Hereditary haemorrhagic telangiectasia (HHT) is a multisystemic vascular dysplasia that leads to nosebleeds, anaemia due to blood loss, and arteriovenous malformations (AVMs) in organs such as the lungs, liver and brain. HHT is estimated to affect 85,000 European citizens, but most health care providers have limited prior HHT exposure or training.

Outcome Measures were developed and implemented by the HHT Working Group of the European Reference Network for Rare Vascular Diseases (VASCERN), in order to maximise the number of patients receiving good care. The measures specifically target areas where optimal management reduces morbidity and mortality in HHT patients, and were designed to be robust to emerging new evidence. Thresholds are the percentage of patients in particular settings who have been recommended screening, or provided with written advice. The 5 Outcome Measures cover (1) pulmonary AVM screening; (2) written nosebleed advice, (3) assessment of iron deficiency; (4) antibiotic prophylaxis prior to dental and surgical procedures for patients with pulmonary AVMs, and (5) written advice on pregnancy. They are not a blueprint for detailed HHT management, but are suitable for all clinicians to be aware of and implement.

In summary, these 5 Outcome Measures provide metrics to identify healthcare providers of good care, and encourage care improvement by all healthcare providers.

Keywords: Anaemia, Antibiotic prophylaxis, Epistaxis, Iron deficiency, Nosebleeds, Pulmonary arteriovenous malformations, Pregnancy

Background

Development and implementation of Outcomes Measures are an effective part of Quality and Safety Frameworks that lead to Service Improvements. More specifically, if the Outcome Measures are carefully selected, their dissemination and implementation can directly improve patient care, including that from health care providers with limited prior exposure or training on the specific disease. Therefore simple, clinical practice-based Outcome Measures are particularly important for rare multisystemic conditions.

The current statement refers to one specific rare disease, hereditary haemorrhagic telangiectasia (HHT; Online Mendelian Inheritance in Man® #187300), which is a multisystemic vascular dysplasia that leads to telangiectasia and arteriovenous malformations (AVMs) in visceral and mucocutanous vascular beds [1]. Based on a conservative population prevalence of 1 in 6000 [2–4], HHT is estimated to affect approximately 85,000 European citizens. The main goal of management is to maximise the number of affected individuals receiving safe and effective preventative strategies in order to limit the number and severity of HHT complications. The reason this is
important, is that where optimal management is instituted, previously reduced life expectancy [3, 5–7] may improve to that of the general population, [8] early strokes, brain abscess, maternal deaths and migraines are prevented, [9–11] nosebleeds are reduced, [12–17] and patients receive timely treatments for iron deficiency anaemia and other complications.

HHT can be diagnosed either clinically using the Curaçao criteria [1] (Table 1), or through a molecular gene test. A patient with definite HHT will have at least 3 of the 4 Curaçao Criteria, or a pathogenic sequence variant in ENG, ACVRL1 or SMAD4.

Identification of pulmonary arteriovenous malformations (PAVMs) is recommended for all HHT patients because PAVMs commonly cause preventable complications in asymptomatic patients [18, 19]. Risk-benefit analyses in asymptomatic individuals are more complex for other AVMs where screening is more controversial [20], limited to specific subpopulations, or not recommended [21].

**Main text**

Outcome Measures have been embedded within the Operational Criteria of the new European Reference Networks (ERNs) for Rare Diseases [22]. The HHT Outcome Measures were developed and implemented by the HHT Working Group of the ERN for Rare Vascular Diseases (VASCERN), [23] in order to maximise the number of patients receiving good care. Details of how the topics were selected and developed into Outcome Measures are provided in the Additional file 1.

Following on from an established diagnosis of HHT or PAVMs, the outcome measure thresholds are the percentage of adult patients in particular settings who have been recommended screening, or provided with written advice (Table 2). These will be met easily by best practice in HHT centres of excellence, but may not be achieved in general specialty care. The current manuscript refers only to the principles of management- details of management lie outside of the scope of this manuscript.

**Table 1 The Curaçao Criteria**

1. **Epistaxis**: spontaneous, recurrent nose bleeds
2. **Telangiectases**: multiple, at characteristic sites (lips, oral cavity, fingers, nose)
3. **Visceral lesions** such as gastrointestinal telangiectasia (with or without bleeding); pulmonary AVM; hepatic AVM; cerebral AVM; spinal AVM
4. **Family history**: a first degree relative with HHT according to these criteria

The HHT diagnosis is **definite** if 3 criteria are present, **possible** or **suspected** if 2 criteria are present, and **unlikely** if fewer than 2 criteria are present. A pathogenic (null) sequence variant in ENG, ACVRL1 or SMAD4 also defines definite clinical HHT according to current understanding. A negative HHT gene test does not exclude HHT unless the gene variant causing HHT has been identified in another affected family member.

**Measure 1**

**At least 90% of definite HHT patients will have a screen for pulmonary arteriovenous malformations (PAVMs)**

As stated elsewhere [18, 19], all HHT patients should be offered a screen for PAVMs in adult life. The screen and subsequent management may require cross-specialist referral. Screening should be repeated after pregnancies. Where a childhood screening test has been performed, screening should be repeated after the patient is fully grown.

HHT-associated PAVMs affect approximately 50% of HHT patients i.e. 40,000 Europeans. Recent European data suggest that untreated, 6–8% may develop a cerebral abscess (usually with fatal or life-changing consequences [24–26]), at least 10–12% an early ischaemic stroke, and 1% of pregnancies will result in maternal death. Diagnosed patients can benefit from stroke reduction strategies, particularly embolization therapy to obliterate PAVMs [9, 27, 28], antibiotic prophylaxis to prevent cerebral and visceral abscesses from silent bacteraemia (see Measure 4), and pregnancy management associated with a statistically improved survival rate in the event of a life-threatening complication [10].

A PAVM screen should be considered in all adult HHT patients. However the 90% threshold takes into account the facts that not all HHT patients choose to take up the option of PAVM screening, and there may also be competing clinical circumstances which render the discussion of screening inappropriate at the time of the clinical review. Overall, the Outcome Measure ensures that the possibility of PAVMs is remembered and addressed for all HHT patients, irrespective of their presentation pattern.

**Measure 2**

**At least 90% of definite HHT patients will have received nosebleed advice in writing**

Nosebleeds (epistaxis) affect >90% of HHT patients, may be the presenting symptom of HHT, but may not be volunteered by patients unless specifically asked. HHT nosebleeds often occur daily, lasting many minutes and even hours: It is poorly appreciated that severe recurrent HHT nosebleeds can generate acute haemodynamic compromise and/or chronic cardiac failure in addition to iron deficiency anaemia.

A nosebleed history is to be evaluated for all HHT patients. The 90% threshold for written advice takes into account the facts that not all HHT patients have nosebleeds at any given time, though these may develop in the future, and the information can be important for family members also affected by HHT.

Overall, this measure ensures that irrespective of the patient’s presentation pattern, epistaxis is not overlooked,
ensures that irrespective of the patient’s presentation pattern, iron deficiency is promptly identified, enabling optimal management.

Measure 4

**100% of patients with PAVMs will have written advice on antibiotics prior to dental and surgical procedures**

This measure is recommended to reduce the rate of cerebral abscess which occurred in 6–8% of referrals to current European centres, usually resulting in substantial morbidity, and health care burdens [24–26]. Despite antibiotic prophylaxis being a long-standing recommendation for PAVM patients, in 2017, only 2/25 (8%) consecutive referrals to a UK centre for PAVM embolization had been advised to use prophylactic antibiotics.

The majority of cerebral abscesses in HHT/PAVM patients are associated with periodontal microbes, and/or precipitating dental and other interventional events that normally lead to transient bacteraemias, i.e. prior to non-sterile invasive procedures (such as dental, endoscopic, and surgical). In the general population, the bacteraemias are cleared (in terms of positive cultures) within minutes in the absence of antibiotics, but prevented or resolved earlier with prior antibiotic administration. [32] Good dental care is also important.

Written management advice to all PAVM patients is anticipated to ensure patients are aware and can communicate to all relevant practitioners, to address the current situation where patients may be refused prophylaxis and go on to develop a cerebral abscess [26].

Measure 5

**100% of pregnant women with PAVMs identified by CT scan/ imaging will be provided with written advice on PAVM/HHT pregnancies**

Although the majority of PAVM pregnancies proceed normally, there is a 1% risk of maternal death in pregnancy that can be reduced by prior awareness. Precise content will vary by country according to obstetric care pathways but may include alerts regarding potential red flag symptoms demanding immediate hospital admission (haemoptysis, sudden acute breathlessness), antibiotic prophylaxis at delivery, and management as “high-risk” pregnancies involving a multiprofessional approach.

### Conclusion

These five Outcome Measures provide metrics to identify healthcare providers of good care, encourage care improvement by all healthcare providers, and should be robust to emerging new evidence. They are not a blueprint for detailed HHT management, but are suitable for all clinicians to be aware of and implement. For the latest information, please see documents on the VASCERN website [23].
Additional file

Additional file 1: Methodological notes. (DOCX 28 kb)

Abbreviations
ACVR1A: Gene encoding the ALK-1 protein; AVM(s): Arteriovenous malformation(s); ENG: Gene encoding the endoglin protein; ERNs: European Reference Networks; HHT: Hereditary haemorrhagic telangiectasia; PAVMs: Pulmonary arteriovenous malformations; SMAD4: Gene encoding the SMAD4 protein; VASCERN: European Reference Network for Rare Vascular Diseases

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Availability of data and materials
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Authors’ contributions
CLS, EB, ADK, JJM, CS, UG, and SDG developed the Outcome Measures; CLS wrote the first draft; CLS, EB, ADK, JJM, CS, UG, SU, and SDG developed the discussions; all authors reviewed and approved the final manuscript.

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CLS is the Chair, SDG is the CoChair and EB the Deputy CoChair of VASCERN HHT. The Outcome measures were developed by the HHT WG between March and June 2016. The discussion text was developed during monthly telecons, face to face meeting and by email October 2017–February 2018.

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References
1. Shovlin CL, Guttmacher AE, Buscarni E, Faughnan ME, Hyland RH, Westernman CJ, Kjeldsen AD, Plaucu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet. 2000;91(1):6–7.
2. Bideau A, Plaucu H, Brunet G, Robert J. Epidemiological investigation of Rendu-Osler disease in France: its geographical distribution and prevalence. Population. 1989;44(1):13–22.
3. Kjeldsen AD, Vase P, Green A. Hereditary haemorrhagic telangiectasia: a population-based study of prevalence and mortality in Danish patients. J Intern Med. 1996;245(1):31–9.
4. Donaldson JW, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. The UK prevalence of hereditary haemorrhagic telangiectasia and its association with sex, socioeconomic status and region of residence: a population-based study. Thorax. 2014;69(2):161–7.
5. Sabbà C, Pasculli G, Suppressa P, D’Ovidio F, Lenato GM, Resta F, Annicott G, Guanti G. Life expectancy in patients with hereditary haemorrhagic telangiectasia. QJM. 2006;99(5):327–34.
6. Donaldson JW, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. Complications and mortality in hereditary hemorrhagic telangiectasia: a population-based study. Neurology. 2015;84(18):1886–93.
7. de Gussem EM, Edwards CP, Hosman AE, Westernman CJ, Snijder RJ, Faughn ME, Mager JJ. Life expectancy of parents with hereditary Haemorrhagic telangiectasia. Orphanet J Rare Dis. 2016;11:46.
8. Kjeldsen A, Aagaard KS, Tarrant PM, Moller S, Green A. 20-year follow-up study of Danish HHT patients-survival and causes of death. Orphanet J Rare Dis. 2016;11(1):57.
9. Shovlin CL, Jackson JE, Bambord KD, Jenkins H, Benjamin AR, Ramadan H, Kulinskaia E. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax. 2008;63(3):259–66.
10. Shovlin CL, Souhi V, McCarthy A, Laajausia P, Jackson JE, Sheppard MN. Estimates of maternal risks of pregnancy for women with hereditary haemorrhagic telangiectasia (Osler-weber-Rendu syndrome): suggested approach for obstetric services. BJOG. 2008;115(9):1108–15.
11. Post MC, Thijss V, Schonewille WJ, Budts W, Snijder RJ, Plokker HW, Westernman CJ. Embolization of pulmonary arteriovenous malformations and decrease in prevalence of migraine. Neurology. 2006;66:202–5.
12. Hoag JB, Terry P, Mitchell S, Reh D, Merlo CA. An epistaxis severity score for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. Laryngoscope. 2009;119(2):284–8.
13. Lund VJ, Darby J, Rimmer J, Amin M, Husain S. Nasal closure for severe nosebleeds by a subgroup of patients with hereditary hemorrhagic telangiectasia. Laryngoscope. 2017;72(12):1154–63.
20. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, Al-Shahi Salman R, Viscut E, Young WL, Houdart E, Cordonnier C, Stefani MA, Hartmann A, von Kummer R, Biondi A, Berkefeld J, Klijn CJ, Harkness K, Libman R, Barreau X, Moskowitz AJ, International ARUBA investigators. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. Lancet. 2014;383(9917):614–21.

21. European Association for the Study of the Liver. EASL clinical practice guidelines: vascular diseases of the liver. J Hepatol. 2016;64(1):179–202.

22. The European Reference Network for Vascular Diseases (VASCERN) HHT WG. https://vascern.eu/expertise/rare-diseases-wgs/hht-wg/ Accessed 09 Feb 2018.

23. Kjeldsen AD, Tørring PM, Nissen H, Andersen PE. Cerebral abscesses among Danish patients with hereditary haemorrhagic telangiectasia. Acta Neurol Scand. 2014;129(3):192–7.

24. Mathis S, Dupuis-Girod S, Plauchu H, Giroud M, Barroso B, Ly KH, Ingrand P, Gilbert B, Godenèche G, Neau JP. Cerebral abscesses in hereditary haemorrhagic telangiectasia: a clinical and microbiological evaluation. Clin Neurol Neurosurg. 2012;114(3):235–40.

25. Booter EJ, Brownlow S, Tighe HC, Bamford KB, Jackson JE, Shovlin CL. Cerebral abscess associated with odontogenic bacteremias, hypoxemia, and iron loading in immunocompetent patients with right-to-left shunting through pulmonary arteriovenous malformations. Clin Infect Dis. 2017; https://dx.doi.org/10.1093/cid/cix373.

26. Lacombe P, Lacout A, Marcy PY, Binse S, Seller J, Bensalah M, Chinet T, Bourgault-Villada I, Blivet S, Roume J, et al. Diagnosis and treatment of pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: an overview. Diagn Interv Imaging. 2013;94:835–48.

27. Woodward CS, Pyeritz RE, Chittams JL, Trescot AA. Treated pulmonary arteriovenous malformations: patterns of persistence and associated retreatment success. Radiology. 2013;269:919–26.

28. Nakayama M, Nawa T, Chonan T, Endo K, Morikawa S, et al. Prevalence of pulmonary arteriovenous malformations as estimated by low-dose thoracic CT screening. Intern Med. 2012;51:1677–81.