


ORIGINAL RESEARCH

Weekly epistaxis duration as an indicator of epistaxis severity in hereditary hemorrhagic telangiectasia—Preliminary results from a randomized controlled trial

Vincent Wu MD¹  | John M. Lee MD MSc FRCSC^{1,2} |
Nicholas T. Vozoris MD MSc FRCPC³ | Marie E. Faughnan MD MSc FRCPC³

¹Department of Otolaryngology – Head and Neck Surgery, St. Michael's Hospital, University of Toronto, Toronto, Canada

²Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

³Division of Respiriology, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Canada

Correspondence

Vincent Wu, MD, Department of Otolaryngology – Head and Neck Surgery, St. Michael's Hospital, University of Toronto, 6 Queen's Park Crescent West, Suite 120, Toronto, ON M5S 3H2, Canada.
Email: vince.wu@mail.utoronto.ca

Funding information

U.S. Department of Defense, Grant/Award Number: W81XWH-17-1-0429; Li Ka Shing Knowledge Institute; Nelson Arthur Hyland Foundation

Abstract

Objectives: There is great interest in developing and studying novel therapies for epistaxis in hereditary hemorrhagic telangiectasia (HHT) given its associated morbidity and impact on patients' quality of life. Several recent randomized controlled trials (RCTs) have been negative, likely attributed to poorly characterized outcome measures. This study reported on and evaluated an epistaxis outcome measure, weekly epistaxis duration (WED) in an ongoing RCT, with the aim of better characterizing the measurement of epistaxis for clinical trials.

Materials and methods: Patients were recruited to an ongoing phase II, double-blind, cross-over RCTs of oral doxycycline for HHT-associated epistaxis. Patients were included for the epistaxis measures analysis if they had already completed the initial 3-month run-in period, and had received treatment of either study drug doxycycline or placebo for a minimum of 6 months. The primary measure of interest was patient-reported outcome (PRO)-WED, captured from prospective daily diaries. Epistaxis severity score (ESS) was collected as a secondary outcome.

Results: Seven patients were included for analysis, with 98% completion of the daily diary. The average PRO-WED across all patients was 85.0 minutes, SD 93.2 at baseline, and 65.6 minutes, SD 59.5 during treatment/placebo. Coefficient of variance for PRO-WED at baseline and during treatment/placebo was 0.49, SD 0.1 and 0.58, SD 0.2, respectively. Statistically significant changes in the mean PRO-WED from baseline to treatment/placebo was noted in six patients (86%). Only two patients (29%) had a significant change in ESS, with both reporting decreased (improved) scores after treatment/placebo as compared to baseline.

Conclusions: PRO-WED was a feasible clinical trials measure, was reasonably stable during baseline measurement, and appeared to be variable with treatment state, suggesting it may provide a sensitive clinical trials PRO in HHT.

KEYWORDS

duration, epistaxis, HHT, outcome, severity

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Laryngoscope Investigative Otolaryngology* published by Wiley Periodicals LLC on behalf of The Triological Society.

1 | INTRODUCTION

More than 90% of adults with hereditary hemorrhagic telangiectasia (HHT) develop chronic epistaxis, resulting in significant morbidity including anemia. Increasing severity of nosebleeds is significantly correlated with worsening quality of life.¹⁻⁷ Currently, promising anti-angiogenic therapies are emerging for chronic bleeding in HHT, in which a small number of clinical trials have been undertaken, including topical bevacizumab in HHT-related bleeding. Two recent multicenter randomized controlled clinical trials (RCTs) of topical bevacizumab for epistaxis in HHT were negative, with authors identifying poorly characterized epistaxis outcomes measures as a contributor.^{8,9}

The epistaxis severity score (ESS) has been validated to assess bleeding severity in HHT, but is of limited utility in clinical trials.^{5,10,11} The ESS contains six questions of varying weight, and asks patients to report severity and frequency of epistaxis over the past 3 months. The questions relate to epistaxis symptoms, but also to outcomes, such as the need for blood transfusions. A normalized final score is then calculated, ranging from 1 to 10, with increasing score denoting more severe epistaxis.¹⁰ Though the ESS may appear to be useful for stratifying HHT patients for clinical trials, it is more limited as an outcome measure as patients, given its retrospective collection, that patients are asked to “average” their “typical symptoms” over the past 3 months, and the specified 3-month period of assessment. The retrospective nature may place greater emphasis on more recent events and it may also be challenging for patients to define “typical” symptoms, as some experience a variable range of bleeds on a daily basis.

Within the context of an ongoing RCT, patients were asked to report every episode of epistaxis, including intensity and duration, with the use of a daily diary. As an exploratory study of preliminary results from our RCT, we aimed to evaluate the measurement characteristics of the patient-reported outcome weekly epistaxis duration (PRO-WED) and its sensitivity to change by treatment period in HHT patients.

2 | METHODS

2.1 | Ethics

This study was approved by the St. Michael's Hospital research ethics board (#17-294).

2.2 | Study design

This was a descriptive report of epistaxis outcomes measures collected in an ongoing phase II, double-blind, placebo-controlled, cross-over, RCT of oral doxycycline for epistaxis, being conducted at the Toronto HHT Centre at St. Michael's Hospital, Toronto, Canada, with active patient recruitment (ClinicalTrials.gov Identifier: NCT03397004).

The RCT is expected to take place over a period of 24-month period for each patient, starting at different time points. This consists

of a run-in period of 3 months, treatment period of 6 months (doxycycline/placebo), washout period of 6 months, followed by the second treatment period of 6 months (doxycycline/placebo), and a final follow-up of 3 months. The order of investigational product is randomized, where approximately one-half start in the doxycycline arm, and one-half in the placebo arm. The research pharmacy staff allocates investigational product and provide medication according to a pre-determined, computerized block randomization scheme using randomly permuted block sizes. Only the research pharmacy staff are aware of the treatment allocation; participants, other study personnel, the treating physician, and other outcome assessors are masked. Monitoring occurs every 2 weeks by phone with clinic visit every 6 weeks; medical history and physical examination is performed at all clinic visits.

2.3 | Patient selection for the clinical trial

A total of 30 patients with a moderate-severe recurrent epistaxis are being recruited for the study. Inclusion criteria for the RCT are: age over 18 years, clinical or genetic diagnosis of HHT, epistaxis at least 15 minutes per week (mean for past month), at least one telangiectasia (skin or mucosal) available for micro-imaging, and ability to give written informed consent, including compliance with the requirements of the study. Exclusion criteria for the RCT are: allergy/intolerance to the doxycycline or related agents, unstable medical illness, acute infection, creatinine > upper limit of normal (ULN), liver transaminases (AST or ALT) > = 2x ULN, recent (within 2 months) use of doxycycline or other tetracycline agents, women who are pregnant or breastfeeding or plan to become pregnant during of the study, beta-HCG level >6 IU/L (retest if 6-24 IU/L), specific contra-indications for doxycycline, and/or on blood thinner and refuses to have family doctor notified of study participation.

2.4 | Patient selection for the current study

Only those patients currently enrolled in the RCT, who have completed the initial 3-month run-in period, and have received treatment of either doxycycline or placebo for a minimal of 6 months were included. Study investigators were blinded to what treatment patients have received, which was either with study drug doxycycline or placebo.

2.5 | Outcome measures

Patients were asked to complete a prospective daily diary, which captured the number of epistaxis per day, duration of each epistaxis, and its severity (gushing or non-gushing). Patients received regular follow-up calls (every 2 weeks) by the research coordinator, in order to encourage ongoing compliance. Completion rate was calculated as the total number of completed daily diary entries over the course of the

TABLE 1 Patient reported outcome WED (minutes) baseline vs treatment

Patient #	Baseline PRO-WED mean (SD)	Baseline PRO-WED range	Treatment/placebo PRO-WED mean (SD)	Treatment/placebo PRO-WED range	P-value
1 ^a	274.4 (150.0)	90-508	194.8 (97.1)	63-378	.031 ^a
2 ^a	34.3 (10.4)	22-51	62.5 (29.5)	10-113	.002 ^a
3 ^a	61.0 (33.7)	30-140	38.7 (23.0)	5-105	.013 ^a
4 ^a	28.7 (14.9)	10-57	40.5 (17.9)	4.3-71.5	.030 ^a
5 ^a	26.3 (14.0)	6.3-52	19.0 (10.5)	6-41	.045 ^a
6	28.4 (12.1)	0-50.5	33.9 (34.4)	0-134	.297
7 ^a	142.1 (87.4)	55-340	70.0 (36.4)	10-145	.003 ^a

Abbreviations: PRO, patient-reported outcome; WED, weekly epistaxis duration.

^aDenotes statistical significance between average WED baseline and treatment/placebo.

study period. The predefined primary outcome measure of interest was PRO-WED and also change in mean PRO-WED from baseline (PRO-WED averaged over 3-month course of run-in) as compared to active treatment/placebo (PRO-WED averaged over 6-month course of treatment/placebo). PRO-WED was calculated as the total minutes of all epistaxis episodes within a given week reported via the daily diary. The secondary outcome measure of interest, ESS, was completed by each patient during clinical visits every 6 weeks.

2.6 | Statistical analysis

Data were first imported into a spreadsheet designed specifically for the study. Descriptive statistics were used to display the data. Categorical variables were reported as frequencies and relative frequencies. Continuous variables were reported as mean and SD. Normality was evaluated, and comparisons of baseline and treatment WEDs means were performed using Student's *t* test for each patient. Mean differences were expressed with 95% confidence interval (CI). Moreover, PRO-WED was plotted against time for each patient at baseline and treatment. With this, the regression best-fit lines were calculated, and analysis of covariance was performed to elicit statistically significant differences in the slope and elevation of regression lines for each patient. Additionally, the coefficient of variance (CV) was calculated for PRO-WED. All statistical analyses were performed using Prism (V7, GraphPad, United States). Statistical significant was set to $P < .05$.

3 | RESULTS

There were seven patients included for analysis, with 29% (2/7) females. The average age was 67.0 years, SD 12.8. Mean duration of treatment/placebo was 160.0 days, SD 18.3. The completion rate of the daily epistaxis diary was 98% for the seven patients. Overall average PRO-WED across all patients (combined baseline and during treatment/placebo) was 75.3 minutes, SD 75.8.

The average PRO-WED for each patient during baseline (averaged over 3-month run-in) and during treatment/placebo (averaged over

6-month course) along with the range of PRO-WED are included as part of Table 1. The average PRO-WED across all patients at baseline was 85.0 minutes, SD 93.2, and 65.6 minutes, SD 59.5 during the treatment/placebo period. In evaluating the stability of PRO-WED, CV was evaluated between PRO-WED at baseline and during treatment/placebo, and was noted to be 0.49, SD 0.1 and 0.58, SD 0.2, respectively.

When comparing the average PRO-WED between baseline and treatment/placebo for each patient (Table 1), statistically significant changes were noted in six of the seven patients (86%). Of these, four (67%) patients had a significant decrease in minutes of average PRO-WED and two (29%) patients had significant increases—patients 2 and 4, with PRO-WED increases of 28 minutes (95% CI 10-46 minutes) and 12 minutes (95% CI 0.5-24), respectively.

PRO-WED over time for each patient can be found as part of Figure 1. Three patients (43%), patients 2, 3, and 7, had significant changes in the elevation/intercept of the regression line from baseline to treatment. Two patients (29%), patients 4 and 5, had significant changes in the slope of the regression line from baseline to treatment. Of the six patients who demonstrated a significant change of the average PRO-WED from baseline to treatment, five (83%) also demonstrated significant changes in either elevation or slope of the best-fit regression line.

The mean ESS for each patient at baseline and during treatment is displaced as Table 2. As seen, there were only two patients (29%), patients 4 and 6, who showed a significant change in their ESS after receiving treatment/placebo. In both of these cases, there were significant decreases noted. When we looked at these two patients' average PRO-WED, we noted there were discordances between changes in ESS and changes in average PRO-WED. For patient 4, who had a significant decrease in ESS, there was a statistically significant increase in the average PRO-WED. For patient 6, while ESS decreased significantly, the reported average PRO-WED did not change statistically.

4 | DISCUSSION

In this study, we characterized PRO-WED as a clinical trial outcomes measure for epistaxis in HHT. We demonstrated that prospective daily diary data collection was feasible with an excellent compliance

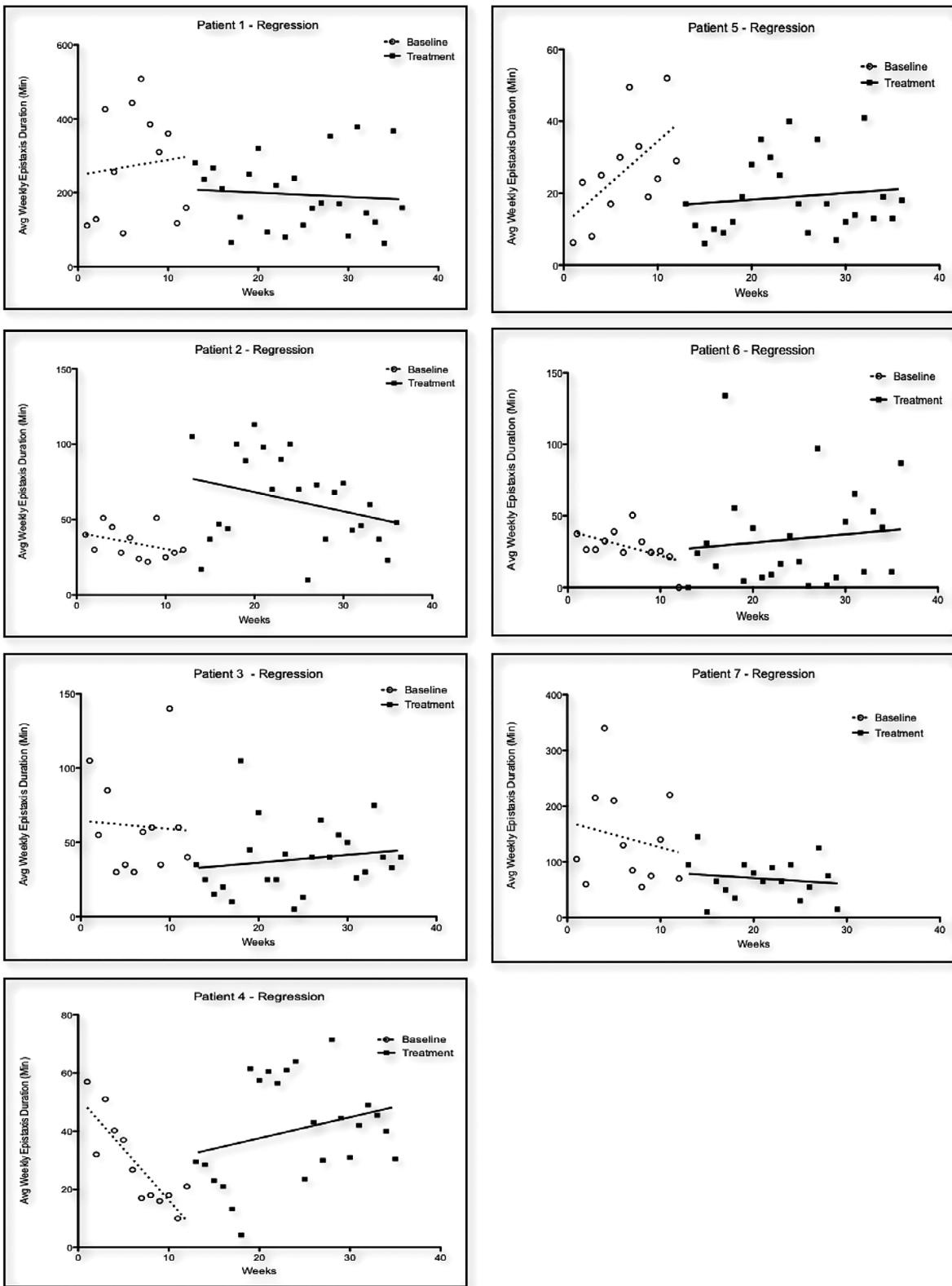


FIGURE 1 Weekly epistaxis duration over time per patient

rate of 98%. We also demonstrated that PRO-WED measurements had reasonable stability at baseline, and detected change in mean PRO-WED with treatment period, suggesting that this may be a sensitive clinical trials outcomes measure.

PRO-WED was derived from an epistaxis diary, which was completed on a daily basis as part of the ongoing RCT. It was a feasible measure to obtain, given the high degree of compliance from patients within the trial. From a stability perspective, CV was 0.49 for baseline

TABLE 2 ESS baseline vs treatment/placebo per patient

Patient #	Baseline ESS mean (SD)	Treatment ESS mean (SD)	Mean difference (95% confidence interval)	P-value
1	4.4 (0.1)	4.3 (0.9)	0.1 (−1.9 to 2.3)	.408
2	4.1 (0.4)	4.8 (0.7)	−0.7 (−2.3 to 1.0)	.164
3	4.8 (0.8)	3.8 (1.6)	1.0 (−2.4 to 4.4)	.229
4 ^a	5.0 (0.6)	3.5 (0.6)	1.5 (0.003-2.9)	.025 ^a
5	4.1 (0.6)	3.9 (0.5)	0.2 (−1.3 to 1.7)	.354
6 ^a	6.4 (0.1)	3.7 (0.8)	2.7 (0.3-5.0)	.019 ^a
7	7.3 (0.1)	7.4 (1.2)	−0.1 (−3.6 to 3.4)	.457

Abbreviation: ESS, epistaxis severity score.

^aDenotes statistical significance.

PRO-WED and 0.68 for treatment/placebo PRO-WED, which is reasonably low variance, and therefore suggests stability of the measure around the mean. Additionally, when we looked at the regression models, slopes of the best-fit models for baseline PRO-WED averaged across all patients was -0.7 , and nonsignificant from a nonzero slope. Both of these characteristics of the baseline PRO-WED measurement reflect its stability, low variability, and potential to be a good outcome measure for epistaxis within a trial setting.

There appeared to be higher rates of sensitivity to change between baseline and treatment/placebo periods with average PRO-WED (6/7 patients had statistically significant changes) as compared to mean ESS score (2/7 patients had statistically significant changes). Within a clinical trial setting, increased sensitivity of a reporting tool to detect change is valuable, as it can detect small changes in patients that may be clinically important.¹² Our findings seemed to indicate that averaged PRO-WED was more sensitive to change, as reflected in the increased number of statistically significant differences with treatment period, as compared to mean ESS. Likewise, other studies and RCTs implementing the use of daily diaries have noted high compliance rates, and improved quality of PRO.¹³⁻¹⁵ As a prospective PRO tool, measurements of PRO-WED collected from a daily diary is likely to be a more accurate reflection of the true epistaxis severity with decreased recall bias, and within a trial setting, more sensitive in detecting changes to epistaxis severity.

The ESS is a disease-specific tool designed for measuring epistaxis severity in HHT. This six-item PRO measure was developed and statistically validated using variables most correlated with epistaxis severity in this population.¹⁰ The ESS has been widely used for clinical assessment of epistaxis in HHT patients.^{11,16-18} However, the score is based on retrospective recall of symptoms over the last 3 months and is therefore inherently subject to recall bias, with more recent or significant episodes potentially influencing the answer. In addition, the questionnaire requires patients to answer based on “typical” symptoms over the last 3 months, which is often challenging for the patient to define, amongst a wide range of bleeding events. The PRO-WED is measured from a daily prospective diary, without asking patients to recall remote bleeds or define “typical” bleeds. With the PRO-WED, we noted more frequent significant differences between

baseline and treatment/placebo, suggesting that this tool is more sensitive to change. Additionally, reliability of the ESS was called into question as we noted two patients reporting ESS results which contradicted their daily diary results. This may be the result of additional questions on the ESS which asks about anemia status, and need for blood transfusions, which may not be directly associated with the degree of epistaxis severity/time, but also of other bleeding sources that HHT patients may encounter.

There were potential limitations to this study. First, as this study was an assessment of preliminary results from an ongoing RCT with active recruitment, and we were limited by the sample size of available participants who have enrolled, completed the 3-month run-in and the initial 6-month period of treatment/placebo. Despite this, we were able to detect significant changes in PRO-WED, and that as a measure, PRO-WED was more sensitive to change within a clinical trial setting. Further validation, with a large sample size, will be helpful. Moreover, as we did not unblind study investigators to the treatment allocation at this time, we have not analyzed PRO-WED results based on the treatment received, and we make draw no conclusions about efficacy of doxycycline. Additionally, although PRO-WED may be indicative of severity, it may not provide a comprehensive picture, in that patients with frequent shorter bleeds and less frequent longer bleeds would have similar PRO-WED, but may be differently affected. Correlating PRO-WED with quality of life measurement tools in the future may be beneficial.

5 | CONCLUSION

We demonstrated that PRO-WED is a feasible clinical trials measure, and was reasonably stable during baseline measurement. PRO-WED appeared to be variable with treatment state, suggesting it may provide a sensitive clinical trials outcome measure in HHT.

ACKNOWLEDGMENTS

This study was supported by U.S. Department of Defense grant (W81XWH-17-1-0429). Dr M. E. F. was also supported by the Nelson Arthur Hyland Foundation and the Li Ka Shing Knowledge Institute.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Vincent Wu  <https://orcid.org/0000-0003-3227-6442>

REFERENCES

1. Plauchu H, de Chadarevian JP, Bideau A, Robert JM. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. *Am J Med Genet.* 1989;32(3):291-297.
2. Porteous ME, Burn J, Proctor SJ. Hereditary haemorrhagic telangiectasia: a clinical analysis. *J Med Genet.* 1992;29(8):527-530.
3. Aassar OS, Friedman CM, White RI Jr. The natural history of epistaxis in hereditary hemorrhagic telangiectasia. *Laryngoscope.* 1991;101(9):977-980.
4. Zarrabeitia R, Fariñas-Álvarez C, Santibáñez M, et al. Quality of life in patients with hereditary haemorrhagic telangiectasia (HHT). *Health Qual Life Outcomes.* 2017;15(1):19.
5. Merlo CA, Yin LX, Hoag JB, Mitchell SE, Reh DD. The effects of epistaxis on health-related quality of life in patients with hereditary hemorrhagic telangiectasia. *Int Forum Allergy Rhinol.* 2014;4(11):921-925.
6. Brinjilji W, Wood CP, Lanzino G, et al. High rates of bleeding complications among hospitalized patients with hereditary hemorrhagic telangiectasia in the United States. *Ann Am Thorac Soc.* 2016;13(9):1505-1511.
7. Kasthuri RS, Montifar M, Nelson J, et al. Prevalence and predictors of anemia in hereditary hemorrhagic telangiectasia. *Am J Hematol.* 2017;1:1-6.
8. Whitehead KJ, Sautter NB, McWilliams JP, et al. Effect of topical intranasal therapy on epistaxis frequency in patients with hereditary hemorrhagic telangiectasia: a randomized clinical trial. *JAMA.* 2016;316(9):943-951.
9. Dupuis-Girod S, Ambrun A, Decullier E, et al. Effect of bevacizumab nasal spray on epistaxis duration in hereditary hemorrhagic telangiectasia: a randomized clinical trial. *JAMA.* 2016;316(9):934-942.
10. Hoag JB, Terry P, Mitchell S, Reh D, Merlo CA. An epistaxis severity score for hereditary hemorrhagic telangiectasia. *Laryngoscope.* 2010;120(4):838-843.
11. Yin LX, Reh DD, Hoag JB, et al. The minimal important difference of the epistaxis severity score in hereditary hemorrhagic telangiectasia. *Laryngoscope.* 2016;126(5):1029-1032.
12. Mirza S, Salisbury C, Hopper C, Foster N, Montgomery A. Comparing sensitivity to change of two patient-reported outcome measures in a randomised trial of patients referred for physiotherapy services. *Trials.* 2013;14(S1):O50.
13. Follick MJ, Ahern DK, Laser-Wolston N. Evaluation of a daily activity diary for chronic pain patients. *Pain.* 1984;19(4):373-382.
14. Fraser SC, Ramirez AJ, Ebbs SR, et al. A daily diary for quality of life measurement in advanced breast cancer trials. *Br J Cancer.* 1993;67(2):341-346.
15. Bingham CO, Gaich CL, DeLozier AM, et al. Use of daily electronic patient-reported outcome (PRO) diaries in randomized controlled trials for rheumatoid arthritis: rationale and implementation. *Trials.* 2019;20(1):182.
16. Chin CJ, Rotenberg BW, Witterick IJ. Epistaxis in hereditary hemorrhagic telangiectasia: an evidence based review of surgical management. *J Otolaryngol Head Neck Surg.* 2016;45(1):3.
17. Begbie ME, Wallace GM, Shovlin CL. Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): a view from the 21st century. *Postgrad Med J.* 2003;79(927):18-24.
18. Lee JM, Wu V, Faughnan ME, Lasso A, Figol A, Kilty SJ. Prospective pilot study of Floseal[®] for the treatment of anterior epistaxis in patients with hereditary hemorrhagic telangiectasia (HHT). *J Otolaryngol Head Neck Surg.* 2019;48(1):48.

How to cite this article: Wu V, Lee JM, Vozoris NT, Faughnan ME. Weekly epistaxis duration as an indicator of epistaxis severity in hereditary hemorrhagic telangiectasia—Preliminary results from a randomized controlled trial. *Laryngoscope Investigative Otolaryngology.* 2021;6:370-375. <https://doi.org/10.1002/lio2.561>