. Dupuis-Girod has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Marie

2. Surname (Last Name): Faughnan

3. Date: 28-July-2020

4. Are you the corresponding author? [✓] Yes [ ] No

5. Manuscript Title: Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? [ ] Yes [✓] No

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Are there any relevant conflicts of interest? [ ] Yes [✓] No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? [ ] Yes [✓] No

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Dr. Faughnan has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Patrick
2. Surname (Last Name): Foy
3. Date: 29-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it):

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Alexion	☐	☑	☐	☐	
Incyte	☐	☑	☐	☐	

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Foy reports personal fees from Alexion, personal fees from Incyte, outside the submitted work; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Urban
2. Surname (Last Name): Geisthoff
3. Date: 19-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name:

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
CureHHT	☑	☐	☐	☐	Travel grant for the consensus conference

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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☐ No other relationships/conditions/circumstances that present a potential conflict of interest

UG is member of the board of directors of the German HHT self-help group (M. Osler-Selbsthilfe) and president of the board of trustees of the German HHT Foundation (Osler-Stiftung)

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Dr. Geisthoff reports grants from CureHHT, during the conduct of the study; and UG is member of the board of directors of the German HHT self-help group (M. Osler-Selbsthilfe) and president of the board of trustees of the German HHT Foundation (Osler-Stiftung).

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): James
2. Surname (Last Name): Gossage
3. Date: 24-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Cure HHT Foundation	☐	☐	☐	☑	Travel reimbursement to attend the guidelines conference; not a conflict of interest.

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Gossage reports other from Cure HHT Foundation, during the conduct of the study; .

Evaluation and Feedback

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Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

Relationships not covered above.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Adrienne
2. Surname (Last Name): Hammill
3. Date: 07/23/2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time**

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
	☐	☐	☐	☐		

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Hammill has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Ketil
2. Surname (Last Name): Heimdal
3. Date: 23-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No Corresponding Author's Name

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Heimdal has nothing to disclose.

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Katharine
2. Surname (Last Name): Henderson
3. Date: 18-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Ms. Henderson has nothing to disclose.

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Steven
2. Surname (Last Name): Hetts
3. Date: 19-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Faughnan

5. Manuscript Title: HHT Guidelines

6. Manuscript Identifying Number (if you know it):

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
National Institutes of Health: NCI and NIBIB	☑	☐	☐	☐	Medical device research
Siemens Healthineers	☑	☐	☐	☐	Angiography system research
Stryker Neurovascular	☐	☐	☐	☑	Core Angiography Lab for Clinical Trial
MicroVention Terumo	☐	☑	☐	☐	DSMB Member for Clinical Trial
Route 92 Medical	☐	☑	☐	☑	CEC Adjudicator for Clinical Trial
ThrombX Medical	☐	☐	☐	☑	Stock Ownership in Stroke Device Startup Company
Imperative	☐	☑	☐	☐	CEC Chair for Clinical Trial

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Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

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Dr. Hetts reports grants from National Institutes of Health: NCI and NIBIB, grants from Siemens Healthineers, other from Stryker Neurovascular, personal fees from MicroVention Terumo, personal fees and other from Route 92 Medical, other from ThrombX Medical, personal fees from Imperative, outside the submitted work; .

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Pending: The patent has been filed but not issued
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Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Vivek
2. Surname (Last Name): Iyer
3. Date: 18-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: "nternational Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

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☑ No other relationships/conditions/circumstances that present a potential conflict of interest

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Iyer has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Raj
2. Surname (Last Name): Kasthuri
3. Date: 18-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 6. Disclosure Statement

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Dr. Kasthuri has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Anette D.
2. Surname (Last Name): Kjeldsen
3. Date: 20-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No Corresponding Author's Name:

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
The Christopher McMahon Memorial	☐	☐	☐	☑	Private funding from an HHT patient, given to support the guideline meeting. The funding covered the meeting and the transportation.

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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☐ No other relationships/conditions/circumstances that present a potential conflict of interest

Member of VASCERN, European reference network on vascular diseases.

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Section 6. Disclosure Statement

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Dr. Kjeldsen reports other from The Christopher McMahon Memorial, during the conduct of the study; and Member of VASCERN, European reference network on vascular diseases. .

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Masaki
2. Surname (Last Name): Komiyama
3. Date: 23-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Komiyama has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Kevin
2. Surname (Last Name): Korenblat
3. Date: 18-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name:

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

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Dr. Korenblat has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Kelly
2. Surname (Last Name): Lang-Robertson
3. Date: 22-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: M.E. Faughnan

5. Manuscript Title: Second International Guidelines for the Diagnosis and Management of HHT

6. Manuscript Identifying Number (if you know it):

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 5. Relationships not covered above

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Ms. Lang-Robertson has nothing to disclose.

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Section 1. Identifying Information

1. Given Name (First Name): Andrea
2. Surname (Last Name): Lausman
3. Date: 27-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it):

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Lausman has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Hans-Jurgen
2. Surname (Last Name): Mager
3. Date: 19-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Dr. Mager has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jamie
2. Surname (Last Name): McDonald
3. Date: 18-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No Corresponding Author's Name:

5. Manuscript Title: "International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia"

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): John
2. Surname (Last Name): McMahon Jr
3. Date: 31-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it)

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Justin

2. Surname (Last Name): McWilliams

3. Date: 18-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Penumbra	☐	☑	☐	☐	Educational seminars

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. McWilliams reports personal fees from Penumbra, outside the submitted work; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Mary
2. Surname (Last Name): Meek
3. Date: 29-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of HHT

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 6. Disclosure Statement

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Dr. Meek has nothing to disclose.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Scott
2. Surname (Last Name): Olitsky
3. Date: 25-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Valerie
2. Surname (Last Name): PALDA
3. Date: 29-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: Guidelines for the diagnosis and management of HHT

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
Cure HHT Foundation	☐	☑	☐	☐	Honorarium for guideline facilitation.	

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. PALDA reports that she was paid an honorarium from the Cure HHT Foundation for her time as guideline facilitator. She did not vote on any of the recommendations.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Sara
2. Surname (Last Name): Palmer
3. Date: 29-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it):

Section 2. The Work Under Consideration for Publication

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Dr. Palmer has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Rose
2. Surname (Last Name): Pantalone
3. Date: 23-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: "International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia"

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

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Dr. Pantalone has nothing to disclose

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4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Marie Faughnan

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Dr. Piccirillo reports personal fees from Bind On-Demand Health Insurance, outside the submitted work; In addition, Dr. Piccirillo has a patent NOSE-HHT licensed to Jay Piccirillo, Andrew Peterson, Dorina Kallogjeri .

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International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

Manuscript# - M20-1443

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Second International Guidelines for the Diagnosis and Management of HHT

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Competing interests: VAP received an honorarium for moderating the HHT Guidelines Conference, DC received an honorarium for conference participation and KLR was compensated for conducting the literature search and evidence review; neither participated in voting.

Potential conflicts of interest were reported prior to the Guidelines Conference: All were classified as "no significant conflict", as per process detailed in the methods.

Contributors: All of the authors contributed to the Guidelines development and the resulting manuscript.

Word Count: 14,091

Abbreviations:

ACVRL1 = activin A receptor like type 1
AE = adverse events
$AgNO_3$ = silver nitrate
APC = argon plasma coagulation
AV = arteriovenous
AVF = arteriovenous fistula
AVM(s) = arteriovenous malformation(s)
CBC=complete blood count
CE = capsule endoscopy
CVM = capillary vascular malformation
CO_2 = carbon dioxide
CT = computed tomography
DVT = deep venous thrombosis
EGD = esophagogastroduodenoscopy
ENG = endoglin
ENT = ear nose and throat
ERCP= endoscopic retrograde cholangiopancreatography
ESS= epistaxis severity score
GI = gastrointestinal
HHT = hereditary hemorrhagic telangiectasia
HHT1= hereditary hemorrhagic telangiectasia type 1
HHT2= hereditary hemorrhagic telangiectasia type 2
HOCF = high-output cardiac failure
IV = intravenous
JP-HHT = juvenile polyposis-hereditary hemorrhagic telangiectasia overlap
MCV = mean corpuscular volume
MELD= Model for End Stage Liver Disease
MR = magnetic resonance
MRI = magnetic resonance imaging
OLT = orthotopic liver transplant
PaO_2 = arterial partial pressure of oxygen
QOL= quality of life
RBC = red blood cell
RCT = Randomized Control Trial
SMAD4= Mothers Against Decapentaplegic homolog 4
TTCE = transthoracic contrast echocardiography
VEGF= vascular endothelial growth factor
VMs = vascular malformations
WHO = World Health Organization

Centers with recognized expertise in the diagnosis and management of HHT can be located at https://curehht.org/, the website for Cure HHT and vascern.eu, the website for the European Reference Network for Rare Vascular Diseases.

ABSTRACT

Background: HHT is an autosomal dominant disease with an estimated prevalence of approximately 1 per 5,000, characterized by the presence of vascular malformations (VMs) that often result in chronic bleeding, acute hemorrhage and complications from shunting through VMs. HHT is under-diagnosed and families may be unaware of the available screening and treatment, resulting in unnecessary and severe complications such as stroke, heart failure and life-threatening hemorrhage in children and adults.

Objective: The goal of the Second International HHT Guidelines process was to develop evidence-based consensus guidelines for the management and prevention of HHT-related symptoms and complications.

Methods: The guidelines were developed using the AGREE-II framework and GRADE methodology. The Guidelines expert panel included expert physicians (clinical and genetic) in HHT from fifteen countries, guidelines methodologists, health care workers, health care administrators, patient advocacy representatives and people with HHT. During the pre-conference process, the expert panel generated clinically relevant questions in six priority topic areas: Epistaxis, Gastrointestinal Bleeding, Anemia & Iron Deficiency, Liver VMs, Pediatric Care, Pregnancy & Delivery. A systematic literature search was conducted, and articles meeting a priori criteria were included to generate evidence tables which were used as the basis for recommendation development. The expert panel subsequently convened during a guidelines conference to partake in a structured consensus process, during which recommendations reaching >=80% consensus were discussed and approved.

Recommendations: Six new recommendations in each of the six priority topic areas (36 recommendations in total) were generated and approved to highlight new evidence in existing topics and provide guidance in three new areas: anemia, pediatrics and pregnancy. These recommendations should facilitate implementation of key components of HHT care into clinical practice.

Word count=274

Funding Sources: The Christopher McMahon Family and Cure HHT.
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Role of Funding Sources: The funding sources had no role in the design, conduct or reporting of the study or in the decision to submit the results for publication. Although the funding sources were not directly involved in the generation of the recommendations, some of the participants in the guidelines process were also board members of Cure HHT, officers of Cure HHT or members of various Cure HHT committees.

BACKGROUND

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease with an estimated prevalence of approximately 1 per 5,000(1, 2). It is characterized by clinically significant vascular malformations (VMs) of skin and mucous membranes of the nose and gastrointestinal tract as well as the brain, lung and liver. HHT is under-diagnosed(3-5) and there is often a long diagnostic delay(3, 6, 7). As such, care providers and families are often unaware of the available screening and treatment, resulting in serious preventable complications such as stroke and life-threatening hemorrhage in children and adults. The first International HHT Guidelines process in 2006 developed evidence-informed consensus guidelines regarding the diagnosis of HHT, the prevention of HHT-related complications and the treatment of symptomatic disease(8).

The goal of this Second International HHT Guidelines process was to develop evidence-informed consensus guidelines regarding the diagnosis of HHT and the prevention of HHT-related complications and treatment of symptomatic disease in areas not previously addressed by guidelines and areas where significant new literature had been published.

Making the diagnosis of HHT in a patient allows the appropriate screening and preventive treatment to be undertaken in the patient and their affected family members. HHT has traditionally been diagnosed on the basis of its clinical features. The most common symptom of HHT, epistaxis, has an age-related expression, as does the appearance of the typical telangiectasia. The average age of onset for epistaxis is 12 years, with 90% affected by age 40 years(9-11). There are limited longitudinal natural history studies of HHT clinical manifestations and how these vary with genotype(12). In 2000, consensus clinical diagnostic criteria known as the Curaçao Criteria were published(13) (**Table 1**), and these were upheld in the first International HHT Guidelines(8). Using these criteria, a diagnosis of HHT is considered ‘definite’ if three or more Curaçao criteria are present, ‘possible or suspected’ if two criteria are present, and ‘unlikely’ if 0 or 1 criterion is present.

Genetic testing is now also available for HHT diagnosis. Causative gene mutations for HHT have been identified in these genes: Endoglin (*ENG*, HHT1), Activin-Receptor Like kinase-1 (*ACVRL1*, HHT2), and Mothers Against Decapentaplegic homolog 4 (*SMAD4*, JP-HHT). In people meeting Curaçao criteria for definite HHT, up to 97% were found to have a mutation in *ENG*, *ACVRL1*, or *SMAD4*(14) . Additional rare genetic conditions associated with HHT phenotype have also been reported, such as mutations in *GDF2* (BMP9), *EPHB4* and *RASA1*(15, 16). As such, genetic testing for HHT mutations was recommended, by the first International HHT Guidelines for asymptomatic or minimally symptomatic people from a family with known HHT, and other select individuals, as detailed in **Table 2.**

Several other recommendations published in the first International HHT Guidelines were not re-assessed during this current process and remain currently recommended. They are detailed in **Table 3**.

METHODS

The Second International HHT Guidelines process was developed using the AGREE-II framework and GRADE methodology, using a systematic search strategy and literature review, with incorporation of expert evidence in a structured consensus process to supplement the published literature. The Guidelines Working Group included clinical and genetic experts in all aspects of HHT from fifteen countries, guidelines methodologists, health care workers, health care administrators, HHT clinic staff, medical trainees, patient advocacy representatives, and patients with HHT. The Working Groups determined clinically relevant questions during the pre-conference process. The literature search was conducted during May and June 2019 using the OVID MEDLINE database. The Working Group subsequently convened at the Guidelines Conference in November 2019 in Toronto Canada to partake in a structured consensus process using the evidence tables generated from the systematic searches.

Scope and Key Questions:

Priority topics for the second guidelines process were determined based on polling the international community for priority areas in need of updating, based on not having been previously addressed or based on presence of significant new evidence. This polling revealed that recommendations for the following topics were not prioritized for updating at this time, and the previously established recommendations would therefore not be reassessed (they are detailed in **Table 3**): Diagnosis of HHT, Brain VMs, Pulmonary AVMs. Other areas that were prioritized for updates, but also had some first International HHT Guidelines recommendations that were not reassessed (they are detailed in **Table 3)** are: Epistaxis, Liver VMs. One topic area from the first guidelines was prioritized and fully updated in the new guidelines: GI Bleeding. New topics that had not been previously addressed included: Anemia, Pediatrics, and Pregnancy. Once the six topic areas (Epistaxis, GI Bleeding, Liver VMs, Anemia, Pediatric HHT and Pregnancy) were defined, the expert panel was selected and topic groups, each with a topic leader, were established. The topic groups then developed a list of key questions, to guide evidence search and retrieval.

Identification of Evidence: Six sets of search strategies were developed and executed between May and June 2019 in Ovid MEDLINE by a medical librarian (KLR) with input from the Chair. Combinations of topic-specific controlled subject headings (MeSH terms) and relevant keywords were used to identify English language studies addressing the key questions developed by each of the topic groups. Two reviewers (MEF and KLR) reviewed the titles and abstracts of each of the 1,576 initial results, and independently applied the pre-established inclusion criteria. Of these, 449 records indicated by either reviewer as potentially meeting the inclusion criteria or requiring additional review were retrieved in full text for further consideration. Both reviewers independently considered the full text of these papers, and where both reviewers agreed, the study was included and progressed to the data extraction stage. Any disagreements were reviewed and resolved by electronic communication until

concordance was fully satisfied. A total of 221 studies met the inclusion criteria and were included in evidence tables. Number of results reviewed at each stage are illustrated in **Figure 1**. Additional papers identified by working group members after the search was conducted were also reviewed and considered for inclusion. Full search strategies and description of inclusion criteria are available in **Appendix 1**.

Data Extraction and Appraisal:

Key data from the included studies was systematically extracted and summarized into evidence tables. Due to the lack of randomized trials for most of the key questions in the area, two categories of studies were included: randomized control trials, which could be considered 'high quality' evidence if of sufficient size and quality, and other studies without blinding or randomization, considered to be 'low quality' evidence according to GRADE(17). The quality of the included RCTs was assessed (**Appendix 4**) using the structured framework of the Cochrane Risk of Bias Tool(18).

Generation of Draft Recommendations: The guidelines chairs and methodologists oriented the full panel on GRADE methodology, during teleconference sessions. The six topic groups met in the months preceding the conference by teleconference and/or email conversations to generate draft recommendations based on the key questions and evidence tables. These recommendations were reviewed and edited with the panel lead (MEF) and methodologist (VP) to be consistent with GRADE formatting for levels of evidence and strength of recommendation. Draft recommendations were distributed to all panel members 2 weeks before the consensus meeting, for full review.

Conflict of Interest Disclosures and Management:

Prior to the conference, all conference attendees filled out a conflict of interest disclosure. All disclosed potential conflicts were reviewed by the chair and, if necessary, discussed in further detail with the attendee to determine if disclosed relationship had any potential influence on a recommendation. The disclosed conflicts were then classified as: "no significant conflict", "disclose in manuscript, but not likely to affect recommendation", "could potentially affect recommendation and attendee should vote "abstain based on conflict of interest". Upon review, it was determined that all attendees had no significant conflict.

Consensus Conference:

At the beginning of the conference, recommendation development methods were reviewed and discussed with the attendees(panel). For each topic area, topic groups met and refined draft recommendations. For each topic group, the topic leader presented the draft recommendation and quality of evidence to the entire panel, with supporting details for clinical considerations, after which time was allowed for discussion. The panel then voted anonymously on the wording of the recommendation and quality of evidence, using a standard format for wording and the evidence levels HIGH-MODERATE-LOW-VERY LOW (consensus). The topic leader then presented the draft strength of recommendation with justification by GRADE methodology (quality of evidence, balance of benefits and harms, values and preferences, cost - not considered explicitly but discussed as relevant). The panel then voted on the strength of

recommendation. Consensus of 80% had to be achieved to allow the recommendation to be included in the guideline. If the initial vote was less than 80% consensus, the recommendation was deferred to the second day of the conference for further discussion and revision. Subsequent voting had also to achieve 80% consensus for the recommendation to be included. In the event that the panel did not achieve 80% consensus for strength of recommendation, the alternate strength was voted upon (STRONG/WEAK). If consensus was still not achieved, discussion continued to clarify the panel's views on which factors (quality of evidence, balance of benefits and harms, values and preferences, cost) were driving dissent. In this way, the panel made every effort to make explicit non-evidentiary factors influencing recommendation strength. After all recommendations were discussed and voted upon, the chair reviewed next steps, surveyed the panel regarding future research and guidelines priorities (**Appendix 2**) and the conference was adjourned.

External Review Process:

External experts and organizations relevant to the care of HHT were asked to comment on the recommendations generated during the conference. Comments were collated and addressed. Details regarding reviewers, their feedback and how it was addressed are available in **Appendix 3**.

Patient Involvement:

Patient representatives (patients with HHT and caregivers as well as Cure HHT and other patient advocacy organizations) were included at every step of the development process. Patient values were incorporated into the recommendations, during discussion and voting. Patients voted anonymously on recommendations and participated as manuscript authors.

Role of Funding Sources:

The funding sources, namely the Christopher McMahon Family and Cure HHT, the Nelson Arthur Hyland Foundation, and the Li Ka Shing Knowledge Institute of St Michael's Hospital, had no role in the design, conduct or reporting of the study or in the decision to submit the results for publication. Although the funding sources were not directly involved in the generation of the recommendations, some of the participants in the guidelines process were also board members of Cure HHT, officers of Cure HHT or members of various Cure HHT committees.

Epistaxis Management

Background:

Epistaxis is the most common symptom of HHT, developing in 90% of adults with the disease, affecting quality of life and often leading to iron deficiency and anemia. Typically, turbulent nasal airflow with breathing leads to mucosal dryness and bleeding from telangiectases of the nasal mucosa. As such, replacing lost moisture to help prevent the telangiectases from cracking and bleeding is a mainstay of epistaxis care. In a randomized clinical trial comparing topical therapies to saline as placebo, saline was found to significantly reduce the epistaxis severity score (ESS) at both 12 and 24 weeks after therapy(19).

In many patients, additional therapies are often considered, when symptoms are persistent or severe, despite moisturization. Tranexamic acid is an oral antifibrinolytic agent that can stabilize clots by preventing premature clot lysis and has been shown to decrease intraoperative bleeding in other conditions. Two RCTs (**Table 4**) of oral tranexamic acid demonstrated a significant decrease in epistaxis severity(20, 21) with minimal adverse events. Neither study showed a significant improvement in hemoglobin but baseline levels were normal or nearly normal in both studies so the opportunity for improvement may have been small. Three studies in HHT have not found an increased risk of thrombosis with tranexamic acid(20-22), though there remains concern that this agent should be avoided in patients at high risk for thrombosis (e.g. patients with a history of arterial thrombosis or unprovoked venous thrombosis), in patients with atrial fibrillation and patients with thrombophilia or elevated factor VIII.

Various ablative therapies have been studied in controlled and uncontrolled case series (**Table 5**). Lasers, including the Argon, potassium-titanyl-phosphate (KTP), and Nd-YAG lasers(23). Outcomes are variable, with at best temporary and partial improvement in epistaxis. However, side effects of laser treatments overall are relatively minor. Access can be limited by required laser safety precautions, local availability of specific lasers and costs. Sclerotherapy with foamed sodium tetradecyl sulfate to the nasal cavity can be performed in the outpatient setting under local anesthesia. Three studies using foamed sodium tetradecyl sulfate, including one RCT, all from the same investigators, concluded that sclerotherapy was effective and safe(24-26). The investigators found that bleeding was substantially better controlled after sclerotherapy than standard therapy with minimal adverse effects. Though rare, potential side effects include septal perforation, transient dizziness, blurred vision and permanent blindness(26). The literature regarding radiofrequency and electrosurgery treatment for nasal telangiectatic lesions is scarce; there are only a few studies showing efficacy of treatment. Bipolar electrosurgery, is preferred over monopolar electrosurgery, given its lower risk for collateral damage, specifically septal perforation. Radiofrequency cauterizes the telangiectasias at a lower temperature than electrocautery and reduces the risk for collateral damage(27). Overall, there is evidence that ablative therapies can provide temporary and partial improvement in epistaxis, and that side effects are mostly minor.

Severe epistaxis can be life threatening and devastating to QOL of HHT patients, and symptoms are often not adequately controlled with moisturization and ablative therapies. As such, systemic therapies and more invasive surgical management is often considered. Low level of evidence studies of antiangiogenic therapies are detailed in **Table 5**. Bevacizumab is a humanized recombinant monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) and has been shown to be effective in several diseases characterized by increased angiogenesis. From 2006 through 2019 there have been 3 prospective(28-30) and 5 retrospective studies(31-35) that evaluated the use of intravenous bevacizumab in HHT in 5 or more patients with HHT-related bleeding (152 total patients, most with epistaxis). Objective improvements were noted in the majority of studies that reported on epistaxis severity, hemoglobin level, RBC transfusion, and/or quality of life (QOL). The most commonly reported adverse events (AE) include hypertension(31) and arthralgia(36). Some studies have noted problems with wound healing, sometimes serious(29, 35). Overall, the evidence supports the effectiveness of IV bevacizumab in reducing epistaxis severity and RBC need, and improving anemia. However, in the absence of RCT, the magnitude of benefit and long-term safety are unclear. Of note, RCTs of topical (nasal) bevacizumab(19, 37) and intranasal bevacizumab injections(38), have not shown any significant benefit (**Table 4**).

Thalidomide and several of its analogs have been shown to downregulate VEGF levels in HHT patients(39) and improve blood vessel wall integrity(40). From 2007 through 2019 there have been 4 prospective(39-42) and 2 retrospective studies(43, 44) that evaluated the use of oral thalidomide in 5 or more patients with HHT-related epistaxis (67 total patients), detailed in **Table 5**. Objective improvements were noted in all but one study that reported on epistaxis severity, hemoglobin level, RBC transfusion, and/or QOL. Neuropathy is one of the most commonly reported side effects, often leading to discontinuation of the drug(36, 42, 43), and known teratogenicity precludes its use in women with child-bearing potential. Overall, low level evidence supports effectiveness of oral thalidomide in decreasing epistaxis severity and RBC need, and in improving anemia. However, AEs are substantial and often a limiting factor with neuropathy persisting even after discontinuation of the drug in two thirds of patients(36, 43).

Several other antiangiogenic agents are under investigation in the treatment of HHT related epistaxis. Pazopanib is a multikinase inhibitor that showed signs of efficacy in one small series(45). Pomalidomide is a thalidomide analog that appears to have a lesser incidence of neuropathy and is under study in a large RCT in HHT related bleeding. Doxycycline is an oral metalloproteinase inhibitor that may have downstream antiangiogenic effects and is under study in two small RCTs at present. The role of these agents in HHT related epistaxis will await additional studies.

Invasive surgical procedures are also often considered when epistaxis is not adequately controlled with moisturization and ablative therapies. Low level of evidence studies of invasive surgical procedures, including septodermoplasty and nasal closure, are detailed in **Table 5**. The expert panel considered invasive surgical procedures as an equal option to the systemic therapies, and that this decision requires extensive consultation with the patient. In addition, comorbid disease, such as atrial fibrillation,

can limit the use of prothrombotic drugs and require even aggressive anticoagulation or antiplatelet therapy instead. In these cases the invasive surgical measures(46-51) may be more appropriate as they could allow use of indicated anticoagulation or antiplatelet treatment. Several studies have evaluated septodermoplasty with the largest study(46) in which eighty-six percent of followed patients reported improved QOL, after mean follow-up of 3.75 years. Complications included worsening sinus infections (30%), decreased sense of smell, (58%) and frequent minor side effects, such as crusting and nasal airflow obstruction. Richer and colleagues(48) reported a series of 43 patients undergoing nasal closure, 83% reporting complete cessation of bleeding and no patients requesting reversal of the procedure. The largest study(50) includes 100 patients that underwent nasal closure with 50 of them having pre and post procedure data; ninety-four percent reported complete cessation of the bleeding. A number of surgical variations have been described for both nasal closure and septodermoplasty, though these have not been compared, and therefore clinical decision making should involve a rhinologic surgeon with expertise in these techniques.

Recommendations:

ER1: The expert panel recommends that patients with HHT-related epistaxis use moisturizing topical therapies that humidify the nasal mucosa to reduce epistaxis. **Quality of Evidence: Moderate (Agreement 98%)**
Strength of Recommendation: Strong (Agreement 100%)
Clinical Considerations: Saline nasal spray or saline gels are typically used twice daily for moisturization.

ER2: The expert panel recommends that clinicians consider the use of oral tranexamic acid for the management of epistaxis that does not respond to moisturizing topical therapies. **Quality of Evidence: High (Agreement 92%)**
Strength of Recommendation: Strong (Agreement 94%)
Clinical Considerations: Typically, tranexamic acid is started at a low dose and increased progressively at 3-4 times per day, to a total dose of approximately 4000-4500mg per day. Oral antifibrinolytics can be administered concurrently with systemic anti-angiogenic therapy, where indicated. Though low risk, oral antifibrinolytics should be withheld in patients with a recent history of DVT or arterial thrombosis and some experts recommend against their use in patients with atrial fibrillation or in patients with thrombophilia or procoagulant tendencies (e.g. elevated factor VIII).

ER3: The expert panel recommends that clinicians should consider ablative therapies for nasal telangiectasias including laser treatment, radiofrequency, electrosurgery, and sclerotherapy in patients that have failed to respond to moisturizing topical therapies. **Quality of Evidence: Moderate (Agreement 83%)**
Strength of Recommendation: Weak (Agreement 94%)
Clinical Considerations: Clinicians should consider destruction of telangiectasias as a temporizing method to decrease the frequency and severity of epistaxis. The specific method used to destroy the lesions is dependent upon the surgeon's preference and skillset. Great care must be taken to avoid perforation of the nasal septum, a known complication of all techniques. It is crucial that the clinician performing the therapy be

appropriately trained and that patients are involved in the decision-making after being fully informed of the risks and expected benefits of the procedure.

ER4: The expert panel recommends that clinicians consider the use of systemic antiangiogenic agents for the management of epistaxis that has failed to respond to moisturizing topical therapies, ablative therapies and/or tranexamic acid. **Quality of Evidence: Moderate (Agreement 92%)**
Strength of Recommendation: Strong (Agreement 82%)
Clinical Considerations: Epistaxis can be devastating for the quality of life of HHT patients and in some, can be life threatening. Anti-angiogenic therapy may be especially beneficial in reducing epistaxis and may even be life-saving in some patients. Intravenous bevacizumab has a favorable risk-benefit ratio in the short term, though long-term data is lacking. The standard initial dosing regimen for bevacizumab is 5 mg/kg intravenous (IV) every 2 weeks for 4-6 doses. Maintenance dosing of bevacizumab is being used routinely in HHT patients (31, 33)although dosing intervals vary amongst centers from every 1-3 months, and the long-term safety has not been studied. Patients on bevacizumab should be routinely monitored for hypertension and other potential complications. Oral thalidomide can also be considered, though side effects often limit long term use. Risks, and benefits of anti-angiogenic medications should be considered, as well as alternatives, such as septodermoplasty and nasal closure, in these patients. Shared decision making with patients is crucial.

ER5: The expert panel recommends that clinicians consider a septodermoplasty for patients whose epistaxis has failed to respond sufficiently to moisturizing topical therapies, ablative therapies, and/or tranexamic acid. **Quality of Evidence: Low (Agreement 92%)**
Strength of Recommendation: Weak (Agreement 88%)
Clinical Considerations: Epistaxis can be devastating for the QOL of HHT patients and in some, can be life threatening. More invasive surgical measures can be especially beneficial in reducing epistaxis and may even be life-saving in some patients. Risks and benefits of septodermoplasty should be considered, as well as alternatives to septodermoplasty, including nasal closure and anti-angiogenic medications. Shared decision making with patients is crucial.

ER6: The expert panel recommends that clinicians consider a nasal closure for patients whose epistaxis has failed to respond sufficiently to moisturizing topical therapies, ablative therapies, and/or tranexamic acid. **Quality of Evidence: Moderate (Agreement 86%)**
Strength of Recommendation: Strong (Agreement 82%)
Clinical Considerations: Epistaxis can be devastating for the QOL of HHT patients and in some, can be life threatening. More invasive surgical measures can be especially beneficial in reducing epistaxis and may even be life-saving in some patients. Risks and benefits of nasal closure should be considered, as well as alternatives such as septodermoplasty and anti-angiogenic medications. Shared decision making with patients is crucial.

Gastrointestinal Bleeding Management

Background:

HHT-related GI bleeding develops in approximately 30% of HHT patients, typically manifesting in the 5^{th}-6^{th} decades(52-57). Though most symptomatic patients have GI telangiectases in the stomach (46-75%) and the small bowel (56-91%), up to 30% also have telangiectases in the colon(53-55, 58, 59). The prevalence of GI telangiectases and HHT-related GI bleeding increases with age, varying by the population studied (unselected HHT vs. those with suspected GI bleeding(53-55, 58, 59)), and by genotype(12).

The cardinal manifestation of GI tract involvement is anemia from occult GI bleeding. Clinically overt bleeding (melena, hematemesis) is less common. Anemia occurs in approximately half of HHT patients(58, 60, 61), with epistaxis often a significant contributor, and this anemia is severe in up to 25% of patients(60). Severe anemia has a considerable effect on QOL(57, 62-64) and cardiovascular morbidity and mortality. Bleeding related complications are also the most common cause for hospitalization amongst HHT patients(65). Given the clinical impact of anemia, and the otherwise occult nature of the GI bleeding, the clinical assessment of the severity of HHT-related GI bleeding is based primarily on anemia severity and hematologic support required to maintain the target hemoglobin. Though some patients are clinically identified as having a “heavy burden” of GI telangiectases, to date endoscopic findings (number, size, distribution of telangiectases) have not correlated well with severity of anemia. Future studies are needed to determine if an endoscopic classification could replace or complement a classification scheme based on anemia severity. A severity classification is needed for HHT-related GI bleeding, as new systemic therapies reach clinical trials and clinical care.

Esophagogastroduodenoscopy (EGD) remains the diagnostic gold standard for upper GI telangiectases. Capsule endoscopy (CE) has an excellent safety profile but lacks the capability of assessing the stomach(54, 66). Limited data are available comparing CE to EGD in the setting of HHT(53, 55, 58) (**Table 6A)**, but suggest the diagnostic yield for the small bowel is similar to EGD. As such, the role of CE remains complementary to EGD when anemia remains unexplained by the severity of epistaxis and gastric involvement, or when the EGD is negative.

Though Argon Plasma Coagulation (APC) is the first line of therapy for acutely bleeding GI vascular lesions(67, 68) for in non-HHT patients, there are insufficient data supporting its systematic and repeated use in HHT. The rate of recurring lesions is high in non-HHT lesions, but has not been studied in HHT. Complications of repeated treatments have not been assessed, and there is considerable variability in expertise among endoscopists(67). Coagulation of bleeding lesions with APC at diagnostic endoscopy is appropriate but repeated sessions should be limited to severe patients who continue to bleed despite systemic therapy. Small series have reported reduction in

RBC transfusion requirement and improvement of hemoglobin after planned (capsule endoscopy driven) eradication of telangiectases with APC during double balloon enteroscopy(54, 69). Clinical trials are needed to explore the efficacy of other endoscopic therapeutics, such as Hemoclips, band ligation, Hybrid APC, etc., which may be particularly relevant for larger lesions that are felt to be at higher risk for severe bleeding.

There are small caser series and case of the use of systemic therapies for HHT-related GI bleeding. Early studies and experience suggested benefit with hormonal therapy(70-72), though more recent studies suggest a better benefit-risk ratio for antifibrinolytics(22) and anti-angiogenic therapies including bevacizumab(31, 33, 35, 45)and thalidomide(36, 73), with the 4 studies meeting evidence criteria reported in **Table 6B**. For mild to moderate GI bleeding, tranexamic acid may prove useful although its effect is probably weak, with studies showing improved nasal bleeding, but no significant improvement in anemia(22). For moderate to severe patients, who are transfusion or IV iron dependent, the use of IV bevacizumab (see also Epistaxis section for additional background details) has shown significant reduction of transfusion requirements in several uncontrolled case series, with a good safety profile(31, 33, 35). Recurrence of GI bleeding after initial response to IV bevacizumab “induction” therapy is common and there isexperience with maintenance dosing; the potential long-term benefits as well as the optimal treatment regimen remain to be defined. Other anti-angiogenic drugs (pazopanib, pomalidomide, doxycycline), and specific estrogen receptor modulators (SERMs, such as tamoxifen, raloxifene, or bazedoxifene) may be useful agents(74-76) however evidence in HHT-related GI bleeding remains limited to small numbers of cases.

Approximately 3% of HHT patients have *SMAD4* mutation and overlap syndrome with juvenile polyposis syndrome(77). These patients are at high risk of colorectal cancer(78-80) and should be screened aggressively starting from age 15 years. HHT patients without Juvenile Polyposis have colorectal cancer risks similar to the general population and should be screened accordingly. Patients with *SMAD4* mutation are also at risk for aortopathy and hyperlaxity and require appropriate screening(81).

Recommendations:

GR1: The expert panel recommends esophagogastroduodenoscopy as the first line diagnostic test for suspected HHT-related bleeding. Patients who meet colorectal cancer screening criteria and patients with SMAD4-HHT (genetically proven or suspected) should also undergo colonoscopy. **Quality of Evidence: Low (Agreement 82%)**

Strength of Recommendation: Strong (Agreement 94%)

Clinical considerations: HHT-related bleeding is often suspected when anemia is disproportionate to epistaxis severity. Investigation should begin with an EGD, the diagnostic gold standard. In suspected or proven SMAD4-HHT, screening colonoscopy is recommended, starting at age 15 years, repeated every three years if no polyps are found OR every year along with EGD if colonic polyp(s) are found. Other HHT patients (non-SMAD4) should be screened as per guidelines for the general population, with

colonoscopy, or by a fecal immunochemical test (FIT-testing), though the latter may have false positive results. In view of potential unusual complications during endoscopy (such as massive epistaxis), consideration should be given to performing endoscopies in experienced centers. In addition, clinicians should be aware of precautions required during endoscopy for HHT patients with pulmonary AVMs, as detailed in **Table 3**.

GR2: The expert panel recommends considering capsule endoscopy for suspected HHT-related bleeding, when esophagogastroduodenoscopy does not reveal significant HHT-related telangiectasia. **Quality of Evidence: Low (Agreement 92%)**
Strength of Recommendation: Strong (Agreement 88%)
Clinical considerations: Despite recent progress, CE remains a costly, non-reusable technology with limited availability in many centers. It has also been demonstrated to inadequately evaluate the stomach, and hence can miss up to 50% of significant gastric lesions. For these particular reasons, the use of CE should be reserved for complementary testing after EGD.

GR3: The expert panel recommends that clinicians grade the severity of HHT-related GI bleeding and proposes the following framework:

- Mild HHT-related GI bleeding: Patient who meets their hemoglobin goals* with oral iron replacement.
- Moderate HHT-related GI bleeding: Patient who meets their hemoglobin goals with IV iron treatment.
- Severe HHT-related GI bleeding: Patient who does not meet their hemoglobin goals despite adequate iron replacement or requires blood transfusions.

* Hemoglobin goals should reflect age, gender, symptoms and comorbidities.
Quality of Evidence: Low (expert consensus) (Agreement 96%)
Strength of Recommendation: Strong (Agreement 96%)
Clinical considerations: Since no clear correlation exists between number, size, appearance, distribution of GI telangiectasia and the severity of HHT-related GI bleeding, the expert panel proposes the above classification, based on the severity of anemia, for grading patients with HHT-related GI bleeding, for future development.
Hemoglobin goals, rather than hemoglobin levels, have been specified, to reflect the patients' individual physiological needs. This classification is not proposed for the classification of the acutely anemic during the initial diagnostic phase, but rather for HHT patients who have had a significant period of iron therapy after diagnosis of HHT-related GI bleeding (three or more months). Need for regular, scheduled IV iron infusions define patients in the moderate (or severe) GI bleeding category. Thus, an isolated dose of IV iron in an otherwise "mild" patient would not qualify as moderate GI bleeding.

GR4: The expert panel recommends that endoscopic Argon Plasma Coagulation be only used sparingly during endoscopy. **Quality of Evidence: Low (expert consensus) (Agreement 88%)**
Strength of Recommendation: Weak (Agreement 81%)

Clinical considerations: Given the multiplicity and the diffuse distribution of lesions in HHT-related GI bleeding, the expert panel recommends that the use of APC should be limited, generally to the initial endoscopic evaluation, to address spontaneously bleeding lesions and a limited number (10 or less) of significant (1-3 mm) non-bleeding lesions. Repeated sessions of APC are discouraged to avoid repeated iatrogenic injury to the intestinal mucosa, with possible short- and long-term complications. However, APC, including via double balloon enteroscopy, can be considered as an adjunct to systemic therapies for severe HHT-related GI bleeding, in the partial or non-responder.

GR5: The expert panel recommends that clinicians consider treatment of mild HHT-related GI bleeding with oral antifibrinolytics. **Quality of Evidence: Low (Agreement 94%)**

Strength of Recommendation: Weak (Agreement 90%)

Clinical considerations: Though the evidence for effectiveness of oral tranexamic acid is weak, it may lead to a reduced need for endoscopic interventions in HHT-related GI bleeding and appears to be a low risk intervention. Typically, the drug is started at a low dose and increased progressively at 3-4 times per day, to a total dose of approximately 4000-4500mg per day. Oral antifibrinolytics can be administered concurrently with systemic anti-angiogenic therapy, where indicated. Though low risk, tranexamic acid should be withheld in patients with a recent history of DVT or arterial thrombosis.

GR6: The expert panel recommends that clinicians consider treatment of moderate to severe HHT-related GI bleeding with intravenous bevacizumab or other systemic anti-angiogenic therapy. **Quality of Evidence: Moderate (Agreement 94%)**

Strength of recommendation: Strong (Agreement 98%)

Clinical considerations: The standard initial dosing regimen for bevacizumab is 5 mg/kg intravenous (IV) every 2 weeks for 4-6 doses. Maintenance dosing of bevacizumab is being used routinely in HHT patients(82) although dosing intervals vary amongst centers from every 1-3 months, and the long-term safety has not been studied. Patients on bevacizumab should be routinely monitored for hypertension and other potential complications.

Anemia and Anticoagulation

Background:

Iron Deficiency Anemia

Anemia is a common complication in people with HHT, with an estimated prevalence of around 50%(61, 83). Anemia is typically diagnosed in adulthood and rarely in children with HHT(84). The primary etiology of anemia is iron deficiency secondary to chronic mucocutaneous bleeding (epistaxis and/or GI bleeding from telangiectases). The average age of onset of epistaxis is 12 years and epistaxis tends to worsen with age(9, 61). GI bleeding is less common than epistaxis, occurring in approximately 30% of older adults(56), and is not typically encountered in the pediatric population.

Manifestations of anemia depend on its severity and can range from fatigue to exertional dyspnea and palpitations. Anemia results in high cardiac output and therefore exacerbates HHT-associated high cardiac output states most commonly encountered with significant liver VMs. Clinical features specific to iron deficiency anemia include a craving to eat certain substances, referred to as pica (typically ice but can include starches, clay, etc.)(85), and findings of angular cheilitis and koilonychia on physical examination(86). Iron deficiency can result in symptoms even in the absence of anemia, such as exercise limitation, fatigue, restless leg syndrome, hair loss, myalgias and decreased attention span(87-89). Correction of the iron deficiency leads to resolution of these symptoms.

Screening for anemia typically involves the following laboratory tests: complete blood count (CBC), iron panel (serum iron, total iron binding capacity, transferrin saturation), and ferritin. A CBC alone could miss underlying iron deficiency without anemia. A low ferritin level is very sensitive and specific for iron deficiency(90, 91). However, as ferritin is an acute phase reactant, it can be normal or slightly elevated in patients with iron deficiency who have a coexisting inflammatory process(86). An iron panel will often help in discerning whether there is underlying iron deficiency in such cases.

While a healthy and balanced diet (per WHO guidelines) is likely to provide the required daily allowance of iron, this will often be inadequate to replete total body iron stores in people with HHT who experience chronic bleeding and have developed iron deficiency either with or without anemia. The initial approach to treatment of iron deficiency in the HHT patients should be with oral iron replacement (with important and common exceptions discussed below). Oral iron preparations come in varying strengths, which are commercially listed in two ways: the total iron content and the amount of elemental iron. Of these, the elemental iron content is the measure of ‘absorbable iron’ and we therefore use elemental iron content in these guidelines. Published guidelines for treatment of iron deficiency anemia typically recommend oral replacement of 100-200 mg of elemental iron in three divided daily doses(92-94). Recent developments in the understanding of iron biology have suggested that lower doses of elemental iron replacement may be more effective. Moretti et al.(95) demonstrated that the levels of hepcidin increase acutely following intake of oral iron. This occurs with both higher amounts of elemental iron per dose as well as multiple daily doses of oral iron, and results in a decreased fractional absorption of iron from the GI tract(95). The optimal

dose of daily elemental iron was identified to be 40-80 mg per dose, with either once daily dosing or every-other-day dosing(96).

The most common cause for poor adherence to oral iron replacement is GI intolerance (constipation, nausea, epigastric pain, diarrhea). This occurs more frequently with non-heme based oral iron preparations compared to heme-sourced iron, and is primarily related to the amount of elemental iron per dose(92, 97). If oral iron replacement is associated with constipation, the use of a daily stool softener or other such bowel regimen should be considered to help with adherence. Various factors can affect absorption of iron from the GI tract. Oral iron is best absorbed from an empty stomach in an acidic environment(98) so is frequently co-administered with Vitamin C. Oral iron can be taken with food if needed, such as in people with GI intolerance, however foods that can interfere with or inhibit iron absorption should be avoided, as well as tea, coffee and milk(99). Many medications and supplements can affect iron absorption, such as aluminum containing phosphate binders, antacids, H2-receptor antagonists, proton-pump inhibitors, calcium supplements, and cholestyramine; these should therefore not be taken at the same time as oral iron.

Intravenous iron replacement should be considered in people with HHT who do not tolerate oral iron despite dosing and interval adjustments, in people in whom oral iron is ineffective in adequately treating iron deficiency anemia, and in people who do not absorb oral iron due to comorbid conditions (e.g. inflammatory bowel disease, people gastric bypass surgery, etc.). Intravenous iron can be considered over oral iron supplementation in the first line setting in patients who present with severe, symptomatic iron deficiency anemia, and where blood transfusion is considered inappropriate, because of the immediate availability of considerable amounts of iron for erythropoiesis with this approach compared to oral iron, particularly in the setting of coexisting chronic bleeding. In patients who have failed a brief trial of oral iron or in whom it is not expected to be effective, immediate initiation of intravenous iron is reasonable.

Intravenous iron is generally well tolerated. Common side effects include nausea/vomiting/cramping, arthralgias, flushing, back pain, low blood pressure, headache, fever, and dark urine. These are dose related and typically short lived when they occur. Allergic/hypersensitivity reactions are rare and include bronchospasm, rash, itching, low blood pressure, and anaphylaxis. Transient but significant worsening of epistaxis following iron infusion has been reported(100, 101). Adverse effects can be minimized by slowing the rate of intravenous iron infusion. Premedication with a single dose of antihistamines and/or steroids can be helpful in patients with a history of or concern for adverse effects like myalgias after intravenous iron infusions(102). Intravenous iron should be avoided in the acute phase of infectious disease given concern over potentiating severity of infections.

Dosing of intravenous iron is dependent on the severity of iron deficiency and the preparation of intravenous iron used. Not all intravenous iron preparations are available in every country and considerations such as distance from the clinic, availability, history

of allergic reactions, cost and patient preference should factor into the decision regarding choice of intravenous iron preparation. Unless chronic bleeding is successfully halted through systemic therapies and/or procedural interventions, repeated administrations of intravenous iron every few months is expected to prevent recurrence of iron deficiency.

Transfusion of packed red blood cells (RBCs) is also required in some people with HHT, typically when the hemoglobin needs to be urgently raised(65), or when aggressive iron supplementation is not sufficient to compensate for rapid blood loss. The hemoglobin value below which transfusion of RBCs is typically recommended in the general population is 7 g/dL. This transfusion threshold is applicable to some people with HHT as well. In addition to acute, large volume blood loss, chronic recurrent bleeding can result in severe anemia requiring RBC transfusions. When HHT patients have comorbidities, such as severe cardiac disease or hypoxemia from pulmonary AVM-associated shunting, they may require maintenance of higher baseline hemoglobin levels to maintain their arterial oxygen content. A higher hemoglobin threshold (such as 8-9 g/dL) may also be considered in HHT patients with poorly controlled chronic and recurrent bleeding, or when there is a need to acutely increase hemoglobin levels to prevent complications related to decreased oxygen delivery, such as during pregnancy or prior to surgical procedures.

It is important to consider alternate causes of anemia in people with HHT, when appropriate. In situations where anemia is normocytic or macrocytic (normal or high MCV), rather than the typical microcytic MCV seen in iron-deficiency, evaluation for an alternate etiology for anemia should be pursued. People with HHT can develop a folate deficiency as a result of chronically increased erythropoiesis due to chronic bleeding, or hemolysis(103). Finally, unrelated primary bone marrow processes, such as myelodysplasia, should also be considered in the evaluation of anemia that persists despite correction of iron deficiency, particularly in older patients.

Anticoagulation and Antiplatelet Therapy in HHT

Though HHT typically results in mucocutaneous bleeding and is recognized as a rare bleeding disorder by the Center for Disease Control, it is important to recognize that HHT does not protect against the development of thrombosis. On the contrary, people with HHT may be at increased risk for thrombotic complications, with one large series reporting a prevalence of thrombotic events at 6%, higher than that for the age matched general population(104, 105). Further, the risk for thrombosis was found to be independent of comorbidities and therapeutic approaches to mitigate bleeding, but interestingly correlated with presence of iron deficiency and elevated levels of circulating coagulation factor VIII(104). In addition, an increased risk for thrombotic stroke has also been observed by the same group(106). Given these considerations, people with HHT should receive appropriate pharmacological thromboprophylaxis during periods of increased risk as any other patient would (e.g. prolonged immobility, following major surgery or orthopedic surgery, etc.). This may prevent need for subsequent therapeutic anticoagulation, which would be associated with a higher risk for bleeding complications. Also, therapeutic anticoagulation and/or antiplatelet therapy

should also not be automatically withheld in all people with HHT given concern over potential increase in bleeding risk. Both anticoagulation and use of antiplatelet therapy can be well tolerated by the majority of HHT patients(107, 108). However, the decision to pursue these therapies will need to be considered on an individual basis, taking into account the personal severity of bleeding and anemia, patient acceptance of possible worsening of bleeds, and other comorbidities. While anticoagulation or antiplatelet therapy in isolation is encouraged when indicated, the bleeding risk with combining anticoagulation and antiplatelet therapy or with dual antiplatelet therapy in people with HHT is considered to be significant. Therefore, these combinations should be avoided if possible.

Recommendations:

AR1: The expert panel recommends that the following HHT patients be tested for iron deficiency and anemia:

- All adults, regardless of symptoms
- All children with recurrent bleeding and/or symptoms of anemia

Quality of Evidence: High (Agreement 98%)

Strength of the Recommendation: Strong (Agreement 96%)

Clinical considerations: Testing for iron deficiency and anemia typically includes a CBC and serum ferritin, with additional serum iron, total iron binding capacity, transferrin saturation if the ferritin is not reduced. In situations where there is difficulty with interpretation of results or diagnosis of iron deficiency with or without anemia, input from a hematologist should be considered. As severe epistaxis and/or GI bleeding is not routinely encountered in children with HHT, routine testing for iron deficiency and anemia is not deemed necessary in asymptomatic children with HHT.

AR2: The expert panel recommends iron replacement for treatment of iron deficiency and anemia as follows:

- Initial therapy with oral iron
- Intravenous iron replacement for patients in whom oral is not effective, not absorbed or not tolerated, or presenting with severe anemia

Quality of Evidence: Moderate (Agreement 88%)

Strength of the Recommendation: Strong (Agreement 100%)

Clinical considerations: Iron replacement should typically be started with once daily dosing of 35-65 mg of oral elemental iron, ideally 2 hours before or 1 hour after meals. If this is not tolerated, every-other-day dosing of oral iron or an alternate oral iron preparation (such as a heme-iron preparation or a non-heme iron preparation with lower elemental iron content) can be attempted. If initial dosing is inadequate for correction of the iron deficiency, increasing the daily dose or twice daily dosing should be considered. The patient should be counseled about various dietary factors and medications which can affect iron absorption. In general, an interval of 2-12 hours between iron supplements and these medications is preferred (www.RXfiles.ca Drug Comparison Charts). Follow-up CBC, iron panel and/or ferritin 1 month after initiation of iron

replacement is recommended to assess response. An increase in hemoglobin of at least 1.0 gram/dL is expected and, if not achieved, should be considered an inadequate response. When oral iron supplementation is pursued in people with iron deficiency without anemia, improvement in ferritin and transferrin saturation is expected after 1 month. For intravenous iron, routine monitoring of CBC and ferritin is necessary and helpful in guiding prescription of dose intervals, understanding that ferritin levels may be unreliable for 2 weeks post-infusion. In patients with chronic, recurrent bleeding, regularly scheduled iron infusions, with interval adjusted based on follow-up bloodwork, may be considered to maintain iron stores and prevent the development of severe anemia. The dose of intravenous iron can be guided by the total iron deficit, which can be calculated using the Ganzoni formula(109). Alternatively, a total initial dose of 1 gram of intravenous iron can be provided, as a single infusion or in divided doses based on institutional protocols and preferences. Unless chronic bleeding is successfully halted through systemic therapies and/or procedural interventions, repeated administrations of intravenous iron every few months is expected to prevent recurrence of iron deficiency. A few considerations specific to the type of intravenous iron preparation warrant mention: a significantly higher incidence of hypophosphatemia (>20%) has been reported in patients receiving multiple doses of ferric carboxymaltose(110, 111); ferumoxytol can affect the quality of MRI imaging and therefore MRIs should be avoided for at least 4 weeks following infusion of ferumoxytol(112, 113).

AR3: The expert panel recommends RBC transfusions in the following settings:

- Hemodynamic instability/shock
- Comorbidities that require a higher hemoglobin target
- Need to increase the hemoglobin acutely, such as prior to surgery or during pregnancy
- Inability to maintain an adequate hemoglobin despite frequent iron infusions

Quality of Evidence: Low (Agreement 92%)
Strength of the Recommendation: Strong (Agreement 96%)

Clinical considerations: Hemoglobin targets and thresholds for RBC transfusion should be individualized in HHT, depending on patient symptoms, severity of HHT-related bleeding, response to other therapies and iron supplementation, the presence of comorbidities and the acuity of the care setting.

AR4: The expert panel recommends considering evaluation for additional causes of anemia in the setting of an inadequate response to iron replacement. **Quality of Evidence: Low (Agreement 100%)**
Strength of the Recommendation: Strong (Agreement 100%)

Clinical considerations: Evaluation for additional causes would typically include measurement of folate, Vitamin B12, TSH and work-up for hemolysis, with referral to hematology in unresolved cases.

AR5: The expert panel recommends that HHT patients receive anticoagulation (prophylactic or therapeutic) or antiplatelet therapy when there is an indication, with consideration of their individualized bleeding risks; bleeding in HHT is not an absolute contraindication for these therapies. **Quality of Evidence: Low (Agreement 98%)**
Strength of the Recommendation: Strong (Agreement 98%)

Clinical considerations: When anticoagulation is pursued, unfractionated heparin, low molecular weight heparin and vitamin K antagonists are preferred over direct-acting oral anticoagulants given recent data suggesting higher bleeding rates with direct-acting oral anticoagulants(114). For HHT patients with atrial fibrillation who do not tolerate anticoagulation or are considered too high risk for anticoagulation can be considered for alternate approaches to decreasing cardioembolic risk, such as left atrial appendage closure(115).

AR6: The panel recommends avoiding the use of dual antiplatelet therapy and/or combination of antiplatelet therapy and anticoagulation, where possible, in patients with HHT. **Quality of Evidence: Low (expert consensus) (Agreement 83%)**
Strength of the Recommendation: Weak (Agreement 92%)
Clinical considerations: Ideally dual and combination therapies should be avoided or used only briefly, and patients should be monitored closely.

Liver VMs in HHT

Background:

Liver VMs occur in 41–74% of HHT patients(116, 117), occurring in all genotypes, but the clinical presentation is typically more severe in patients with *ACVRL1* mutation (HHT2)(12, 118, 119). The mean age of patients at diagnosis of liver VMs is 48 years(12, 117, 119) with a female predominance of 4.5 to 1. Liver VMs in HHT typically present as diffuse small lesions throughout the liver, and rarely as discrete large AVMs. Three different and often concomitant types of intrahepatic shunting (hepatic artery to portal vein, hepatic artery to hepatic vein and/or portal vein to hepatic vein) can lead to different and potentially overlapping clinical features, including high-output cardiac failure (HOCF), portal hypertension, encephalopathy, biliary ischemia and mesenteric ischemia(120, 121). Liver VMs in HHT may be associated with either diffuse or partial hepatocellular regenerative activity(122); the prevalence of focal nodular hyperplasia in patients with HHT is 100-fold greater than in general population(123).

HHT liver involvement is not associated with liver insufficiency(120, 121). Whereas only 8 to 14% of patients with liver VMs are symptomatic at baseline(116, 117, 124), prospective study has shown significant development of morbidity and mortality. The incidence of fatal outcome and of morbidity was 1.1% and 3.6% per person-years, respectively(119, 124). HOCF represents the predominant reported complication associated with HHT, but complicated portal hypertension occurs at a rate comparable to that of HOCF (1.4 and 1.2, per 100 person-years, respectively)(119). In patients with a high-output cardiac state due to liver VMs, the incidence of atrial fibrillation is1.6 per 100 person-years(83, 119). Much rarer presentations of liver VMs in HHT include encephalopathy, mesenteric angina and ischemic cholangitis that can cause bilomas or more ominously lead to a catastrophic complication termed “hepatic disintegration”(8, 121, 125-127).

The suspicion of liver involvement in HHT comes from history, physical examination, laboratory assessment of liver function tests, echocardiographic evaluation (with measurement of cardiac index and estimation of pulmonary hypertension)(128), and screening for signs, symptoms and biomarkers of heart failure. Anicteric cholestasis is observed in one third of patients with liver VMs, with a direct correlation with the severity of VMs and their complications(119, 124, 129). Doppler ultrasound (US) has been proposed as the preferred first-line investigation for the assessment of liver VMs due to its safety, tolerability, low costs and accuracy for the detection of liver VMs(8, 117, 121, 130-132) and very good interobserver agreement for the presence/absence of liver VMs (Kappa = 0.85-0.93)(133) (**Table7A**). Doppler US also allows grading of severity of liver VMs (from 0.5 to 4) which correlates with patient outcome and has been shown to be a predictor of clinical outcome(119). Abdominal computed tomography (CT) with a standardized protocol (multiphasic contrast-enhanced) provides detailed anatomic assessment and has the potential for reproducible results across centers, with excellent accuracy(116). However, CT findings do not correlate however with liver VMs severity(134) or clinical presentation(135), although CT has been recommended previously when expertise in Doppler US is lacking for diagnosing liver VMs(121). Magnetic resonance imaging (MRI) of the liver provides excellent accuracy with both multiphase anatomic assessment and hemodynamic characterization of liver VMs(136).

The abnormalities are better depicted on MR angiograms and dynamic MRI images, providing a map of anomalous vessels and analysis of filling kinetics; MRI has been proven to be as accurate as CT for liver VMs, and involves no ionizing radiation(137). Moderate to good interobserver reproducibility for MR imaging has been demonstrated. In the case of pregnant patients, US is preferred to avoid ionizing radiation or gadolinium exposure to the fetus. We continue to recommend against liver biopsy, as we did in the first International HHT Guidelines(8) (**Table3**), as a major and unnecessary bleeding risk.

Echocardiographic evaluation is recommended at the time of liver VM diagnosis, to evaluate of the impact liver VMs on cardiac function and morphology, particularly cardiac index and pulmonary artery pressures, and to provide a baseline for comparisons over time(121, 138, 139). In those with signs or symptoms of heart failure and an intermediate or high probability of pulmonary hypertension, right-heart catheterization should be performed to accurately assess cardiac and pulmonary hemodynamics(121, 138, 139). Right heart catheterization is also essential for diagnosing different forms of pulmonary hypertension, for example pre-capillary pulmonary arterial hypertension characterized by high pulmonary vascular resistance and normal pulmonary artery wedge pressure which can be associated with HHT(140).

In patients diagnosed with liver VMs, follow-up with Doppler US and echocardiography should help identify complications and disease progression. The assessment of prognosis of symptomatic liver VMs using available outcome predictors can assist in decision-making. Identified disease progression predictors include: stage 4 liver VMs at baseline and *ACVRL1* mutation(119). Clinical factors that can be used to predict low, moderate and high risk categories for significant disease from liver VMs include: age at presentation >47 years, female gender, hemoglobin level at presentation < 8 g/dL (or < 5 mmol/L) and alkaline phosphatase level at presentation > 300 UI/L(124). A retrospective cohort (141) has demonstrated other worrisome features including mean pulmonary artery pressure (≥25 mmHg at catheterization), elevated bilirubin, weight loss, GI bleeding and any biliary ischemia, atrial fibrillation, high blood transfusion requirement, right upper quadrant pain, and sepsis.

Presently, no treatment is recommended for asymptomatic liver VMs. An intensive therapeutic approach, tailored to the type of complication present, is recommended for symptomatic liver involvement in HHT(121). Patients with HOCF should have care supervised by a specialist experienced in managing HOCF; treatments include aggressive treatment of anemia, salt restriction and the use of diuretics, as needed. Management of atrial fibrillation in HOCF follows the same principles as in the general population. Anticoagulation for stroke prevention should be considered based on individualized risk assessment, as discussed in the Anemia and Anticoagulation section. Patients with pulmonary hypertension should be evaluated and treated by a physician with expertise.

Antibiotic treatment is administered in HHT patients with liver VMs and cholangitis. Endoscopic retrograde cholangiopancreatography (ERCP) with stenting is not an option as large duct obstruction is usually not present and ERCP may increase the risk of infection, in ischemic ducts. Necrotizing cholangitis with hepatic necrosis is an ominous complication of liver VMs, requiring emergent liver transplantation. Management of portal hypertension follows the same principles as in patients without HHT. The use of non-selective beta-blockers in patients with severe HOCF should be supervised by a cardiologist. Transjugular intrahepatic portosystemic shunt placement may worsen hyperdynamic circulation and precipitate cardiac failure. Management of encephalopathy follows the same principles as in patients without HHT who have cirrhosis, including the use of lactulose and rifaximin.

The reported response to first-line treatment in patients with symptomatic liver VMs in HHT is complete in 63%, partial in 21% and absent (with progression to death) in 14%(119). These data support the recommendation to consider aggressive options only for otherwise intractable complications, after the assessment of response to first line treatment has been made, after 6-12 months(121). Outcomes of orthotopic liver transplantation (OLT) (**Table 7B**)for liver VMs in HHT are excellent with 82-92% survival(127, 142). Liver VMs in HHT are included in MELD (Model for End Stage Liver Disease) exceptions: suggested MELD exception points for HHT include a score of 40 to patients with acute biliary necrosis and 22 to patients with HOCF(121). Potential morbidity and mortality rates associated with OLT are a cause for concern and the optimal timing for OLT in HHT with symptomatic liver involvement should be supported by predictors of outcome(119, 124, 141). Recurrence of liver VMs after OLT has been demonstrated in only a small number of cases, many years post-OLT, and has been asymptomatic(143). Other surgical or interventional options for treating complicated liver VMs such as hepatic embolization and/or banding of the hepatic arteries are associated with a high rate of serious complications including death and cholangiopathy and should be reserved as a last resort when medical therapies fail and OLT is not an option(8, 121, 144).

There is growing evidence for the role of intravenous bevacizumab in patients with severe liver VMs (**Table 7B**), primarily in those with HOCF(28). However, potential adverse events (AE) related to bevacizumab need careful consideration: in 69 HHT patients who received bevacizumab treatment for a total of 63.8 person-years treatment, an average AE incidence rate of 50 per 100 person-years, including 1 fatal event probably related to bevacizumab, have been described(36). Furthermore, rates of non or partial response to bevacizumab(28), and recurrence of symptoms/signs after drug withdrawal make this drug unsuitable to replace OLT for complicated liver VMs in HHT. Bevacizumab may offer a potential “bridging” role to OLT, and if a response is obtained with resolution/improvement of the liver VM complication, the option of OLT should be re-assessed. Bevacizumab complicates wound healing and transplant teams should closely coordinate with HHT providers so that bevacizumab can be stopped long enough prior to OLT to minimize complications, while still minimizing the time off of therapy. The optimal OLT window is likely between 2 and 6 months after the last dose of bevacizumab.

Recommendations

LR1: The expert panel recommends that screening for liver VMs be offered to adults with definite or suspected HHT. **Quality of Evidence: Low (Agreement 84%)**
Strength of Recommendation: Weak (Agreement 93%)
Clinical considerations: The rationale for screening is based on the concept that awareness of liver VMs could improve subsequent patient management. In some cases, documenting presence of liver VMs can help to clarify the diagnosis of HHT by establishing an additional Curaçao criterion. The imaging test of choice for liver VM screening in HHT is the Doppler US due to its accuracy, safety, tolerability, low costs and operating characteristics. However, depending on local expertise and availability of Doppler US testing, as well as patient preference, patients may be screened clinically (history, physical and blood work) or alternative imaging may be considered, such as multiphase abdominal CT or MRI.

LR2: The expert panel recommends diagnostic testing for liver VMs in HHT patients with symptoms and/or signs suggestive of complicated liver VMs (including heart failure, pulmonary hypertension, abnormal cardiac biomarkers, abnormal liver function tests, abdominal pain, portal hypertension or encephalopathy), using Doppler US, multiphase contrast CT scan or contrast abdominal MRI for diagnostic assessment of liver VMs.
Quality of Evidence: High (Agreement 98%)
Strength of Recommendation: Strong (Agreement 100%)
Clinical considerations: The choice of liver imaging modality should be informed by patient characteristics, the risk/benefit balance, as well as local expertise and availability/cost. CT contrast and MRI contrast should be avoided in patients with chronic kidney dysfunction. Echocardiographic evaluation is also recommended at diagnosis of liver VMs to estimate their hemodynamic impact. These tests will be most informative when performed in a center with HHT expertise, and in the context of a clinical assessment at an HHT Center of Excellence.

LR3: The expert panel recommends an intensive first-line management only for patients with complicated and/or symptomatic liver VMs, tailored to the type of liver VM complication(s).
The expert panel recommends that HHT patients with high-output cardiac failure and pulmonary hypertension be co-managed by the HHT Center of Excellence AND an HHT cardiologist OR a pulmonary hypertension specialty clinic. **Quality of Evidence: Moderate (Agreement 88%)**
Strength of Recommendation: Strong (Agreement 88%)
Clinical considerations: Considering the complexity of liver VM complications, management by an expert team at an HHT Center of Excellence, with at least annual follow-up, is recommended.

LR4: The expert panel recommends that clinicians estimate prognosis of liver VMs using available predictors, to identify patients in need of closer monitoring **Quality of Evidence: Moderate (Agreement 89%)**

Strength of Recommendation: Strong (Agreement 82%)

Clinical considerations:

Clinicians should assess prognosis and plan follow-up for liver VMs patients based on either identified predictors or high risk stigmata or worrisome features, as detailed above(119, 124, 141).

LR5: The expert panel recommends considering intravenous bevacizumab for patients with symptomatic high-output cardiac failure due to liver VMs who have failed to respond sufficiently to first-line management. **Quality of Evidence: Moderate (Agreement 98%)**

Strength of Recommendation: Strong (Agreement 98%)

Clinical considerations: The standard initial dosing regimen is 5 mg/kg intravenous (IV) every 2 weeks for 4-6 doses. Maintenance dosing of bevacizumab is being used routinely in HHT patients(82) though intervals vary from every 1-3 months, and the long-term safety has not been studied. Patients receiving bevacizumab should be routinely monitored for hypertension and other typical adverse events.

LR6: The expert panel recommends referral for consideration of liver transplantation for patients with symptomatic complications of liver VMs, specifically refractory high-output cardiac failure, biliary ischemia or complicated portal hypertension. **Quality of Evidence: Moderate (Agreement 83%)**

Strength of Recommendation: Strong (Agreement 92%)

Clinical considerations: The best timing to list a symptomatic patient for OLT should be based on prognostic predictors, the severity of liver VMs complications, including pulmonary hypertension. Liver transplant can be undertaken in the presence of pulmonary hypertension if pulmonary vascular resistance, estimated by right heart catheterization, is < 3 Woods Units. Portal pressure measurement with hepatic venous pressure gradient is reserved for selected patients with complicated liver VMs when evaluated for OLT(121).

Pediatric Care

Background

The previous guidelines regarding diagnosis and management of HHT(8) focused on screening and treatment of adults. While some manifestations such as telangiectasia and epistaxis manifestations are age dependent and may be absent in young children with HHT, potentially serious and even life-threatening complications of visceral AVMs can occur at any age. Currently, the literature about diagnosis and management in children with HHT is limited, but protocols for screening and treatment of children with HHT have been developed in HHT centers around the world. Complications described in the literature are mostly due to pulmonary arteriovenous malformations (AVMs) and brain vascular malformations (VMs). Therefore, the focus of the pediatric HHT guidelines is on screening and management of pulmonary AVMs and brain VMs.

Since establishing the diagnosis of HHT based on clinical criteria is less reliable in children than in adults(145), a different approach is required in this age group, with genetic testing playing a more important role than in adults(146-148). HHT is an autosomal dominant disease with age-related but high penetrance; therefore, every child of a parent with HHT has a 50% chance of inheriting the disease. Genetic testing in children is usually performed in a stepwise approach in which the affected parent is tested first (see overall Background section). If a pathogenic variant has been identified in the index case or in other affected member of the family(8), genetic testing can be used to establish the diagnosis in children prior to screening for visceral AVMs. Equally important, genetic testing can identify non-affected children who can be released from follow-up.

The prevalence of pulmonary AVMs varies with the type of HHT: pulmonary AVMs are found in about 50% of patients with HHT1 and in about 10% of patients with HHT2(12, 118). While these estimates are based on studies in adults, data suggest that the prevalence of pulmonary AVM is comparable in children(149-152). This is supported by one study that found a similar prevalence of pulmonary AVM in children with HHT1 as in their parents suggesting that the vast majority of pulmonary AVMs are present early in life(153). This has important implications for screening as the yield in genetically confirmed cases is high. Pulmonary AVMs are found in children with all types of HHT and at any age. Pulmonary AVMs associated with low oxygen saturations (< 96% at sea level), as well as large pulmonary AVMs, can cause serious, sometimes life-threatening complications, including hemorrhage, brain abscess and stroke(151, 152, 154). For that reason, screening children with HHT or at risk for HHT is indicated after birth, or at the time of presentation. Two screening protocols have been studied in children (**Table8A**); at present both are seen as equivalent. The first screening approach (“Dutch protocol”) uses a conservative screening strategy of oximetry and chest X-ray. As small pulmonary AVMs cannot be excluded in this setting, procedural antibiotic prophylaxis is recommended to all subjects. Evidence from the Dutch cohort suggests that this protocol is sufficient to prevent pulmonary AVM related complications(155). Transthoracic contrast echocardiography (TTCE) is used in the second screening

protocol and has a higher sensitivity as a screening test for pulmonary AVMs(156, 157). It requires an intravenous access and has not clearly been shown to detect additional pulmonary AVMs that would cause complications in childhood. TTCE has the advantage of being a non-radiating test. The use of a quantitative scoring system for analysis of TTCE can increase the specificity of the test and can be used to determine whether a CT-scan should be performed(158), as the diagnostic confirmatory test(158, 159).

Embolotherapy of pulmonary AVMs has a high success rate in children(154) (**Table 8B**). There are however no data to suggest that small pulmonary AVMs associated with normal oxygen saturation need to be treated in children. In rare cases, larger pulmonary AVMs with normal saturation can occur and treatment can be considered, especially in the case of symptoms. Growth of pulmonary AVMs over time has also been documented in children(160); therefore follow-up of children is important to capture these changes.

Brain VM is a general term that encompasses three principal types of vascular lesions in HHT: nidus brain AVM, brain arteriovenous fistula (AVF), and capillary vascular malformation (CVM)(161). These vascular malformations are thought to have significantly different natural history risk for spontaneous brain hemorrhage, ranging from extremely low in CVM, to intermediate in brain AVM (as can be further risk-stratified with detailed angio-architectural information, see CR6 below), to high in AVF. Overall, brain VM are less common than pulmonary AVMs in HHT. The prevalence in children is not well defined; data from studies in adults suggest that brain VMs are found in 8-16% of patients with HHT1 and 1-2% of patients with HHT2(162-164), though the AVF type appears to be over-represented in children(165, 166). Brain VMs can be present from birth and there are often no warning signs or symptoms prior to hemorrhage of a brain VM(167, 168). Clinical symptoms are subtle or absent in children and case series from different centers have described brain hemorrhage in children prior to diagnosis or screening procedures(167, 169, 170). The purpose of imaging screening of children with HHT is to identify if a brain VM is present and, to the extent possible, differentiate between the three common subtypes of brain VM. The most sensitive and specific non-invasive imaging modality to identify brain VM is MRI(171-173).

Observational studies suggest that treatment of brain VM is successful and can prevent brain hemorrhage(165, 174) (**Table 8B**). Brain VM with relatively high natural history risk for rupture include pial AVFs as well as nidus brain AVMs with specific angio-architectural features or evidence of prior hemorrhage(161, 175-178). High risk features for future nidus brain AVM rupture, sometimes identifiable on MRI but more reliably identified on digital subtraction angiography (DSA), include but are not limited to: feeding artery aneurysms, nidus aneurysms, venous outflow stenoses, and deep venous drainage. Intra-lesional microhemorrhage seen on brain MRI is an independent risk factor for future nidus brain AVM rupture(176).

It is important to appreciate that while the recommendations below are based on consensus of experts in the field, different approaches regarding pre-symptomatic

genetic testing and screening procedures are used in different countries. Whenever possible, these different strategies are mentioned in the recommendations.

Recommendations

CR1: The expert panel advises that diagnostic genetic testing be offered for asymptomatic children of a parent with HHT. **Quality of Evidence: High (Agreement 96%)**

Strength of the Recommendation: Strong (Agreement 94%)

Clinical considerations: If the disease-causing mutation is known in the family, the accuracy of genetic testing is very high (Therefore, it is recommended that an affected family member should be tested first to determine a causative mutation, prior to testing an asymptomatic child). The established clinical diagnostic criteria (Curaçao criteria)(13) for HHT are less reliable in young children, because many symptoms of HHT have onset in late childhood or even adulthood (age related penetrance)(145). It is generally accepted that for children to have pre-symptomatic testing for a genetic condition, there should be a clinical benefit to this testing. The value of this testing may be viewed differently depending on the specifics of the routinely recommended organ screening protocol in a given country for children with HHT. The alternatives, pros and cons should be discussed especially with younger patients or – if applicable – their parents to achieve the best result for the patient.

CR2: The expert panel recommends screening for pulmonary AVMs in asymptomatic children with HHT or at risk for HHT at the time of presentation / diagnosis **Quality of Evidence: Moderate (Agreement 94%)**

Strength of the Recommendation: Strong (Agreement 94%)

Clinical considerations: Primary screening may be performed with either chest X-ray and pulse oximetry OR transthoracic contrast echocardiography (TTCE). Primary screening with CT of the chest is not recommended, though CT remains the confirmatory diagnostic test when screening tests are positive.

CR3: The expert panel recommends that large pulmonary AVMs and pulmonary AVMs associated with reduced oxygen saturation be treated in children to avoid serious complications. **Quality of Evidence: Moderate (Agreement 98%)**

Strength of the Recommendation: Strong (Agreement 98%)

Clinical considerations: Criteria for embolotherapy are not different from those used in adults, which means that pulmonary AVMs with feeding arteries ≥3 mm in diameter qualify for treatment. Follow-up after treatment of PAVMs is advised; intervals are not well defined but may vary according to size and number of pulmonary AVMs. Follow-up after treatment can be done with low-dose CT, TTCE, and /or saturation measurement. Protocols vary between centers. Follow-up is indicated, because recanalization and reperfusion of treated pulmonary AVMs can occur and / or small pulmonary AVMs can increase in size.

CR4: The expert panel recommends to repeat pulmonary AVM screening in asymptomatic children with HHT or at risk for HHT; typically at 5 year intervals. **Quality of Evidence: Low (Agreement 92%)**
Strength of the Recommendation: Strong (Agreement 86%)
Clinical considerations: Growth of pulmonary AVMs occurs in children with HHT but is slow in most cases. One study suggests that pulmonary AVMs in children may double in size in 5 years(160). The recommended interval for repeat screening varies between centers and evidence to support a specific time interval is limited. Many centers repeat screening at 5 year intervals, but whether pulmonary AVMs occur *de novo* in this time interval in children is not entirely clear(179). If screening has been performed with oximetry and chest X-ray, a 5 year interval is advisable, because the presence of small pulmonary AVMs is not excluded in cases with normal oxygen saturation. In children with borderline screening results, either based on imaging or oximetry, screening should be repeated sooner. Methods for screening and re-screening do not differ.

CR5: The expert panel recommends screening for brain VM in asymptomatic children with HHT or at risk for HHT at the time of presentation / diagnosis. **Quality of Evidence: Low (Agreement 86%)**
Strength of the Recommendation: Strong (Agreement 86%)
Clinical considerations: The purpose of imaging screening of children with HHT is to identify if a brain VM is present and, to the extent possible, differentiate between the three common subtypes of brain VM. The most sensitive and specific non-invasive imaging modality to identify brain VM is MRI and contrast enhanced MRI has a higher sensitivity than non-contrast MRI. Screening with MRI in infants and young children generally requires sedation or anesthesia. The outcome of screening can result in a "wait and see" approach, because not all brain VMs need treatment. The decision whether to treat or not, is based on the risks of complications of treatment versus the risk of bleeding of the brain VM. Whether or not to screen the child should be a shared decision among clinicians, caregivers and the child (where possible). There are currently important differences in clinical practice with regards to brain VM screening amongst countries: in some countries asymptomatic children with HHT are screened for brain VM with an MRI as early in life as possible, but in other countries asymptomatic children are not routinely screened for the presence of brain VM. Patient representatives felt strongly that children should be screened for brain VMs citing anecdotal evidence of disastrous outcomes in unscreened patients.

CR6: The expert panel recommends that brain VMs with high risk features be treated.
Quality of Evidence: Low (Agreement 100%)
Strength of the Recommendation: Strong (Agreement 98%)
Clinical considerations: Given the need to balance natural history risk with treatment risk, the expert panel recommends that people with HHT who have brain VM be referred for evaluation at a center with multidisciplinary (neurology, neurosurgery, neurointerventional radiology, radiation therapy) expertise in neurovascular disease management. Treated brain VMs require close follow-up; the follow-up for small (untreated) brain VMs is not well defined.

Pregnancy and Delivery

Background:

A pregnant woman with HHT should be assessed for their risk of pregnancy and delivery related complications and have access to, as needed, to a multidisciplinary maternal-featl medicine team that includes HHT experts. At the initial obstetrical visit, pregnant patients should have a thorough review of their diagnosis history and past evaluations as well as recent status, symptoms and concerns. In addition, given that offspring are at 50% risk of inheriting the pathogenic mutation, pre-pregnancy consultation with an obstetrician is recommended, for consideration of options before and during and after pregnancy for genetic diagnosis.

The term “high-risk pregnancy” is a label used to describe situations in which a pregnant woman, her fetus, or both, are at higher risk when compared to a “typical” pregnancy for complications during pregnancy, labor & delivery or post-partum. Many pregnant women with HHT are labeled as “high-risk”, as there is 1% overall risk of complication in pregnancy in patients with HHT(180). However, it is possible to stratify this risk. Risk stratification can be based upon the results of a patient’s AVM screening and/or treatment. Unscreened patients and patients with known but untreated pulmonary AVMs of significant size (>2-3 mm) are at highest risk.

The physiologic changes of pregnancy to the circulatory system include an increase in cardiac output by 30-50% and an increased blood volume by 40% by 28 weeks. Pregnancy also results in high progesterone levels, which may increase venous distensibility(181). This collective effect of these factors may result in enlargement and/or rupture of untreated pulmonary AVMs during pregnancy(182). Recent studies have estimated a risk of about 17% for non-fatal complications(183) and 2% for mortality(180). Hemothorax, hemoptysis, ischemic stroke, and pulmonary deterioration have all been reported(180, 182, 183). Pulmonary AVMs should be screened for and treated prior to pregnancy(183). If a HHT patient becomes pregnant and pulmonary AVMs have not been excluded, screening should be performed either with TTCE or with chest CT. TTCE using agitated saline is considered safe during pregnancy(184). Chest CT requires radiation, but the fetal dose is minimal(185) and can be delayed until after organogenesis as is discussed below. No IV contrast is required, and a low-dose non-contrast protocol is adequately sensitive for detecting and characterizing pulmonary AVMs.

If a pregnant patient with HHT is diagnosed with pulmonary AVMs, the decision to embolize and subject the fetus to ionizing radiation and periprocedural complications should be weighed against the risk of no treatment. The feeding artery size threshold at which to embolize asymptomatic pregnant patients has not been established but it should likely follow recommendations for the general population of 2-3 mm. Pregnant patients who are symptomatic from pulmonary AVM (e.g. hemorrhagic or neurologic

complication), should undergo diagnostic CT and immediate treatment with embolization, regardless of gestational age.

In asymptomatic pregnant women, diagnostic chest CT imaging and treatment with embolization should be delayed until after organogenesis is complete (12 weeks). This timing is supported by the observation that 85-90% pulmonary AVM complications occur in the second or third trimesters(182, 186). Thus, screening and treatment of asymptomatic pulmonary AVMs should typically occur between 12-20 weeks of gestational age. The estimated fetal dose for a maternal chest CT is less than 0.5 mGy, and estimated fetal dose for pulmonary embolization is about 1-2 mGy(187). Fetal radiation doses below 50 mGy are considered negligible (The American College of Obstetricians and Gynecologists) and there are no known health effects associated with fetal radiation at these levels of exposure. Considering the high risk of non-fatal pulmonary AVM related complications during pregnancy (17%)(183) and mortality (2%)(180), the benefit of embolization is favored over no treatment ,in most cases.

Pregnant women with HHT who screen negative for pulmonary AVMs have similar pregnancy risk as their non-HHT counterparts. After initial evaluation at a tertiary center, they may be advised that they are suitable candidates for management outside of tertiary level care with careful attention to known complications such as worsening epistaxis and anemia. Patients should be counselled that they are not at higher risk of miscarriage than the general population(183), outcomes are generally good, but they need to be educated regarding signs and symptoms of severe complications.

Given the absence of evidence that pregnancy increases the size of brain VMs or the likelihood of hemorrhage, a diagnosis of pregnancy is not an indication for screening for brain VMs. A retrospective series from 1995(182) did not include any cases of intracranial hemorrhage among 161 pregnancies in 47 affected women. A second cohort study from the same institution in 2008(180) (both retrospective and prospective) followed up on 484 pregnancies in 197 non screened HHT women. There was one case of subarachnoid hemorrhage during the second trimester of pregnancy and another case of hemorrhage in the third trimester due to a brain AVM (0.4% rate of bleeding). A third retrospective case series published in 2014(183) analyzed 244 pregnancies in 87 women with one case of intracranial hemorrhage (0.4%) in the postpartum period in a previously unscreened patient. These published risks of brain AVM hemorrhage during pregnancy appear similar to the hemorrhage rate of brain VMs in non-pregnant patients with HHT, which is estimated at 0.4-1.0% per year(178, 188).

In cases of known, asymptomatic brain VMs, no intervention is typically required during pregnancy, due to the low risk of hemorrhage(189, 190). There is no conclusive evidence of an increased risk of first hemorrhage during pregnancy from brain VM(191). However, some higher-risk situations should be recognized, including patients with high-flow AV fistulae, patients with brain AVM and recent (< 2 years) clinical bleed, patients with brain AVM and history of bleeding during a previous pregnancy, and patients with complex brain VM with a neurosurgical opinion of higher bleeding risk. If a brain VM ruptures during pregnancy, the re-bleed rate in the 2^{nd}/3^{rd} trimester and postpartum and is high ~27-30%(192, 193). Mortality from a brain VM bleed in pregnancy is ~28%, which is higher than in the non-pregnant state(194). Even

considering these higher-risk situations, there is no evidence justifying treating unruptured and asymptomatic brain VMs in a pregnant person, given the risks of radiosurgery, embolization and surgical resection, but a multi-disciplinary team should make decisions on a case by case basis as to whether any intervention is required.

Pregnant women with a known brain VM may labor and attempt to undergo a spontaneous vaginal delivery. There are no reports of pregnant people with HHT having a brain VM bleed during labor. This supports the recommendations for vaginal delivery as is done in pregnant people with brain VMs who do not have HHT. There may be cases in which the opinion of the multidisciplinary team is that the patient should undergo a caesarean section. This might include patients presenting with brain VM symptoms in pregnancy, or patients with prior hemorrhage from brain VMs. In all patients with brain VM, diligent management of blood pressure is imperative, to avoid swings in either direction. Modification of general anesthesia to avoid hypertension is prudent(194).

The prevalence of spinal VMs in the HHT population is very low, although higher than the general population. Routine screening for spinal VMs is not recommended due to the rarity of spinal VMs in the thoracolumbar spine in asymptomatic people with HHT. Pregnant women with HHT who have never had a spinal MRI should not have one just because pregnancy is diagnosed. Unenhanced MRI only excludes medium or large spinal VMs and gadolinium is contraindicated in pregnancy. Lomax et. al(194) mentions that pregnancy may exacerbate the symptoms of spinal VM. In a case of a known spinal VM, an anesthesiologist should be consulted to address anesthetic options on a case by case basis. The prevalence of spinal VMs in HHT is 0.5%. Spinal VMs are predominantly symptomatic in males and the pediatric population(195), are generally perimedullary (rarely in the dural space), and usually involve the thoracic spine, with a minority extending into the lumbar region (196). Since the majority of spinal VM in patients with HHT are located perimedullary, this should not affect epidural anesthesia.

There are two large studies of pregnancy in HHT and neither reported complications from epidural or spinal anesthesia(180, 183). In one study there were 92 spinal/epidurals in 185 deliveries, and in the other study, there were 484 pregnancies; no spinal hemorrhages were reported. Likewise, there are no case reports of patients with HHT, who are asymptomatic of spinal VM, developing complications from spinal VM secondary to spinal/epidural anesthesia. There is no evidence for routine screening, and no evidence to deny an unscreened pregnant person an epidural. Epidural anesthesia can safely be offered, and patients should be counseled that the risk of complication with an epidural is theoretical. It is prudent to have an epidural/spinal anesthetic performed by an experienced anesthetist.

Recommendations

PR1: The expert panel recommends that clinicians discuss pre-conception and pre-natal diagnostic options including pre-implantation genetic diagnosis with HHT affected individuals. **Quality of Evidence: Very Low (Agreement 86%)**
Strength of the Recommendation: Strong (Agreement 83%)

Clinical Considerations: If the causative familial pathogenic variant is identified during genetic testing of a parent, then it can be screened for in the future off-spring. Available options vary internationally and are detailed below. The discussion will be influenced by local legislation pertaining to pre-implantation diagnosis and termination of pregnancy.

- **Pre-implantation genetic diagnosis** where there is the option to transfer non-affected embryos. The course of action desired should be discussed as part of the pretest counselling.
- **Post-conception options** include Chorionic Villus Sampling (CVS) and Amniocentesis. These invasive diagnostic options carry a small risk of miscarriage (1% and <0.5% respectively). Given the risks, a discussion about what path the pregnant person would take once results were available is imperative. If there is no consideration of termination of pregnancy based on the HHT status of the fetus, then these tests may be reserved for other indications, such as fetal anomalies or other screen positive results.
- **Post-delivery**: parents can be offered genetic testing on cord blood of the infant at time of delivery. While concerns exist for the testing of asymptomatic children for adult onset conditions for which there is no potential benefit of testing in childhood, childhood AVM screening is recommended in HHT (see pediatric section), with treatment in selected cases,

PR2: The expert panel recommends testing with unenhanced MRI in pregnant women with symptoms suggestive of brain VMs. **Quality of Evidence: Very Low (Agreement 98%)**
Strength of the Recommendation: Strong (Agreement 92%)

Clinical Considerations: MRI, without gadolinium, should be planned in second trimester for symptomatic patients. Patients with previous cerebral hemorrhage likely have a higher risk for re-bleeding in pregnancy, especially during 2nd and 3rd trimester. Asymptomatic patients do not require routine screening during pregnancy, as there no conclusive evidence of an increased risk of first hemorrhage during pregnancy from brain VM(191).

PR3: The expert panel recommends that pregnant women with HHT who have not been recently screened and/or treated for pulmonary AVM should be approached as follows:

- In asymptomatic patients, initial pulmonary AVM screening should be performed using either agitated saline transthoracic contrast echocardiography (TTCE) or low-dose non-contrast chest CT, depending on local expertise. Chest CT, when performed, should be done early in the second trimester.

- In patients with symptoms suggestive of pulmonary AVM, diagnostic testing should be performed using low-dose non-contrast chest CT. This testing can be performed at any gestational age, as clinically indicated.
- Pulmonary AVMs should be treated starting in the second trimester unless otherwise clinically indicated.

Quality of Evidence: Moderate (Agreement 88%)
Strength of the Recommendation: Strong (Agreement 83%)
Clinical Considerations: The technique for pulmonary angiography and embolization for pregnant patients(187) is similar to that in non-pregnant patients, with additional measures to reduce radiation exposure to the fetus. This includes avoidance of fluoroscopy over the abdomen and pelvis, use of low-dose fluoroscopy mode and/or pulsed fluoroscopy, minimizing digital subtraction angiography (DSA) runs, and use of tight collimation. For both CT and angiography, abdominal shielding is not helpful, and may in fact increase scattered radiation to the fetus, and is therefore avoided.

PR4: The expert panel recommends that pregnant women with HHT be managed at a tertiary care center by a multi-disciplinary team, if they have untreated pulmonary AVMs and/or brain VMs OR have not been recently screened for pulmonary AVMs.
Quality of Evidence: Very Low (Agreement 94%)
Strength of the Recommendation: Strong (Agreement 85%)

Clinical Considerations: Pregnant women with untreated pulmonary AVMs, and those who have not been screened, should be considered high risk for hemorrhagic and neurologic complications, and be managed accordingly by a high-risk team with HHT expertise. Pregnant women with untreated brain AVMs should be assessed for high-risk features, and managed accordingly.

PR5: The expert panel recommends not withholding an epidural because of a diagnosis of HHT, and that screening for spinal vascular malformations is not required.
Quality of Evidence: Low (Agreement 98%)
Strength of the Recommendation: Strong (Agreement 92%)
Clinical Considerations: Patients should meet with an anesthetist during early third trimester to discuss anesthesia options and review the only theoretical but unsubstantiated risk of complications from spinal VM during epidural anesthesia.

PR6: The expert panel recommends that women with known, non-high risk brain VMs can labor and proceed with vaginal delivery. Patients may require an assisted second stage on a case by case basis. **Quality of Evidence: Moderate (Agreement 94%)**
Strength of the Recommendation: Strong (Agreement 94%)
Clinical Considerations. If a brain VM has not previously ruptured, patients may proceed with mode of delivery based on obstetrical indications and discussion with their obstetrical care provider. A vaginal delivery is not contra-indicated in this case. Patients with “high risk” brain VMs should be considered for Cesarean section, OR epidural, to

allow passive descent of the presenting part, with consideration for an assisted second stage. Diligent management of blood pressure is imperative, in these higher risk cases, and obtaining the opinion a multi-disciplinary neuro vascular team is prudent.

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Table 1. Curaçao Criteria for clinical diagnosis of HHT.

Criteria	Description
Epistaxis	Spontaneous and recurrent
Telangiectases	Multiple, at characteristic sites: lips, oral cavity, fingers, nose
Visceral lesions	GI telangiectasia, pulmonary, hepatic, cerebral or spinal AVMs
Family history	A first degree relative with HHT according to these criteria

Table 2. HHT genetic testing is recommended for people at risk of HHT, in the following situations:

1. To identify the causative mutation in a family with clinically confirmed HHT
2. To establish a diagnosis in relatives of a person with a known causative mutation, including:
    a. Individuals who are asymptomatic or minimally symptomatic
    b. Individuals who desire prenatal testing
3. To assist in establishing a diagnosis of HHT in individuals who do not meet clinical diagnostic criteria

Table 3: Currently recommended clinical recommendations from the first International HHT Guidelines (1). Listed below are the clinical recommendations with >=80% consensus at the first International HHT Guidelines AND which the 2019 International Guidelines Working Group agreed to maintain as current, and not reassess in 2019.

Diagnosis of HHT:
1: **The expert panel recommends that clinicians diagnose HHT using the Curaçao Criteria** (see Table1) or by identification of a causative mutation (Level of evidence: III, strength of recommendation: weak, 82% agreement). 2: **The expert panel recommends that clinicians consider the diagnosis of HHT in patients with one or more Curaçao criteria** (see **Table 1**) (Level of evidence: III, strength of recommendation: weak, 91% agreement). 3: **The expert panel recommends that asymptomatic children of a parent with HHT be considered to have possible HHT, unless excluded by genetic testing** (Level of evidence: III, strength of recommendation: weak, 87% agreement). 4: **The expert panel recommends that clinicians refer patients for diagnostic genetic testing for HHT** **1. To identify the causative mutation in a family with clinically confirmed HHT** **2. To establish a diagnosis in relatives of a person with a known causative mutation, including:** **a. Individuals who are asymptomatic or minimally symptomatic** **b. Individuals who desire prenatal testing** **3. To assist in establishing a diagnosis of HHT in individuals who do not meet clinical diagnostic criteria** (Level of evidence: III, strength of recommendation: weak, 80% agreement) 5: **The expert panel recommends that for individuals who test negative for ENG and ACVRL1 coding sequence mutations, SMAD4 testing should be considered to identify the causative mutation** (Level of evidence: III, strength of recommendation: weak, 93% agreement).
Epistaxis:
1: **The expert panel recommends that physicians advise patients with HHT-related epistaxis to use agents that humidify the nasal mucosa to prevent epistaxis** (Level of evidence: III, strength of recommendation: weak, 94% agreement). 3: **The expert panel recommends that clinicians refer HHT patients with epistaxis and who desire treatment to otorhinolaryngologists with HHT expertise for evaluation and treatment** (Level of evidence: III, strength of recommendation: weak, 87% agreement). 4: **The expert panel recommends that when considering nasal surgery for reasons other than epistaxis, the patient and clinician obtain consultation from an otorhinolaryngologists with expertise in HHT-related epistaxis** (Level of evidence: III, strength of recommendation: weak, 100% agreement). 5: **The expert panel recommends that the treatment for acute epistaxis requiring intervention include packing with material or products that have a low likelihood of causing re-bleeding with removal (e.g., lubricated low-pressure pneumatic packing)** (Level of evidence: III, strength of recommendation: weak, 93% agreement).
Brain VMs:

2: **The expert panel recommends the use of MRI for brain VM screening in adults with possible or definite HHT using a protocol with and without contrast administration and using sequences that detect blood products, to maximize sensitivity**
(Level of evidence: III, strength of recommendation: weak, 100% agreement).
4: **The expert panel recommends that adults presenting with an acute hemorrhage secondary to a brain VM be considered for definitive treatment in a center with neurovascular expertise**
(Level of evidence: III, strength of recommendation: strong, 94% agreement).
5: **The expert panel recommends that all other adults with brain VMs be referred to a center with neurovascular expertise to be considered for invasive testing and individualized management**
(Level of evidence: III, strength of recommendation: strong, 84% agreement).
6: **The expert panel recommends that pregnant women with suspected or confirmed HHT harboring an asymptomatic brain VM during pregnancy have definitive treatment of their brain VM deferred until after delivery of their fetus. The expert panel recommends that the delivery of the fetus follow obstetrical principles**
(Level of evidence: III, strength of recommendation: weak, 80% agreement).

Pulmonary AVMs:

1: **The expert panel recommends that clinicians screen all patients with possible or confirmed HHT for pulmonary AVMs**
(Level of evidence: III, strength of recommendation: strong, 96% agreement).
2: **The expert panel recommends that clinicians use transthoracic contrast echocardiography as the initial screening test for pulmonary AVMs**
(Level of evidence: II, strength of recommendation: weak, 96% agreement).
3: **The expert panel recommends that clinicians treat pulmonary AVMs with transcatheter embolotherapy**
(Level of evidence: II, strength of recommendation: strong, 96% agreement).
4: **The expert panel recommends that clinicians provide the following long-term advice to patients with documented pulmonary AVMs (treated or untreated):**
   1. Antibiotic prophylaxis for procedures with risk of bacteremia
   2. When IV access is in place, take extra care to avoid IV air
   3. Avoidance of SCUBA diving
(Level of evidence: III, strength of recommendation: weak, 87% agreement).
5: **The expert panel recommends that clinicians provide long-term follow-up for patients who have pulmonary AVMs, in order to detect growth of untreated pulmonary AVMs and also reperfusion of treated AVMs**
(Level of evidence: II, strength of recommendation: strong, 100% agreement).

Liver VMs:

2: **To clarify the diagnosis of HHT, the expert panel recommends screening for liver VMs, using Doppler US, in patients with 1 or 2 HHT diagnostic criteria and in whom genetic testing is either inconclusive or unavailable**
(Level of evidence: III, strength of recommendation: strong, 78% agreement)
3: **The expert panel recommends that liver biopsy be avoided in any patient with proven or suspected HHT**
(Level of evidence: III, strength of recommendation: strong, 97% agreement).
4: **The expert panel recommends that hepatic artery embolisation be avoided in patients with liver VMs as it is only a temporizing procedure associated with significant morbidity and mortality**
(Level of evidence: III, strength of recommendation: strong, 94% agreement)

Table 4: Randomized Controlled Trials for Treatment of Epistaxis in HHT. All trials were performed in adults (Age 18+) and included only patients with definite clinical diagnosis of HHT

Citation	Participants	Intervention	Design and Methods	Primary Outcome Measures	Primary Outcome Results
Boyer H. et al. Int Forum Allergy Rhinol. 2015. (25)	N=17	Sclerotherapy versus Control ("standard treatment", defined as continuation of any treatment that the patient had previously undergone)	RCT (crossover) Treatment= 6 weeks, each Washout period: None	Epistaxis severity score (ESS).	Improved ESS scores (0.95 difference, 1-sided p = 0.027), The standard deviation of the difference scores was 1.82. Treatment order was not statistically significant.
Dupuis-Girod S. et al. JAMA 2016 (37)	N=80	Bevacizumab nasal spray (25mg, 50mg, or 75mg) for 4 weeks vs placebo nasal spray	RCT Phase II-III (placebo controlled) Treatment: doses 14 days apart for a total treatment duration of 4 weeks, resulting in a total dose of 75mg, 150mg, and 225mg in each treatment group.	Mean monthly epistaxis duration for 3 months AFTER end of treatment compared with 3 month BEFORE beginning of treatment.	No statistical difference was observed in mean monthly epistiaxs duration among treatment groups and placebo (P = .57), with higher standard deviatio than expected in trial design.
Gaillard S. et al. J Thromb Haemost. 2014 ATERO. (20)	N=135	Oral tranexamic acid (3g per day) versus placebo	RCT (double-blind, placebo controlled crossover): Treatment: 3 months, each	Mean monthly epistaxis duration for last 2 months of the treatment compared with the last 2months on placebo.	The mean duration of epistaxis per month was significantly shorter with tranexamic acid than placebo (0.19 on the log scale; SD = 0.07; P = 0.005). Thi difference corresponded to a decrease of 17.3% in the duration of epistaxis p month (95% CI, 5.5–27.6).
Geisthoff U.W. et al. Thromb Res.2014 (21)	N=22	Oral tranexamic acid (3g per day) versus placebo	RCT (double-blind, placebo controlled crossover): Treatment: 3 months, each. Washout period: None.	Delta Hemoglobin (final minus initial) for each treatment period	No significant difference in Delta Hemoglobin between tranexamic acid and placebo was detected (p=0.33, Mann–Whitney-U test). Post-hoc analysis: Mean Hemoglobin concentrations were significantly greate for tranexamic acid versus placebo (p=0.013, Mann– Whitney-U test).
Riss D. et al. Head Neck. 2015 (38)	N=15	Single dose of intranasal submucosal injection of bevacizumab	RCT (double-blind, placebo controlled, parallel group, stratified by age and epistaxis severity). Patients received a single intranasal submucosal injection of 100 mg of bevacizumab in 10 mL saline or placebo (10 mL saline). 5 mL were injected into each side of the nose.	The relation of the average daily post treatment epistaxis VAS score (range, 0–100) compared to the average daily pretreatment score in the month before the intervention (R = VAS-post/VAS-pre), for days 11 84.Patients recorded in a diary their daily epistaxis VAS scores ranging from 0 (best situation) to 100 (wors case).	Average daily VAS scores dropped from 18.8 (±16.5 SD) pretreatment to 13.4 (±11.6 SD) posttreatment in the bevacizumab group and from 20.5 (±13.4 SD) to 19.7 (±12.6 SD) in the placebo group, though the relation of the average daily posttreatment VAS score compared to the average daily pretreatment score, did not show a statistically significant difference (p = .57).
Whitehead K. et al. JAMA 2016 (19)	N=121	Topical therapy with bevacizumab 1% (4 mg/d) OR estriol 0.1% (0.4 mg/d) OR tranexamic acid 10% (40 mg/d) nasal sprays	RCT Phase II (double-blind, placebo controlled, stratified by epistaxis frequency) 4 treatment groups (bevacizumab 1% (4 mg/d), estriol 0.1% (0.4 mg/d), tranexamic acid 10% (40 mg/d), or placebo (0.9% saline) for 12 weeks.	Median weekly epistaxis frequency (weeks 5-12) for each patient	Epistaxis frequency was not significantly different between any of the active drug groups and the placebo group or between any of the therapeutic agents
Yaniv E. et al. Laryngoscope 2009	N=25	Oral antiestrogen, Tamoxifen 20mg once daily	RCT (double-blind, placebo controlled) Treatmer period=6 months. Washout period: None.	Frequency of epistaxis, duration of epistaxis, hemoglobin level	Epistaxis frequency was signficantly less in the treatment groups (P = .01), as was epistaxis severity (P = .049) at 6 months. The was no significant difference n hemoglobin between groups at 6 months.

Table 5: Lower Quality Uncontrolled Clinical Trials for Treatment of Epistaxis in HHT. All trials were performed in adults (Age 18+) and included only patients with HHT diagnosis.

Citation	Study Design	Intervention	Outcome of Interest	Outcome Results
Reh D.D. et al. Laryngoscope 2013	Prospective study (N=20)	topical lubricant	ESS	Mean ESS improved (p<0.0001) at 3mo.
Fernandez-L A. et al. Thromb Haemost 2007	Prospective study (N=14)	oral tranexamic acid	Epistaxis frequency&severity	100% patients improved
Zaffar N. et al.Ann Hematol. 2015 (22)	Retrospective study (N=29)	oral tranexamic acid	ESS	Mean ESS improved (p<0.001)
Jorgensen G. et al. Eur Arch Otorhinolaryngol 2011	Prospective study (N+30)	laser	Epistaxis duration	Epistaxis duration reduced (p<0.05) at 1.5 mo.& 6 mo.
Kuan E.C. et al.Lasers Med Sci 2017 (23)	Retrospective study (N=20)	laser	SNOT-22	Mean SNOT-22 improved at 1.5mo
Fiorella M.L. et al. ACTA otorhinolaryngologica italica 2012	Retrospective study (N=24)	laser (diode)	Epistaxis frequency&severity	Group improved
Poje G. et al. ENT-Ear, Nose & Throat Journal 2017	Retrospective study (N=17)	laser (diode)	Epistaxis frequency&severity	Group improved
Papaspyrou G. et al. ORL 2016	Retrospective study (N=38)	laser (Nd:YAG)	Need for recurrent intervention	Recurrent intervention in 18% at 3 years
Papaspyrou G. et al.Journal of Cranio-Maxillo-Facial Surgery 2017	Prospective study	laser (Nd:YAG) +/- APC	Need for recurrent intervention	Recurrent intervention in 20-33%% at 3-10 years
Abdelghany A. Clinical Otolaryngology 2013	Prospective study (N=16)	radiofrequency coblation	Epistaxis frequency&intensity	100% patients improved
Luk L. et al.Int Forum Allergy Rhinol 2014	Prospective cohort study (N=11)	radiofrequency coblation vs laser (KTP)	ESS	No significant difference in mean ESS, at 12mo.
Mortuaire G. et al. Rhinology 2013	Prospective study (N=16)	radiofrequency coblation	Epistaxis frequency&duration	Reduced mean epistaxis frequency (P<0.05) at 6mo.
Rotenberg B et al. Am J Rhinol Allergy 2015 (27)	Retrospective stufy (N=37)	radiofrequency coblation	ESS	Mean ESS improved (p=0.02) at 6 mo.
Boyer H. et al. Int Forum Allergy Rhinol 2011 (24)	Retrospective study (N=7)	sclerotherapy	Epistaxis frequency&severity	100% patients improved
Morais D. et al .Rhinology 2012	Retrospective study (N=45)	sclerotherapy	Epistaxis frequency&severity	95% patients improved
Pagella F. et al. Acta Oto-Laryngologica 2013	Retrospective study (N=26)	thermal coagulation (APC)	Epistaxis score	Mean score improved (P=0.005) at 12 mo.
Pagella F. et al. Am J Rhinol Allergy 2006	Prospective study (N=36)	thermal coagulation (APC)	Reported bleeding	100% reported reduction in bleeding at 6mo.
Al-Samkari H. et al. Blood 2018	Retrosepctive stydu (N=13)	IV bevacizumab	Epistaxis control	Epistaxis control (reduction in epistaxis grade to <2) was achieved in 85% of patients, from 0 patients at baseline (P< 0.001)
Dupuis-Girod S. et al. JAMA 2012 (28)	Prospective study (N=25)	IV bevacizumab	Reported bleeding duration	Mean duration of epistaxis, significantly decreased from 221 minutes per mo. at baseline to 43 minutes per mo. at 3 mo. (p= 0.008).
Epperla N. et al. American Journal of Hematology 2016 (32)	Retrospective study (N=5)	IV bevacizumab	blood transfusions	blood transfusions were reduced from baseline in 5/5 patients
Iyer V. et al. Mayo Clin Proc 2018 (31)	Retrospective study (N=34)	IV bevacizumab	ESS	Significant reduction in ESS from baseline to 3mo (p<0.001)
Faughnan ME. et al. Angiogenesis 2019 (45)	Prospective study (N=7)	oral pazopanib	Epistaxis duration	6/7 patients had >50% decrease, from baseline to during treatment
Baysal M. et al. Turk J Hematol 2019 (44)	Retrospective study (N=6)	oral thalidomide	ESS	Mean ESS improved from pre-treatment (7.40+/-2.02) to post-treatment (3.10+/-1.79), significantly (p=0.028)
Fang J. et al. Otolaryngology–Head and Neck Surgery 2017 (41)	Prospective study (N=7)	oral thalidomide	ESS	Mean ESS improved from pre-treatment (5.03 +/- 2.05), to end treatment (0.90 +/- 0.84, p= 0.003) and to 3 mo. after end treatment (1.98 +/- 1.33, p= 0.006), respectively.
Invernizzi R. et al. Lancet Haematol 2015 (42)	Prospective, Phase II (N=31)	oral thalidomide	frequency, intensity, or duration of epistaxis.	All patients responded to therapy with a significant decrease in all epistaxis parameters (p<0.0001 for frequency, intensity, and duration)
Lebrin F. et al. Nature Medicine 2010 (40)	Prospective study	oral thalidomide	Epistaxis severity	Self-reported severity of epistaxis improved in 5/7 (71%) of patients after treatment
Peng H. et al. Chin Med J 2015 (39)	Prospective study (N=5)	oral thalidomide	ESS	Mean ESS improved from pre-treatment (6.966 +/- 3.093) to post-treatment (1.799 +/- 0.627) significantly (p = 0.009)
Ichimura K. et al. Auris Nasus Larynx 2012	Prospective study (N=7)	nasal closure	Epistaxis cessation	57% had cessation of epistaxis
Lund V. et al. Rhinology 2017 (50)	Retrospective study (N=100)	nasal closure	Epistaxis cessation	50% of patients responded: 94% had cessation of epistaxis
Richer S. et al. Am J Rhinol Allergy 2012 (48)	Retrospective study (N=43)	nasal closure	Epistaxis cessation	84% of patients responded: 83% had cessation of epistaxis
Wirsching K. et al. Eur Arch Otorhinolaryngol 2017	Prospective study (N=20)	temporary nasal occlusion with tape	ESS	ESS decreased from pre-treatment median of 3.59 to post-treatment (at 3 mo.) median of 2.43, significantly (p = 0.01).
Harvey R. et al. Am J Rhinol Allergy 2008	Retrospective study (N=33)	septodermoplasty	Frequency of KTP laser	Number of KTP laser treatments decreased from 1.83 (+/-1.99) pre-septdermoplaty to 0.78 (+/-0.85) post-septodermoplasty, significantly (p=0.012).

Ichimura K. et al. Auris Nasus Larynx 2006	Retrospective study (N=15)	septodermoplasty	Patient satisfaction	100% of patients satisfied with procedure
Lesnik G. et al. Am J Rhinol Allergy 2007 (47)	Retrospective study (N=9, severe)	septodermoplasty plus septectomy	Epistaxis frequency, QOL and blood transfusions	All patients had improved self-reported QOL. blood transfusions were reduced from baseline 22.61/year to 9.57/year post-procedure ($p < 0.05$).
Levine C. et al. Am J Rhinol Allergy 2008 (46)	Retrospective study (N=106)	septodermoplasty	QOL	62% of patients responded: 86% patients had improved QOL at mean 3.75 years
Rimmer J. et al. Laryngoscope 2014 (51)	Prospective study (N=7)	septodermoplasty	Epistaxis frequency&severity	100% of patients reported reduction in epistaxis frequency and severity

Table 6A: Diagnostic yield of gastrointestinal diagnostic procedures in adults with definite HHT. All studies were in adults (18 years+).

Citation	Population	Tests	Diagnostic Yields
Canzonieri C. et al. Genetics in Medicine 2014 (55)	Definite HHT, consecutive adults, 22 (13 male), mean age 59yrs (+/-9)	Esophagogastroduodenoscopy Capsule endoscopy Colonoscopy	82% 91%. 10%
Chamberlain SM et al. Endoscopy 2007 (59)	Definite HHT, consecutive adults with suspected GI bleeding, 32/38 complete (18 male), mean age 54yrs (+/-13)	Capsule endoscopy	Any GI telangiectasia=81%. Gastric=28%. Proximal small bowel=56%. Mid small bowel=59% Distal small bowel=63%
Chetcuti Zammit S et al. Turk J Hematol 2018 (69)	Definite HHT, consecutive adults with suspected GI bleeding, 10 patients (6 male), mean age 63yrs (+/-14)	Capsule endoscopy (N=7)	Proximal small bowel=86%. Mid small bowel=11% Distal small bowel=33%
Greve E. et al. Gastrointestinal Endoscopy 2010 (54)	Definite HHT, consecutive adults with anemia and suspected GI bleeding, 30 patients (10 male), mean age 58yrs (+/-11)	Capsule endoscopy	Gastric=47%. Small bowel=87%
van Tuyl SA et al. Gastrointestinal Endoscopy 2007	Definite HHT, consecutive adults with anemia, 25 patients (13 male), mean age 49yrs (+/-15)dy	Esophagogastroduodenoscopy Capsule endoscopy Colonoscopy	67% 76% 32%

Table 6B: Lower Quality Uncontrolled Clinical Trials for Treatment of GI Bleeding in HHT. All trials were performed in adults (Age 18+) and included only patients with HHT diagnosis.

Citation	Study Design	Intervention	Outcome of Interest	Outcome Results
Zaffar N. et al. Ann Hematol 2015 (22)	Retrospective study (N=29, with 10 with GI bleeding)	oral tranexamic acid	Requirement for any GI-endoscopic intervention	Reduced from 80% pre-treatment to 40% on treatment (trend, p=0.07)
Al-Samkari H. et al. Journal of Internal Medicine 2019 (33)	Retrospective study (N=13, of whom 10 have GI bleeding)	IV bevaciuzmab	Change in hemoglobin. Reduction in pRBCs	Mean hemoglobin imprvoed by 4g/dL or by 45% from the pre-treatment period to the maintenance period (P<0.001). pRBC requirements decreased by 92% from the pretreatment period to
Iyer V. et al. Mayo Clin Proc 2018 (31)	Retrospective study (N=34, with 19 with GI bleeding)	IV bevaciuzmab	Requirement for any GI-endoscopic intervention	Significant reduction in RBC transfusions (p=0.007) in the entire group (GI bleeders not reported separately)
Faughnan ME et al. Angiogenesis 2019 (45)	Prospective study (N=7)	oral pazopanib	Epistaxis duration	6/7 patients had >50% decrease, from baseline to during treatment

Table 7A: Diagnostic accuracy of testing for Liver VMs in adults with definite HHT. All studies were in adults (18 years+) and reported measures of diagnostic accuracy or agreement, for liver VMs.

Citation	Population	Tests	Operating Characteristics
Buonamico et al. 2008	Definite HHT (N=153)	US Doppler "colour spots". Using Multiphase CT as reference standard	Sensitivity=95.% Specificity=68% Diagnostic accuracy = 92%,
Buscarini et al. 2008	Definite HHT (N=110)	US Doppler	Sensitivity=97-99% Specificity=97-99% Moderate inter-observer agreement (Kendall's coefficient of concordance=0.26) for severity
Cavel et al. 2016	Confirmed or suspected HHT (N=62)	US Doppler versus Multiphase CT	Significant disagreement with kappa=0.376 and a Bhapkar critical probability of P=0.0053. Staging of liver involvement was significantly more severe with CT in cases of disagreement.
Milot et al. 2008	Definite HHT (N=23) versus Controls (N=23)	MRI liver	Hepatic artery diameter: greater in patients with HHT than in the controls: 8.69+/-1.63 mm versus 5.17+/-0.44 mm, respectively (P<0.05). Vascular abnormalities: 91% HHT vs 0% Controls Ischemic cholangitis: 39% HHT vs 0% Controls Good interobserver agreement for vascular abnormalities (0.62) Moderate interobserver agreement (0.42) with biliary iscehmia.
Scardapane A. et al. Radiol med 2012 (137)	Definite HHT (N=52)	Multiphase CT versus 4D-MRA	CT Diagnostic Yield=69% MRA Diagnostic Yield=69% No significant difference accuracy Kappa=0.9 (good) for type of shunt
Wu J. et al. American Journal of Roentgenology 2006 (135)	Definite HHT and symptomatic liver VMs (N=24)	Multiphase CT	Diffuse telangiectasias: 100%. Dilated hepatic artery: 100%. Cardiomegaly: 48%. Hepatic arteriovenous shunt: 54%. Arterioportal shunt: 25%. Agreement between CT and clinical type: 54%

Table 7B: Lower Quality Uncontrolled Clinical Trials for Treatment of Liver VMs in HHT. All trials were performed in adults (Age 18+) and included only patients with HHT				
Citation	**Study Design**	**Intervention**	**Outcome of Interest**	**Outcome Results**
Dupuis-Girod S. et al. JAMA 2012 (28)	Uncontrolled series (N=25, HHT with HOHF from liver VMs)	IV bevacizumab	Decrease in cardiac output (from high-output state)	Cardiac output improved or normalized in 83%
Azzopardi N. et al. mAbs 2015.	Uncontrolled series (N=25, HHT with HOHF from liver VMs)	IV bevacizumab (maintenance dosing)	Maintenance of improved cardiac output with different length bevacizumab intervals, after induction	Every 3 months: Maintained in 41% Every 2 months: Maintained in 45% Every 1 month: Maintained in 50% All at 24 months, respectively.
Chavan A. et al. American Journal of Jematology 2017 (30)	Uncontrolled series (N=21, HHT with symptomatic liver VMs)	IV bevacizumab	Clinical symptom improvement	Abdominal pain grade improved from 3·0 ± 2·2 (95% CI 1·99–3·91) pretherapy to 0·9 ± 1·0 post-therapy (95% CI 0·48–1·33) (P < .001). Mean NYHA stage improving from 2·8 ± 0·7 (95% CI 2·49–3·13) pretherapy to 1·6 ± 0·9 (95% CI 1·25–1·99) (P < .0001) following therapy. Mean epistaxis grade fell significantly from 2·4 ± 0·8 (95% CI 2·04–2·73) to 0·9 ± 0·4 (95% CI 0·70–1·01) (P < .0001).
Lerut J et al. Annals of Surgery 2006 (127)	Uncontolled case series (N=40)	Liver transplant	Survival post-transplant	1-, 5- and 10-year survival rates= 82.5%.
Dupuis-Girod S. et al. Liver Transplantation 2010 (142)	Uncontolled case series (N=13)	Liver transplant	Survival post-transplant	Mean follow-up 109mo., Survival 92.3%
Liu ZC et al. Eur J Vasc Endovasc Surg 2016	Uncontrolled series (N=13, HHT with symptomatic liver VMs)	Double banding/ligation of hepatic arteries	Clinical effectiveness measures	Cardiac function, classified per the New York Heart Association (NYHA) cardiac functional grading, improved (NYHA III-IV vs. NYHA I-II) Pulmonary arterial pressure significantly decreased in all patients (48 +/- 8 mmHg vs.24 +/- 4 mmHg; P < .001). Gamma-glutamyl transpeptidase and alkaline phosphatase decreased in 11 patients (144 +/- 94 U/L vs. 71 +/- 34 U/L; P = .003) and 10 patients (207 +/- 71 U/L vs. 105 +/- 32 U/L; P = .001), respectively.

Table 8A: Diagnostic accuracy of testing for Pulmonary AVMs in children with definite HHT. All studies were in children (<18 years) with reported measures of diagnostic accuracy or agreement for pulmonary AVMs.

Citation	Population	Tests	Operating Characteristics
Soysal N. et al. Eur J Vasc Endovasc Surg2017	Definite HHT (N=59)	High-resolution CT chest	Yield: pulmonary AVMs 25%
Al-Saleh S. et al. Eur Respir 2012	Definite HHT (N=75)	TTCE screening chest (reference standard)	Intraobserver and interobserver agreement for interpreting TTCE results were excellent (kappa = 0.97 and 0.92, respectively) Sensitivity=100% , Specificity=82% PPV=39% , NPV=100%
Karam C. et al. Echocardiography 2015	Definite HHT (N=93)	TTCE screening chest (reference standard)	Yield: Pulmonary AVMs 52%. Sensitivity=100%, Specificity= 95%, PPV=96%, NPV=100%
Fernandopulle N. et al. The Journal of Pediatrics 2018 (158)	Possible HHT (N=293)	TTCE screening chest (reference standard)	TTCE positve: 26%. Bubble timing was significantly associated with need for treatment (p=0.008) Shunt intensity was significantly associated with presence of CT-detectable PAVMs (p<0.001) and need for intervention (p=0.005)
Westermann C. et al. American Journal of Medical Genetics 2003	Definite HHT (N=112)	Screening with pulse oximetry and chest X-ray	Yield: Pulmonary AVMs 22%, of whom 48% had had serious complication
Hosman A. et al. Pediatric Pulmonology. 2017 (155)	Definite HHT (N=175)	Screening with pulse oximetry and chest X-ray	Yield: Pulmonary AVMs 22%, of whom 85% required embolization

Table 8B: Lower Quality Uncontrolled Clinical Trials for Treatment of Pulmonary AVMs and Brain VMs in HHT. All trials were performed in children (<18 years) and included only patients with HHT diagnosis.

Citation	Study Design	Intervention	Outcome of Interest	Outcome Results
Faughnan ME et al. The Journal of Pediatrics 2004 (154)	Definite HHT and pulmonary AVMs(N=42)	Transcatheter embolization of pulmonary AVMs	Reperfusion rate and safety	Reperfusion in 15% of embolized pulmonary AVMs No serious or long-term procedural complications
Meybodi AT et al. Neurosurgery 2018 (174)	Definite HHT and brain VMs (N=6 children treated)	Surgical management of brain VMs	Neurlogical outcomes	5/6 children: improved or stable mRS post-op and 1/6 had temporarily worsended mRS worsened post-op
Krings T. et al. Neuroradiology 2005	Definite HHT and brain VMs (N=25 children treated, including 14 with brain AVFs)	Embolization	Clinical outcomes	87% patients had stabilization of the disease, ameliorating the symptoms or even complete resolution.

Figure 1: Literature Search Results

Topic Group	Total Search Results Screened (Title / Abstract)	Results Reviewed in Full Text	Total Number of Studies Included
Anemia / iron deficiency and anticoagulation	189	47	20 (lower quality)
Liver VMs	240	60	43 (lower quality)
GI bleeding	332	28	20 (lower quality)
Epistaxis	293	121	8 (RCTs) 89 (lower quality)
Pregnancy	92	31	6 (lower quality)
Pediatrics	430	162	35 (lower quality)
Total	1,576	449	221

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3. Date: 23-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

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Dr. Poetker reports grants from CureHHT, during the conduct of the study; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Mary
2. Surname (Last Name): Porteous
3. Date: 29-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M201443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 6. Disclosure Statement

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Dr. Porteous has nothing to disclose.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Marco
2. Surname (Last Name): Post
3. Date: 19-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Ivan
2. Surname (Last Name): Radovanovic
3. Date: 05-August-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name:

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia"

6. Manuscript Identifying Number (if you know it): M20-1443

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Felix
2. Surname (Last Name): Ratjen
3. Date: 19-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it):

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Vertex	☑	☑	☐	☐	PI for grants, consulting or honorarium for CF related activities
Novartis	☐	☑	☐	☐	I have acted as a consultant for this company on CF related activities
Boehringer Ingelheim	☐	☑	☐	☐	I have acted as a consultant for this company on CF related activities
Roche	☐	☑	☐	☐	I have acted as a consultant for this company on CF related activities
Genentech	☐	☑	☐	☐	I have acted as a consultant for this company on CF related activities

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Dr. Ratjen reports grants and personal fees from Vertex, personal fees from Novartis, personal fees from Boehringer Ingelheim, personal fees from Roche, personal fees from Genentech, personal fees from Vertex. personal fees from Proteostasis outside the submitted work.

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Section 1. Identifying Information

1. Given Name (First Name): Paul
2. Surname (Last Name): Rochon
3. Date: 7/26/20

4. Are you the corresponding author? ☐ Yes ☐ X No

5. Manuscript Title
"International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia"

6. Manuscript Identifying Number (if you know it)
M20-1443

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☐ XNo

ADD

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Are there any relevant conflicts of interest? ☐ Yes ☐ XNo

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Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ XNo

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I have no relevant financial disclosure related to this project.

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Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Josanna
2. Surname (Last Name): Rodriguez-Lopez
3. Date: 28-July-2020

4. Are you the corresponding author? ☐ Yes ☐ No

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Bayer	☑	☑	☐	☐	consulting, site PI for trial
Actelion	☑	☑	☐	☐	consulting, site PI for trial

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Rodriguez-Lopez reports grants and personal fees from Bayer, grants and personal fees from Actelion, outside the submitted work; .

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Carlo
2. Surname (Last Name): Sabbà
3. Date: 29-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: M.E. Faughnan

5. Manuscript Title: Second International Guidelines for the Diagnosis and Management of HHT

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 6. Disclosure Statement

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Dr. Sabbà has nothing to disclose.

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Section 1. Identifying Information

1. Given Name (First Name): Marcelo
2. Surname (Last Name): Serra
3. Date: 18-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title
"International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia"

6. Manuscript Identifying Number (if you know it)
M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Serra has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Claire
2. Surname (Last Name): Shovlin
3. Date: 22-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No Corresponding Author's Name

5. Manuscript Title: "International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Dennis
2. Surname (Last Name): Sprecher
3. Date: 22-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: "International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia"

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ No

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I am a Board member of the advocacy group, and have no financial conflicts with these guidelines

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Relationships not covered above.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) 2. Surname (Last Name) 3. Date

4. Are you the corresponding author? ☐ Yes ☐ No

5. Manuscript Title

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time**

Are there any relevant conflicts of interest? ☐ Yes ☐ No

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Are there any relevant conflicts of interest? ☐ Yes ☐ No

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ No

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4. Intellectual Property.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Kevin
2. Surname (Last Name): Whitehead
3. Date: 22-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Whitehead has nothing to disclose.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Ingrid
2. Surname (Last Name): WInship
3. Date: 19-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

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Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
Matty's Soldiers (HHT Support Group)	☑	☐	☐	☐	Funding toward study	

Section 3. Relevant financial activities outside the submitted work.

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Dr. WInship reports grants from Matty's Soldiers (HHT Support Group), during the conduct of the study; .

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Section 1. Identifying Information

1. Given Name (First Name): Meir
2. Surname (Last Name): Mei-Zahav
3. Date: 23-July-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Marie Faughnan

5. Manuscript Title: International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

6. Manuscript Identifying Number (if you know it): M20-1443

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Section 1. Identifying Information

1. Given Name (First Name): ROBERTO
2. Surname (Last Name): ZARRABEITIA
3. Date: 19-May-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: MARIE FAUGHNAN

5. Manuscript Title: INTERNATIONAL GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF HEREDITARY HEMORRHAGIC TELANGIECTASIA

6. Manuscript Identifying Number (if you know it): M20-1443

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Dr. ZARRABEITIA has nothing to disclose.

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