Supplement 2: Supplementary Materials*

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* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

Part 1: Literature Search and Inclusion Criteria

Literature Search

Six sets of search strategies were developed and executed in Ovid MEDLINE between May and June 2019 to identify studies that addressed the key questions for each of the topic groups. Search strategies combined both topic-specific controlled subject headings (MeSH terms) and relevant keywords in order to capture the broad topics of interest for each topic. Searches for topics addressed in the previous version of the guideline were limited to the date the last literature search was conducted in 2006, and topics which were not addressed in the previous guideline were expanded to include publications since 1990.

Anemia / Iron Deficiency and Management of Anticoagulation

1	telangiectasia, hereditary hemorrhagic/	3148
2	hereditary h$emorrhagic telangiectasia$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1847
3	(Osler adj2 Weber adj2 Rendu).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	938
4	or/1-3	3761
5	limit 4 to (english language and humans and yr="1990- 2019")	1866

6	exp Anemia/	156539
7	exp Vitamin B 12 Deficiency/	11021
8	exp Hemolysis/	28388
9	exp Folic Acid Deficiency/	4823
10	(anem$ or iron deficie$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	186564
11	5 and (6 or 7 or 8 or 9 or 10)	106
12	exp Hematologic Agents/	584824
13	(anticoagula$ or antithromb$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	146153
14	exp Atrial Appendage/	2899
15	5 and (12 or 13 or 14)	83

Liver Vascular Malformations

1	telangiectasia, hereditary hemorrhagic/	3148

2	hereditary h$emorrhagic telangiectasia$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1847
3	(Osler adj2 Weber adj2 Rendu).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	938
4	or/1-3	3761
5	limit 4 to (english language and humans and yr="2006- 2019")	1212
6	(liver or biliary or hepatic or portal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1205347
7	5 and 6	240

GI Bleed

1	telangiectasia, hereditary hemorrhagic/	3148

2	hereditary h$emorrhagic telangiectasia$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1847
3	(Osler adj2 Weber adj2 Rendu).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	938
4	or/1-3	3761
5	limit 4 to (english language and humans and yr="2006- 2019")	1212
6	(gastr$ or GI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	756254
7	5 and 6	164
8	exp colonoscopy/ or exp endoscopy, gastrointestinal/	85291
9	fecal immunochemical test$.mp.	636

10	(colon cancer screen$ or screen$ for colon cancer or colorectal cancer screen$ or screen$ for colorectal cancer or colonoscopic screen$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7430
11	5 and (8 or 9 or 10)	31
12	7 or 11	168

Epistaxis

1	telangiectasia, hereditary hemorrhagic/	3148
2	hereditary h$emorrhagic telangiectasia$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1847
3	(Osler adj2 Weber adj2 Rendu).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	938
4	or/1-3	3761
5	limit 4 to (english language and humans and yr="2006- 2019")	1212

6	Epistaxis/	4646
7	(nose$ or nasal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	162481
8	5 and (6 or 7)	293

Pregnancy

1	telangiectasia, hereditary hemorrhagic/	3134
2	hereditary h$emorrhagic telangiectasia$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1831
3	(Osler adj2 Weber adj2 Rendu).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	929
4	or/1-3	3735
5	limit 4 to (english language and humans and yr="1990- 2019")	1854
6	exp Pregnancy/	861509

7	pregnan$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	962143
8	5 and (6 or 7)	61

Pediatrics

1	telangiectasia, hereditary hemorrhagic/	3134
2	hereditary h$emorrhagic telangiectasia$.mp.	1831
3	(Osler adj2 Weber adj2 Rendu).mp.	929
4	or/1-3	3735
5	limit 4 to (english language and humans and yr="1990- 2019")	1854
6	exp Pediatrics/	55263
7	(pediatr$ or paediatr$ or adolescen$ or children).mp.	2768438
8	(6 or 7) and 5	298
9	limit 5 to "all child (0 to 18 years)"	381
10	8 or 9	399

Genetic Testing

Note: A supplemental search was conducted to address key questions regarding genetic testing for both the pediatrics and pregnancy topic groups, in order to capture relevant studies that didn't specifically include pregnancy or pediatric terms. The search strategy was as follows:

1	telangiectasia, hereditary hemorrhagic/	3134
2	hereditary h$emorrhagic telangiectasia$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1831
3	(Osler adj2 Weber adj2 Rendu).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	929
4	or/1-3	3735
5	limit 4 to (english language and humans and yr="1990- 2019")	1854
6	exp Genetic Testing/	42765
7	5 and 6	55
8	7 not (results from full pediatric or pregnancy searches as executed separately)	31

Inclusion Criteria

- Patients diagnosed with or suspected of having hereditary hemorrhagic telangiectasia
- Intervention: As specified for each panel topic, based upon key questions
- Comparison: Any, including placebo, regular treatment, or no intervention
- English language publications
- Human subjects
- ≥ 5 subjects
- Original results published in an indexed journal (i.e. no data from abstracts/posters included)

Part 2: Quality Assessment for Epistaxis RCTs

Cochrane Risk of Bias Tool										
Study, Year (Reference)	**Adequate Sequence Generation ?**	**Allocation Concealment?**	**Blinding ?**	**Incomplete Outcome Data Addressed?**	**Free of Selective Outcome Reporting?**	**Free of Other Bias?**	**Source of Funding**	**Other Comments**	**ClinicalTrials.gov**	**Quality Summary: Cochrane Risk of Bias Tool**
Boyer et al. 2015 (15)	U	U	N	Y	Y	U	American Rhinologic Society New Investigator Research Grant (HB)	Unblinded	NCT01408732	Unclear if adequate sequence generation or allocation concealment Unblinded.
Dupuis-Girod et al. 2016 (27)	Y	Y	Y	Y	Y	Y	Hospices Civils de Lyon grant supported by PHRC 2013 and Association Pour la Maladie de Rendu-Osler		NCT02106520	Low risk of bias.
Gaillard et al. 2014 (135)	Y	Y	Y	Y	Y	Y	Hospices Civils de Lyon and the French Ministry of Health (2005 Hospital Clinical Research Programme (PHRC) grant.	Even though the recruitment target (213) was not met at the end of the planned enrolment period, recruiting stopped because not enough patients met eligibility criteria, and the	NCT00355108	Low risk of bias.

								treatment units reached their expiration date.		
Geisthoff et al. 2014 (11)	Y	Y	Y	Y	Y	Y	Pharmacia GmbH, (now part of Pfizer) & Baxter Deutschland GmbH. After completion MEDA Pharma GmbH & Co. KG, paid 3500 Euros to UWG for access to the data to gain government approval of TA for epistaxis in HHT in Germany. "No funding source was involved in study design, collection, analysis and interpretation of the data nor in the decision to submit the manuscript"	Results presented mainly derived from ITT analysis including 20 patients. Per protocol analyses including 18 patients, were also performed but did not reveal any relevant changes to the results (data not shown).	NCT01031992	Funding provided by Pharmacia GmbH, (now part of Pfizer) and Baxter Deutschland GmbH. After study completion, MEDA Pharma GmbH & Co. KG, paid 3500 Euros for access to the data.

Riss et al. 2015 (28)	Y	Y	Y	Y	Y	Y	An unrestricted grant by Roche Austria to two of the authors (M.B. and D.R.). "The company was not involved in any other part of the study (eg, protocol design, data acquisition, statistical analysis, or manuscript editing)."	A random block size of 6 was used, but because of the 2 stratification criteria and the low number of patients, 9 patients were randomized by chance to the bevacizumab group and 6 patients to the placebo group.	NCT01314274	Two of the authors received an unrestricted grant by Roche Austria.
Whitehead et al. 2016 (9)	Y	Y	Y	Y	Y	Y	Cure HHT		NCT01408030	Low risk of bias.
Yaniv et al. 2009 (64)	U	Y	U	Y	U	U	Not stated	No description of blinding or of sequence generation. Pre-specified outcomes not clearly described. QoL outcome added after study began.	NCT00375622	No description of blinding or of sequence generation. Pre-specified outcomes not clearly described. QoL outcome added after study began. Source of funding not stated.

Part 3: External Review Process

The draft guideline manuscript was reviewed by a diverse group of experts representing people with HHT, patient advocacy groups, a variety of relevant specialties and guidelines experts. Reviewers were from eight countries and excluded individuals from the centers of current HHT guidelines authors. Reviewers were recommended by the Guidelines Working Group. Those with relevant expertise were invited by the Guidelines chair (MEF). Of the 33 invited reviewers, 21 indicated a willingness to provide a review, 8 declined and 4 did not respond. In total, 20 reviews were completed.

Reviewers were asked to read the confidential draft manuscript and then to answer a survey. The purpose of the external review was to obtain input on the Guidelines manuscript and the clinical relevance of the recommendations, and to identify potential barriers and enablers to implementation. Given that the clinical recommendation statements were generated and already finalized at the consensus conference, reviewers were not asked for revisions of the recommendation statements. The survey instrument was hosted on Survey Monkey. Two reviewers provided feedback in separate emails in addition to completing the survey instrument.

Responses to overall questions (yes/no closed questions):

Question	**Total responses N (%)**	**Yes N (%)**	**No N (%)**	**Not applicable N (%)**
Would you make use of this guideline in your professional decisions?	20 (100%)	15 (75%)	2 (10%)	3 (15%)
Are these guidelines flexible enough to allow for clinical judgement?	20 (100%)	17 (85)	2 (10%)	1 (5%)
I would recommend these guidelines for use in practice.	**19 (95%)**	**18 (95%)**	**1 (5%)**	**0 (0%)**

One reviewer, with specific expertise in the GRADE methodology, highlighted areas where transparency of the recommendation decision process could be increased.

Ratings of guideline quality: Reviewers were asked to rate the quality of the Guidelines using a 1 to 5 scale (1=poor quality, 5 =high quality). High quality was defined as impactful, rigorous methodology, clear and clinically relevant. Poor quality was defined a low impact, unclear, lack of clinical relevance and weak methodology.

Question	**1 (poor)**	**2**	**3**	**4**	**5 (high)**	**Weighted average**	**Total responses N**
Rate the quality of these guidelines.	0	0	2	5	12	4.63	19

Note: high quality was defined as impactful, rigorous methodology, clear, clinically relevant.

Implementation Input: Reviewers were asked several open-ended questions related to perceived implementation barriers and enablers that the Working Group will consider in planning for dissemination and implementation. Responses included comments and suggestions about systemic and educational barriers and evaluating the impact of the recommendations on daily practice. When asked which guidelines were likely to have the biggest impact, responses were generally aligned with reviewer specialties. The two reviewers representing patient advocacy organizations perceived Pediatrics, Epistaxis and Pregnancy and Delivery as the topic areas likely to have the biggest impact.

Reviewers' specific comments on the draft manuscript and guideline panel response

Comments	Responses
Multiple (N = 20) text suggestions that strengthen the background and clinical considerations sections:	Manuscript has been clarified with respect to these comments.
Several topics were raised as relevant but not addressed in these Guidelines (N=8)	Added to future research priorities and future guidelines priorities clinical question.

Part 4: Future Directions

Future Priorities for Guidelines

Adult BAVM screening (how, when)
Pulmonary Hypertension and HOCF
Geriatrics
Antiangiogenic dosing, maintenance strategy
Antiangiogenics propranolol, lenalidomide and pomalidomide, somatostatin analogues...
Re-screening and when to stop screening due to age
Multidisciplinary team care (care models and utilization; care outside of center versus in a center and impact on outcomes) - no care, non-disease specific care, disease specific care in nonspecialized centers by nonspecialized providers, care in nonspecialized centers by specialized providers, integrated care model - Should integrated care or nonintegrated care be used.
Long term outcomes
Manage anemia, GI and epistaxis to better define grading or severity
PAVM's
Cerebral AVM's in adults
Updating current recommendations where new research that has dramatically improved treatment

Future Priorities for Research

The expert panel identified many areas for further research in HHT, which are outlined below. Thematically, these areas fall into several categories: improved analysis of existing retrospective data and collection of harmonized prospective data through multicenter collaboration, standardization of diagnostic and treatment algorithms, technology development, technique refinement, and an increased focus on prenatal and pediatric disease detection and treatment.

Diagnosis
- Sensitivity and specificity of Curacao criteria; incorporate genetic testing into criteria
- App based / phone-based diagnosis of skin lesions

Screening Methods
- Full body imaging exam for HHT
- Optimal MRI imaging protocols for HHT-Optimized full-body imaging for HHT diagnosis and surveillance (brain, lungs, liver, etc).
- Value of screening programs

Pediatrics
- Review of Curacao Criteria-diagnosis in children
- Pediatric rescreening strategies
- Brain AVMs in children with HHT e.g. prevalence of hemorrhage, success of various treatment modalities; This could include collecting MRI data on children and combining case series data from multiple centers
- Natural history of PAVM in children
- Outcomes for PAVM treatment in children
- Clarifying screening yield and disease course in pediatric patients though multi-center collaborations
-

Pre-Natal
- Prenatal imaging: Fetal MRI and ultrasound to detect pulmonary AVM, brain VM, Liver VM, SMAD4 features
- Development of recommendations for Prenatal screening for PAVM and BAVM with advanced prenatal ultrasound and fetal MRI in pregnant patients

- Does prenatal screening for pulmonary AVM and brain VM with advanced prenatal ultrasound and fetal MRI in pregnant patients, increase the detection rate of pulmonary AVM/brain VM during the antenatal period through the first year of life?

Anemia and Blood Loss
- Algorithmic approach to anemia: Quantification of total bleeding (GI, epistaxis), scoring system- Development of a hematologic support score (HSS) that is a precise measurement of total burden of chronic HHT-associated bleeding; HHT related bleeding scoring system specific to anemia
- Impact of chronic anemia in HHT patients beyond the hematologic effects (neurocognitive, musculoskeletal function, heart failure)
- New endoscopic techniques of hemostasis

Quality of Life
- Exercise and improvement in HHT symptoms
- Can we improve morbidity/mortality by targeting specific things: hemoglobin level, ESS, ferritin level

Epistaxis
- Costs of epistaxis treatment
- Evaluate the effectiveness of embolization of the nasal arteries for patients in life threatening situations or for those who have failed all surgical modalities
- Develop a validated tool to record bleeding frequency, severity and quality of life in patients with HHT.
- Long-term outcomes of laser and sclerotherapy
- Validate patient-based outcome measures for epistaxis
- Validate clinimetric system for grading nasal telangiectasias
- Evaluate effectiveness of nasal packing

Brain AVM
- Develop standardized brain imaging protocols
- When to repeat brain screening
- Pooled data on: de novo and enlarging brain VMs in patients of all ages
- Pooled data on manifestations of HHT (e.g., children with brain VMs or central nervous system hemorrhages)
- Risk of VM in pregnancy

Spinal AVM
- Pooled data on spinal AVM

Genetics
- Genotype phenotype correlation in HHT
- Unknown genes that yield HHT phenotype

PAVM
- Sac embolization/venous embolization in PAVM
- Management of systemic artery reperfusion
- Growth rates of pulmonary AVM by noninvasive imaging
- Outcomes for pulmonary AVM treatment in children
- Follow up of pulmonary AVM based on TTCE, how often and when to stop?
- IV filter recommendations
- Should treatment be repeated multiple times, or does this cause more AVMs to form?
- Long-term effects of pulmonary AVM treatment (incidence of arterial reperfusion and how to treat it

Gastrointestinal Bleeding
- Systemic treatments for GI bleeding .

Liver VMs

- Natural history of liver VM in adults
- Ultrasound versus MRI in liver VM flow and portal vein shunting
- Treatment of asymptomatic liver VM with high cardiac output to prevent progression to HOCF
- Targeted embolization/interventional treatment of liver VM
- Determinants of hepatic phenotype
- Outcomes in screened versus non-screened patients (liver VM)
- Overlap between Liver AVM and pulmonary hypertension
- Mechanisms of non-response to antiangiogenics in liver VMs (vessel caliber, other)
- Study prevalence of symptomatic liver VM in persons with an Endoglin mutation
- Does screening for Liver AVMs change outcomes?

Women and HHT
- Heavy Menstrual periods and incidence of uterine AVM's/ telangiectasia's/AVM
- Incidence of miscarriages in women with HHT

Pregnancy
- Exact risk of lung/liver/brain AVMs during pregnancy

Therapeutics
- Developing advanced anti-angiogenic guidelines: dosing, maintenance strategy, development of trials comparing one agent with another, long-term monitoring
- Evaluate antiangiogenics with different dosing on HAVM's and nosebleeds (topical and systemic)
- Mechanism of proposed pharma agents
- Effect of bevacizumab in vascular beds
- Thrombosis risk in HHT (case-control HHT vs non-HHT CHADS scores/AFIB risks)
- Therapeutic risks of prothrombotic medications
- Development of trials: comparing different agents with each other and with invasive therapies
- Predictors of response to antiangiogenic therapy (for epistaxis, GI bleeding, HOCF, biliary ischemia, portal hypertension).
- treatment strategies - case series versus case control studies
- Comparative treatment effectiveness studies
- Development of valid outcome measures to be used in clinical trials of various interventions
- International registry
- gene therapy

HHT and Thrombosis
- Thrombosis risk in HHT (case-control HHT vs non-HHT CHADS scores/AFIB risks)
- Therapeutic risks of prothrombotic medications
- General interface of cardiology/antithrombotic therapy and HHT
- Risks of thrombolysis in HHT