

BMJ Open Identifying Children with HEreditary Coagulation disorders (iCHEC): a protocol for a prospective cohort study

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ABSTRACT

Introduction It is challenging to obtain a reliable bleeding history in children who are referred for a suspected inherited bleeding disorder. Bleeding symptoms may be subtle as children face fewer haemostatic challenges compared with adults. In order to standardise bleeding histories, questionnaires have been developed, called bleeding assessment tools (BATs). Although it has been shown that high bleeding scores are associated with the presence of a mucocutaneous bleeding disorder, these BATs lack sensitivity, efficiency and flexibility in the paediatric setting. We developed a new BAT (the iCHEC (identifying Children with HEreditary Coagulation disorders) BAT) to improve on these characteristics. We aim to evaluate the diagnostic accuracy of the iCHEC BAT as a screening tool for children who are suspected for having a bleeding disorder.

Methods and analysis This is a prospective cohort study. Children (age 0–18 years) suspected for a bleeding disorder who present at tertiary haematology clinics, and/or their parents/guardians, will be asked to complete the iCHEC BAT. Sensitivity was increased by inclusion of paediatric-specific bleeding symptoms and novel qualitative questions per bleeding symptom. Efficiency was improved by developing a self-administered (online) version of the questionnaire. Flexibility for changes in the bleeding phenotype of developing children was improved by including questions that define when the bleeding symptoms occurred in the past. The diagnostic accuracy of the specific bleeding items will be evaluated by receiver operator characteristic curves, using classification based on the results from laboratory assessment as the reference standard. Analysis of the discriminative power of individual bleeding symptoms will be assessed.

Ethics and dissemination The study has been approved by the medical ethics committees of all participating centres in the Netherlands, Canada and the UK. All paediatric subjects and/or their parents/guardians will provide written informed consent. Study results will be submitted for publication in peer-reviewed journals.

INTRODUCTION

The diagnosis of an inherited bleeding disorder is based on the results derived from a patient's bleeding history from birth, a family history and laboratory test results.

Strengths and limitations of this study

- A self-administered (online) version of the iCHEC BAT (identifying Children with HEreditary Coagulation disorders bleeding assessment tool) is available; patients and/or their parents/guardians can fill in the questionnaire prior to their visit to the doctor, which makes the assessment of the bleeding history more efficient.
- The iCHEC BAT is designed to pick up subtle cues in the bleeding history of a child, thereby improving the measurement properties of BATs for use in children.
- The results of this study are not generalisable to primary and secondary care due to a different spectrum of prevalence of inherited bleeding disorders compared with tertiary haematology centres; additional studies will be required to determine the diagnostic performance of the iCHEC BAT in these settings.

Patients with mild bleeding disorders usually exhibit mild to moderate bleeding tendencies and are therefore difficult to distinguish from normal subjects. Especially in children it is difficult for the doctor to obtain a reliable bleeding history, as bleeding symptoms can be subtle, children face fewer haemostatic challenges compared with adults and, for example, bruises in toddlers may be caused by normal activity. Also, some of the classic bleeding symptoms which are often present in adults with a bleeding disorder, such as menorrhagia and postsurgical bleeding, are usually not yet present in young children. Nevertheless, these children may have other bleeding symptoms that are caused by a bleeding disorder and require treatment. In order to standardise bleeding histories, bleeding assessment tools (BATs)¹ have been developed. Typically, a BAT consists of questions about various bleeding symptoms, such as epistaxis, bleeding from minor wounds and bleeding after surgical procedures. After completion of the questionnaire, a



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Table 1 Bleeding symptoms recorded in the PBQ² and ISTH-BAT³

Item number	PBQ	Item number	ISTH-BAT
1	Epistaxis	1	Epistaxis
2	Cutaneous symptoms	2	Cutaneous bleeding
3	Bleeding from minor wounds	3	Bleeding from minor wounds
4	Oral cavity bleeding	4	Oral cavity bleeding
5	Tooth extraction	5	Bleeding after tooth/teeth extraction
6	Gastrointestinal bleeding	6	Gastrointestinal bleeding
7	Surgery	7	Bleeding after surgery or major trauma
8	Menorrhagia	8	Menorrhagia
9	Postpartum haemorrhage	9	Postpartum haemorrhage
10	Muscle haematomas	10	Muscle haematomas (spontaneous)
11	Haemarthrosis	11	Haemarthrosis
12	CNS bleeding	12	CNS bleeding (spontaneous)
	–	13	Haematuria
13	Other bleeding ▶ Umbilical stump bleeding. ▶ Cephalohaematoma. ▶ Bleeding at circumcision. ▶ Venipuncture bleeding. ▶ Suction bleeding. ▶ Haematuria, macroscopic.	14	Other bleeding ▶ Excessive umbilical stump bleeding. ▶ Cephalohaematoma. ▶ Bleeding at circumcision. ▶ Venipuncture bleeding. ▶ Suction bleeding. ▶ Ovulation bleeding (woman).

CNS, central nervous system; ISTH-BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; PBQ, Pediatric Bleeding Questionnaire.

summative bleeding score can be calculated. In 2009, the Pediatric Bleeding Questionnaire (PBQ) was developed and validated for the screening of a child for von Willebrand disease (vWD).² Then, in 2010, the International Society on Thrombosis and Haemostasis/Scientific and Standardisation Committee (ISTH/SSC) developed the ISTH-BAT,³ which is recommended for use in haematology clinics. Both the PBQ and the ISTH-BAT contain categories with questions for various bleeding symptoms, 12 and 13 different bleeding symptoms, respectively, and one category that includes paediatric-specific bleeding symptoms (table 1).

It has been shown that high bleeding scores are associated with the presence of an inherited bleeding disorder.⁴ However, none of the existing questionnaires/scores were designed with the evaluation of paediatric symptoms being the primary aim. The PBQ and ISTH-BAT are not sensitive enough to pick up subtle cues in the bleeding history of a child because not all the information that is collected about the bleeding is used for calculating the bleeding score and this may lead to underestimation of bleeding symptoms. Also, the PBQ and ISTH-BAT are inflexible with respect to changes in the bleeding phenotype of rapidly developing children. Finally, a self-administered BAT would help to optimise the efficiency of bleeding history assessment. Thus, optimisation of this screening tool is necessary.

Therefore, we have developed a novel BAT: the iCHEC (identifying Children with HEreditary Coagulation

disorders) BAT. For construction of the iCHEC BAT, the PBQ and ISTH-BAT were used as templates. From a thorough literature review and consultation with experts, we have identified additional paediatric-specific bleeding symptoms and qualitative questions per bleeding symptom. These items and questions were added to the iCHEC BAT to increase its sensitivity for detection of subtle cues in the bleeding history. The PBQ and ISTH-BAT calculate a bleeding score based on information about the medical treatment of the most severe bleeding episode for specific bleeding symptoms. With the use of such a scoring system, the majority of information about the bleeding symptoms is not used for calculating the bleeding score and, with that, this potentially valuable information is not used for diagnostic purposes. In contrast to the scoring systems of the PBQ and ISTH-BAT, the iCHEC BAT scoring system will use all the information that has been collected from the completed questionnaire for calculating a bleeding score. For example, the iCHEC BAT includes and scores more detailed information about epistaxis, whereas the PBQ and ISTH-BAT only score information about the presence (no/trivial) and the treatment of the most severe epistaxis episode for calculating the bleeding score. We hypothesise that including more detailed information about a bleeding symptom may contribute to a better measurement of the bleeding tendency of a child. The sensitivity, specificity, positive predictive value and negative predictive value of the PBQ for diagnosing vWD are 83%, 79%, 0.14 and 0.99, respectively. Although the

95% CIs for specificity are reasonable (72% to 86%), they are quite wide for sensitivity (42% to 124%) because of the small number of true positives.² Thus, we believe that there is room for improvement in the measurement properties of BATs for use in children. We have improved the flexibility of the iCHEC BAT by addressing time-dependent occurrence of bleeding symptoms, which makes it sensitive to changes in the bleeding phenotype of a child. To improve efficiency, we have developed a self-administered version of the iCHEC BAT, using careful wording and lay terms that are easy to understand.⁵ The iCHEC BAT was first designed in English language and has been translated forward into Dutch and backward to English to uncover mistakes in the Dutch translation. No major differences occurred between the original version and the backward translated version. From the age of 12 years, children are allowed to fill in the questionnaire by themselves or with the help of their parents/guardians. Who completed the iCHEC BAT will be recorded. Eventually, we will compare the diagnostic performance of the iCHEC BAT with the PBQ and ISTH-BAT, which is possible because the iCHEC questionnaire includes the essential questions that are required for calculating the PBQ and ISTH-BAT bleeding scores.

The main goal of this study is to evaluate the diagnostic accuracy of the iCHEC BAT, using results from laboratory screening tests as reference (gold standard).

METHODS

Study design

This is a prospective cohort study. The cohort will include 200 children who are suspected for having an inherited bleeding disorder at tertiary haematology clinics in the Netherlands, Canada and the UK. Data collection will continue until the required number of 200 patient inclusions has been reached and is expected to take approximately 1 year.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet the following criteria:

- ▶ Aged 0–18 years.
- ▶ Patients presenting with (1) the history, signs and symptoms of bleeding, and/or (2) referred for evaluation of abnormal laboratory results (of blood coagulation parameters), and/or (3) a positive family history of an inherited bleeding disorder.

Exclusion criteria

A subject who meets any of the following criteria will be excluded from participation in this study:

- ▶ Patients with a previous diagnosis of an inherited bleeding disorder.
- ▶ Patients with a known, acquired cause of bleeding, for example renal or liver disease, or use of medication that is known to cause an increased bleeding tendency.

- ▶ Patients and/or caregivers who are not capable to fill in the questionnaire, for example due to illiteracy.

Sample size calculation

The prevalence of an inherited bleeding disorder in children presenting with bleeding symptoms at a tertiary clinic is approximately 20%–25%.^{6–8} Assuming a sensitivity of 90% and specificity of 70%, a sample size of 200 children, of whom about 45 will be affected, will yield 95% CIs of 76% to 96% and 64% to 78% for sensitivity and specificity, respectively, which we consider sufficiently narrow.

Recruitment and consent

Recruitment and consent procedures of patients at participating centres in the Netherlands will be as follows: after referral and scheduling the appointment for evaluation of bleeding symptoms at the participating tertiary haematology clinic, subjects will be informed by email or by letter about this study. The secured link to the online version of the iCHEC BAT will be sent by email to the study participants. Patients and/or caregivers will fill in the questionnaire prior to the doctor's appointment. Informed consent will be signed by one of the investigators or the treating physician when the patient visits the hospital with both parents/guardians of the patient, and the patient when 12 years or older.

Recruitment and consent procedures of patients at participating centres outside the Netherlands will proceed according to local standard procedures.

OUTCOMES

The main study outcome is the diagnostic accuracy of the iCHEC BAT, as reflected by the area under the curve (AUC) of a receiver operating characteristics (ROC) curve using results from the laboratory assessment as the reference standard. The secondary outcomes are the influence of age, sex and type of bleeding disorder on the total cumulative bleeding score and the score of individual bleeding items.

Data collection

Patient characteristics

The following patient data will be collected: month and year of birth to calculate age; body weight and height to calculate body mass index; family history; medical history; and use of medication.

iCHEC BAT

An online version of the iCHEC BAT is available for patients included in the Netherlands. Patients and/or their parents/guardians fill in the questionnaire on a computer before they visit the doctor in the hospital. For patients included outside the Netherlands, a paper version of the questionnaire is available. These patients and/or parents/guardians fill in the questionnaire in the waiting room before they visit the doctor. The questions that are necessary to calculate the PBQ

and ISTH-BAT bleeding scores are incorporated in the iCHEC BAT. Bleeding scores will be calculated, including the total summative bleeding score, scores per bleeding item and scores of individual questions per bleeding item.

Diagnostic work-up

Participants will undergo a uniform diagnostic laboratory work-up for haemorrhagic disorders, which is similar to the standard work-up that is performed as part of routine care. Parameters include the following:

- ▶ ABO blood group.
- ▶ Complete blood count, including mean platelet volume.
- ▶ Activated partial thromboplastin time.
- ▶ Prothrombin time.
- ▶ Fibrinogen.
- ▶ Thrombin time.
- ▶ Platelet function analyser-100–200.
- ▶ Factor VIII activity (FVIII:C), FIX:C, von Willebrand factor antigen level (vWF:Ag) and von Willebrand factor activity.
- ▶ FVII:C, FXI:C, FXIII:C.
- ▶ Platelet aggregation tests (when indicated).

Additional laboratory tests

In participating centres in the Netherlands, we will collect extra blood for additional platelet tests in a subgroup of patients. This subgroup includes subjects with a high iCHEC bleeding score, who were not diagnosed with a bleeding disorder on the basis of routine diagnostic laboratory tests. In particular, we will perform additional screening tests for platelet function disorders (PFDs), because, to date, it is still very difficult to diagnose inherited PFDs in children, for example, due to large amounts of blood required for analyses. The following tests will be performed for this specific subgroup of children only:

- ▶ Proteomic screen by mass spectrometry for PFDs.
- ▶ Flow cytometry approaches to assess expression levels of critical platelet receptors such as glycoprotein (GP) Ib, GPV, GPIX and GPIIb-IIIa (integrin $\alpha_{IIb}\beta_3$).
- ▶ Electron microscopy.
- ▶ DNA isolation for genetic screening of rare PFDs.

Blood sample collection

Blood samples will be collected and analysed at the central laboratory of the participating centre. The amount of blood taken will essentially be the same as usual for the diagnostic work-up in the haematology clinics.

Results from the laboratory tests will be used as the reference standard. Based on these results, patients will be classified according to the presence or absence of an inherited bleeding disorder such as vWD, haemophilia or a PFD. The 'in-house' laboratory norm will be used to define the normal ranges of laboratory parameters. The diagram in [figure 1](#) provides an overview of the standard diagnostic and study-specific procedures for eligible patients.

Disease definitions

von Willebrand disease^{9 10 11}

- ▶ Type 1: partial quantitative deficiency of vWF; vWF:Ag at least once and/or vWF: Ristocetin (RCo) at least twice <50 IU/dL, vWF:RCo/vWF:Ag >0.6 and normal vWF multimer pattern (in the absence of blood type O).
- ▶ Type 2: qualitative vWF defects, subclassified in:
 - Type 2A: decreased vWF-dependent platelet adhesion and a selective deficiency of high-molecular-weight VWF multimers; vWF:Ag and/or vWF:RCo <50 IU/dL on at least two occasions, vWF:RCo/vWF:Ag ≤0.6 and loss of high-molecular-weight multimers.
 - Type 2B: increased affinity for platelet GPIIb; defined similarly to type 2A with the additional requirement of a hyperactive ristocetin-induced platelet agglutination and/or positive genetic testing.
 - Type 2M: decreased vWF-dependent platelet adhesion without a selective deficiency of high-molecular-weight vWF multimers; vWF:Ag and/or vWF:RCo <50 IU/dL on at least two occasions, vWF:RCo/vWF:Ag ≤0.6 and normal vWF multimers.
 - Type 2N: markedly decreased binding affinity for FVIII; ratio of FVIII:C to vWF:Ag ≤0.6.
- ▶ Type 3: virtually complete deficiency of vWF; vWF:Ag and/or vWF:RCo <5 IU/dL.

Platelet function disorders

PFDs can be classified into inherited and acquired disorders. Inherited disorders can be further classified into adhesion, activation, secretion and aggregation defects. Acquired disorders can be caused by a variety of factors including certain drugs, uraemia and liver disease. A PFD will be diagnosed according to the criteria defined by the Rare Inherited Bleeding Disorders Committee of the Association of Haemophilia Centre Directors of Canada (<https://www.ahcdc.ca/rare-inheritedbleeding-disorders>).

Classification of factor levels for coagulation factor disorders (tested at least twice):

1. Haemophilia A: FVIII:C <40 IU/mL.
2. Haemophilia B: FIX:C <40 IU/mL.
3. FVII deficiency: FVII <30 IU/mL.
4. FXI deficiency: FXI <60 IU/mL.
5. FXIII deficiency: FXIII <30 IU/mL.
6. Fibrinogen deficiency: fibrinogen <1.5 mg/mL.

Statistical analysis

The primary aim of the study is to evaluate the diagnostic accuracy of the iCHEC BAT. In addition, the influence of age, sex and type of bleeding disorder on the total bleeding score and the score of individual bleeding items will be analysed.

We will analyse differences between affected (children diagnosed with an inherited bleeding disorder) and unaffected children (not diagnosed with an inherited bleeding

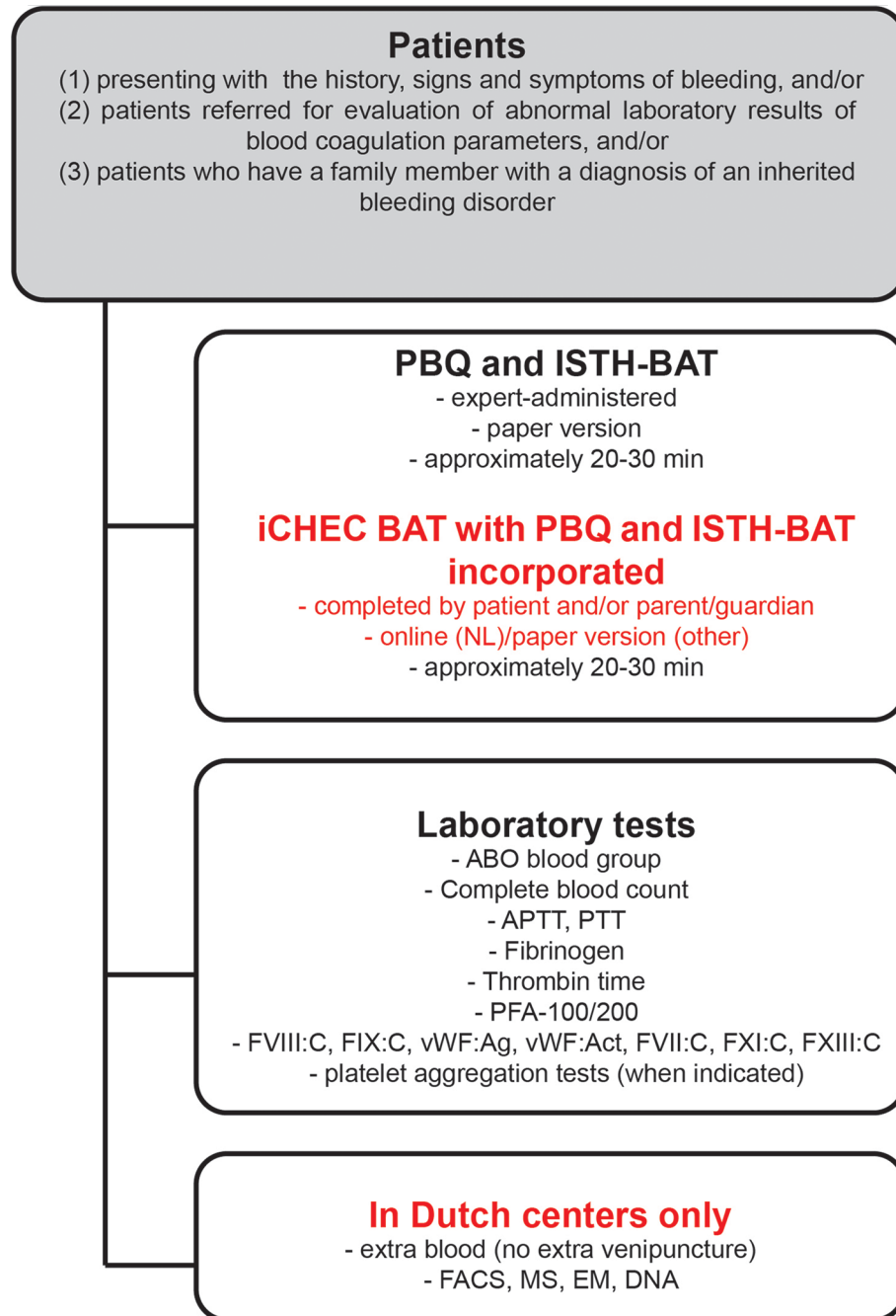


Figure 1 Overview of the standard diagnostic (in black) and study-specific procedures (in red). Ac, activity; Ag, antigen; APTT, activated partial thromboplastin time; EM, electron microscopy; FACS, fluorescence-activated cell sorting; FVII, factor VII; FVIII, factor VIII; FIX, factor IX; FXI, factor XI; FXIII, factor XIII; iCHEC, identifying Children with HEreditary Coagulation disorders; ISTH-BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; MS, mass spectrometry; NL, the Netherlands; PBQ, Pediatric Bleeding Questionnaire; PFA, platelet function analyser; PTT, partial thromboplastin time; vWF, von Willebrand factor.

disorder). Patients are classified as affected or unaffected based on the results of the diagnostic laboratory work-up, as described above. Affected and unaffected children will be compared with respect to the following:

- ▶ Total cumulative bleeding score.
- ▶ Scores for each individual bleeding item of the iCHEC BAT to determine which individual bleeding items are useful in distinguishing affected from unaffected children.
- ▶ Scores on individual questions per bleeding item to determine which questions addressing specific characteristics of an individual bleeding item are useful in distinguishing affected from unaffected children.

Differences between the two groups of affected and unaffected children will be analysed statistically by the Mann-Whitney U test for continuous variables or χ^2 test for categorical variables. Diagnostic performance of the iCHEC BAT bleeding score will be analysed by calculating

the AUC of the ROC curves. The AUC of the iCHEC BAT will be compared with the AUC of the PBQ and the ISTH-BAT. To address the association of bleeding score with age, sex and type of bleeding disorder, we will analyse these determinants in a multivariate model. If significant associations are present, we will determine the cut-off value to diagnose an inherited bleeding disorder in the relevant patient subgroups. Furthermore, we will compare the bleeding scores between patients who used the online tool versus patients who filled in the paper version of the iCHEC BAT to analyse the effect of administration route of the questionnaire.

Ethical considerations

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. All participants provide written informed consent.

Safety reporting

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product/trial procedure/the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

The iCHEC study consists of a questionnaire and a blood draw. In current practice, patients and/or caregivers also fill in a bleeding questionnaire (ISTH-BAT or PBQ) for diagnostic purposes. The iCHEC BAT contains questions that are of similar intention and will therefore not be more burdening to the patient. A blood draw is also part of the current diagnostic work-up for haemorrhagic disorders. Thus, this study will not change the standard diagnostic procedures. We do not expect that drawing an extra amount of (maximum 5 mL) blood in a selected group of patients in Dutch centres will lead to an increased risk for the patient.

Study status

The first patient was enrolled on 28 March 2017. Data collection is expected to take approximately 1 year. Results will be presented at scientific meetings and published in peer-reviewed journals. All publications and presentations related to the study will be authorised and reviewed by the study investigators.

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Contributors ES conceived the work and designed the study protocol, initially drafted, revised and accepted the version to be published, is involved in data acquisition, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MLR conceived the work and designed the study protocol, initially drafted, revised and accepted the version to be published, is involved in and supervises data acquisition, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MHC, TTB, PDJ, MHS, MP, BP, ABM and VSB substantially contributed to the conception and design of the protocol, is involved in data acquisition, critically revised the protocol for important intellectual content, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JHvdL substantially contributed to the conception and design of the protocol, critically revised the protocol for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KF conceived the work and designed the study protocol, initially drafted, revised and accepted the version to be published, supervises data acquisition, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent Not required.

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REFERENCES

1. Rydz N, James PD. The evolution and value of bleeding assessment tools. *J Thromb Haemost* 2012;10:2223–9.
2. Bowman M, Riddel J, Rand ML, *et al.* Evaluation of the diagnostic utility for von Willebrand disease of a pediatric bleeding questionnaire. *J Thromb Haemost* 2009;7:1418–21.
3. Rodeghiero F, Tosetto A, Abshire T, *et al.* ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost* 2010;8:2063–5.
4. Bidlingmaier C, Grote V, Budde U, *et al.* Prospective evaluation of a pediatric bleeding questionnaire and the ISTH bleeding assessment tool in children and parents in routine clinical practice. *J Thromb Haemost* 2012;10:1335–41.
5. Casey LJ, Tuttle A, Grabell J, *et al.* Generation and optimization of the self-administered pediatric bleeding questionnaire and its validation as a screening tool for von Willebrand disease. *Pediatr Blood Cancer* 2017;64:1–7.

6. Boelaars MF, Peters M, Fijnvandraat K. Evaluation of a self-administrated pediatric bleeding questionnaire measuring bleeding severity in children. *Thromb Haemost* 2012;108:1006–7.
7. Biss TT, Blanchette VS, Clark DS, *et al*. Quantitation of bleeding symptoms in children with von Willebrand disease: use of a standardized pediatric bleeding questionnaire. *J Thromb Haemost* 2010;8:950–6.
8. Biss TT, Blanchette VS, Clark DS, *et al*. Use of a quantitative pediatric bleeding questionnaire to assess mucocutaneous bleeding symptoms in children with a platelet function disorder. *J Thromb Haemost* 2010;8:1416–9.
9. Sadler JE, Budde U, Eikenboom JC, *et al*. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. *J Thromb Haemost* 2006;4:2103–14.
10. Ng C, Motto DG, Di Paola J. Diagnostic approach to von Willebrand disease. *Blood* 2015;125:2029–37.
11. Leebeek FW, Eikenboom JC. Von Willebrand's Disease. *N Engl J Med* 2016;375:2067–80.