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# Is pharmacokinetic-guided dosing of desmopressin and von Willebrand factor-containing concentrates in individuals with von Willebrand disease or low von Willebrand factor reliable and feasible? A protocol for a multicentre, non-randomised, open label cohort trial, the OPTI-CLOT: to WiN study

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## ABSTRACT

**Introduction** Von Willebrand disease (VWD) is a bleeding disorder, caused by a deficiency or defect of von Willebrand factor (VWF). In case of medical procedures or bleeding, patients are treated with desmopressin and/or VWF-containing concentrates to increase plasma VWF and factor VIII (FVIII). However, in many cases these factor levels are outside the targeted range. Therefore, population pharmacokinetic (PK) models have been developed, which aim to quantify and explain intraindividual and interindividual differences in treatment response. These models enable calculation of individual PK parameters by Bayesian analysis, based on an individual desmopressin test or PK profile with a VWF-containing concentrate. Subsequently, the dose necessary for an individual to achieve coagulation factor target levels can be calculated.

**Methods and analysis** Primary aim of this study is to assess the predictive performance (the difference between predicted and measured von VWF activity and FVIII levels) of Bayesian forecasting using the developed population PK models in four different situations: (A) desmopressin testing (n≥30); (B) medical procedures (n=70; 30 receiving desmopressin, 30 receiving VWF-containing concentrate and 10 receiving a combination of both); (C) bleeding episodes (n=20; 10 receiving desmopressin and 10 receiving VWF-containing concentrate) and (D) prophylaxis with a VWF-containing concentrate (n=3 to 5). Individuals with all types of VWD and individuals with low VWF (VWF 0.30–0.60 IU/mL) will be included. Reliability and feasibility of PK-guided dosing will be tested by assessing predictive performance, treatment duration, haemostasis, patient satisfaction and physician satisfaction.

### Strengths and limitations of this study

► We will include individuals with von Willebrand disease (VWD) and low von Willebrand factor (VWF) from different haemophilia treatment centres in the Netherlands.
► This is the first study to assess reliability and predictive performance of population pharmacokinetic models for desmopressin and VWF-containing concentrates in clinical practice.
► This study will not intervene in treatment choice (desmopressin and/or VWF-containing concentrate) or brand of medication, to approach the real-life situation as much as possible.
► The developed population pharmacokinetic models will be tested in different situations: during desmopressin testing, during treatment for medical procedures or bleeding and during prophylactic treatment.
► Due to the relatively small patient numbers in each of the different situations, randomisation of treatment is not possible.

**Ethics and dissemination** The OPTI-CLOT:to WiN study was approved by the medical ethics committee of the Erasmus MC, University Medical Centre Rotterdam, the Netherlands. Results of the study will be communicated through publication in international scientific journals and presentation at (inter)national conferences.

**Trial registration number** NL7212 (NTR7411); Pre-results, EudraCT 2018-001631-46.

## INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder.[1] It is caused by low or absent von Willebrand factor (VWF), or by a functional defect of VWF. VWF is essential for primary haemostasis as it facilitates platelet plug formation at sites of vascular injury. It also plays a role in secondary haemostasis, as it protects factor VIII (FVIII) from being cleared from the circulation. Symptoms of VWD include bleeding after trauma or surgery and (spontaneous) mucocutaneous bleeding. VWD is classified into three main types: type 1 and type 3 are respectively; a partial (VWF <0.30 IU/mL) and a complete (VWF <0.05 IU/mL) absence of VWF, whereas type 2 comprises several functional defects of VWF.[2] In type 2A, binding of VWF to platelets is decreased, while in type 2B, affinity of VWF for platelets is increased. In both types 2A and 2B, there is an absence of high molecular weight VWF multimers (HMWM). In type 2M, platelet binding is decreased, but this is not caused by the absence of HMWM. In type 2N, often VWF levels are normal, however affinity of VWF for FVIII is decreased, leading to decreased FVIII levels. Individuals with low VWF have a bleeding tendency associated with VWF levels between 0.30 and 0.60 IU/mL.[3]

Individuals with VWD are treated with desmopressin or—in more severe cases or when prophylactic therapy is needed—VWF-containing concentrates. The main reasons for treatment are acute bleeding and prevention of bleeding during medical procedures (eg, dental procedures, surgery or in-hospital childbirth). Prophylactic treatment to prevent spontaneous bleeding is seldom necessary and mainly applied in type 3 and severely affected type 1 and 2 patients. The aim of treatment is to accomplish sufficient haemostasis by achieving physiologically normal plasma coagulation factor levels. However, it has been previously reported in a study on perioperative treatment of VWD patients with Haemate P, that a majority of patients (65% in type 1, 53% in type 2% and 57% in type 3 VWD) achieve higher VWF activity (VWF:Act, or VWF function) levels than aimed for, and a minority (16% in type 1, 38% in type 2% and 29% in type 3 VWD, respectively) does not reach sufficient levels for adequate haemostasis.[4] This may lead to an increased risk of either thrombosis or bleeding. Moreover, costs of treatment are high as VWF-containing factor concentrates are expensive and frequent laboratory monitoring of plasma VWF and FVIII is required. As rising healthcare costs are an increasing concern, it is important to investigate alternative dosing strategies that facilitate more precise dosing, to improve quality of care with potential reduction of costs.

Currently, desmopressin dosage and dosing frequency are solely based on body weight and estimated degree of tachyphylaxis. Dosing of VWF-containing concentrates is also based on body weight, and dose calculations are made according to target VWF and FVIII values based on the severity of the bleed or the type of medical procedure.[5] However, pharmacokinetics (PK) of desmopressin and VWF-containing concentrates differ within and between patients (ie, intraindividual and interindividual differences), and large interindividual differences in response to desmopressin are observed.[6–8] Population PK models that describe plasma VWF:Act and FVIII after administration of desmopressin or VWF-containing concentrates have been constructed by our group (however not all models have been published yet).[9 10] These models are based on retrospective DDAVP-testing data and VWF-containing concentrate treatment data from multiple haemophilia treatment centres in the Netherlands and in the UK. In a population PK model, the typical PK parameters and their corresponding variability are estimated. Subsequently, covariate relationships (eg, patient characteristics and procedure characteristics) can be used to (partially) explain the estimated variability.[11]

With these population PK models, we are able to perform Bayesian forecasting: all information and sources of uncertainty are combined into a predictive distribution for the future values, after which point forecasts (the predicted future values) and interval forecasts (the uncertainty level surrounding these predicted future values) can be obtained.[12] In our models, individual VWF:Act and FVIII PK parameters are calculated. These PK-parameters are based on patient characteristics, combined with VWF:Act and FVIII measurements obtained after an individual test dose of desmopressin or VWF-containing concentrate, or measurements obtained during a bleeding episode or medical procedure. Based on the estimated individual PK parameters, we are able to design a personalised dosing strategy for each patient. We hypothesise that PK-guided dosing of desmopressin and VWF-containing concentrates may improve safety and efficacy of therapy, and lower treatment costs. It is essential to first evaluate the predictive performance of PK-guided dosing and the feasibility of this approach prospectively, in order to prove its effectiveness and safety.

### Objective

To prospectively investigate the reliability and feasibility of PK-guided dosing of desmopressin and VWF-containing concentrates in individuals with VWD and low VWF.

## METHODS
### Trial design

The OPTI-CLOT: To WiN trial is a multicentre, non-randomised, open label cohort study. The study was approved by the Medical Ethics Committee of the Erasmus MC, University Medical Centre Rotterdam, the Netherlands, and was registered in the Netherlands Trial Register with trial registration number NL7212 and to EudraCT with number 2018-001631-46. The first patient was included on 8 April 2019. The planned end date of the study is 1 October 2023.

## Study population

After obtaining informed consent, individuals with congenital VWD or low VWF will be enrolled if they will, for medical reasons, have to undergo a desmopressin test, require haemostatic treatment with monitoring of VWF:Act and FVIII during a medical procedure or during a bleeding episode or receive prophylaxis with a VWF-containing concentrate. Patients will be recruited from Haemophilia Treatment Centres in the Netherlands.

## Inclusion criteria

► Individuals of all ages with any type of VWD or low VWF with historically lowest VWF antigen (VWF:Ag), VWF:Act and/or VWF collagen binding (VWF:CB) level <0.60 IU/mL or historically lowest FVIII level <0.40 IU/mL (only in case of type 2N VWD).
► Who provide informed patient consent (if patient is ≥12 years), or parental informed consent (if patient is <12 years) or both (if patient is between 12 and 16 years).
► Who re scheduled to undergo a desmopressin test.
► Who are scheduled to undergo an elective medical procedure (eg, dental procedure, surgery, diagnostic procedure or in-hospital child delivery), requiring treatment with desmopressin and/or a VWF-containing concentrate (Haemate P, Wilate, Wilfactin or Veyvondi) with monitoring of VWF and FVIII levels.
► Have a bleeding episode requiring treatment with desmopressin and/or a VWF-containing concentrate with monitoring of VWF and FVIII levels.
► Require prophylaxis with a VWF-containing concentrate due to frequent bleeding episodes;

## Exclusion criteria

► Any other known hemostatic abnormalities.
► Acquired VWD.
► Presence of VWF antibodies (>0.2 BU).

## Intervention

Predictive performance will be tested in all study arms, and feasibility of PK-guided dosing will be tested in arm B, C and D:

Arm A: patients who will undergo a desmopressin test.
Arm B: patients who will undergo an elective medical procedure.
Arm C: patients with a bleeding episode.
Arm D: patients receiving or requiring prophylaxis.

## Desmopressin testing (arm A)

In standard VWD care, most patients (except most type 2B VWD patients and all type 3 VWD patients) undergo a desmopressin test to determine their individual response to desmopressin. Desmopressin testing comprises measuring VWF:Act and FVIII before desmopressin administration and at 1 hour and 3–4 hours after desmopressin administration (0.3 μg/kg intravenously or subcutaneously or 300 μg or 150 μg if body weight is <50 kg) intranasally), to assess the effect of desmopressin in the individual patient.

**Table 1** Guidelines for substitution with VWF-containing concentrate in VWD according to Dutch national guidelines

| Indication | Target levels |
|---|---|
| Dental extraction | FVIII:C and VWF:Act>0.50 IU/mL |
| Surgery | Prior to surgery and 36 hours postoperatively FVIII:C and VWF:Act>0.80 IU/mL |
| Major surgery | FVIII:C>0.50 IU/mL during 7–10 days |
| Minor surgery | FVIII:C>0.50 IU/mL during 3 days and >0.30 IU/mL during 4–7 days |

FVIII:C, Factor VIII activity; VWD, Von Willebrand disease; VWF, Von Willebrand factor.

In individuals who will undergo a desmopressin test, VWF:Act and FVIII response will be predicted a priori based on the constructed population PK-model and individual patient characteristics.

## On demand treatment (arms B+C)

During elective medical procedures and during bleeding episodes, we will aim for VWF:Act and FVIII target plasma levels as defined in the national guidelines (table 1).[13] However, the treating physician will be able to set specific VWF:Act and FVIII target levels if needed, as is standard practice. These patient-specific target levels will be recorded prior to treatment and will be communicated to the clinical pharmacologist performing PK modelling. The pharmacologist will then provide a dosing strategy based on the patients' characteristics and individual desmopressin test and/or VWF-containing concentrate PK profile (performed prior to the procedure with the specific concentrate that will be used during the procedure), combined with the specific population PK model. When, at any time during the treatment period, target VWF:Act and FVIII plasma levels are not reached, additional desmopressin and/or VWF-containing concentrate can be administered by the treating physician to secure haemostasis. Therefore, bleeding risk for patients participating in the study will not be higher than in patients treated according to standard protocol.

## Prophylaxis (D)

In individuals receiving or requiring prophylaxis with a VWF-containing concentrate due to frequent bleeding episodes, patients will first undergo PK-profiling. This will be done in order to determine the optimal dosage of VWF-containing concentrate on basis of VWF:Act or FVIII target trough and peak values as set by the treating physician and patients' individual PK parameters (as derived by Bayesian analysis). Patients will initially receive PK-guided treatment for 12 weeks. During this period, plasma VWF:Act and FVIII will be measured and will be compared with predicted VWF:Act and FVIII to validate the advised dosing regimen. Information on bleeding episodes will be obtained from medical records. Participants will be followed up for a period of 24 weeks in which additional data will be collected in order to assess the

association between plasma VWF:Act and FVIII concentrations and bleeding events.

### Individual pharmacokinetic profiling

For every patient in arms B, C and D, an individualised dosing strategy will be provided based on actual body weight, type and severity of the procedure or bleeding, target VWF:Act and FVIII, baseline VWF:Act and FVIII and, if possible, an individual PK profile. Patients who will undergo a procedure requiring VWF-containing concentrate and patients who will receive prophylaxis, will undergo PK profiling with the VWF-containing concentrate of choice. Blood sampling for VWF and FVIII will be performed directly before bolus infusion and at approximately 10 min, 2–6 hours, 24 hours and 48 hours after infusion. Measuring VWF and FVIII at these time points will enable the construction of a concentration-time curve.

### Population PK models

Population PK models for desmopressin and different VWF-containing concentrates have been constructed using NONMEM software (however not all of our models have been published yet).[9 10] These models are able to predict average PK parameters for VWF:Act and FVIII (as well as the interindividual variability of these PK parameters, and intraindividual variability of some of the PK parameters), in a population of individuals with VWD and low VWF.

In these PK models, the relationship between different patient factors and treatment factors (eg, age, sex, weight, baseline VWF and FVIII, blood group type and VWF levels and PK parameters) are described. This allows prediction of the PK of VWF:Act and/or FVIII after desmopressin and VWF-containing concentrate administration. Combining an individual PK profile with the population PK model will allow for better prediction of the required doses and dosing frequency—as well as better prediction of plasma coagulation factor levels—than prediction based on the population PK model alone.

### Primary endpoints

Arm A (desmopressin testing): predictive performance of the desmopressin population PK model: reliability of predicted VWF:Act and FVIII levels, defined as the difference between predicted and actual VWF:Act and FVIII levels.

Arm B (elective medical procedures requiring treatment with desmopressin and/or VWF-containing concentrate): predictive performance of the Bayesian adaptive approach using the population PK model for desmopressin and/or VWF-containing concentrate (ie, reliability of the predicted VWF:Act and FVIII levels, defined as the difference between predicted and actual VWF:Act and FVIII levels achieved after dosing).

Arm C (bleeding episode requiring treatment with desmopressin or VWF-containing concentrate): predictive performance of the respective population PK models

(ie, reliability of the predicted VWF:Act and FVIII levels, defined as the difference between predicted and actual VWF:Act and FVIII levels achieved after dosing).

Arm D (prophylactic treatment with a VWF-containing concentrate): predictive performance of the VWF-containing concentrate population PK models (ie, reliability of the predicted VWF:Act and FVIII levels, defined as the difference between predicted and actual VWF:Act and FVIII levels achieved after dosing).

### Secondary endpoints

(Only in arms B, C and D): number and timing of desmopressin administrations (desmopressin dose will be standardised at 0.3 µg/kg) and/or timing and dosing of VWF-containing concentrate infusions.

(Only in arms B, C and D): haemostasis quantified by haemoglobin levels, blood loss (mL), incidence of bleeds, incidence of thrombosis and need for blood transfusion and/or reoperation because of bleeding.

(Only in arms B and C): duration of hospitalisation (days), number of clinical visits.

(Only in arms B, C and D): feasibility of the procedure with regard to patient and physician satisfaction and economic impact.

(Only in case of desmopressin testing or desmopressin treatment (in arms A, B and C)): desmopressin plasma concentrations.

### Sample size

In this prospective study, we will explore the predictive performance of the constructed population PK models for desmopressin and VWF-containing concentrates. In bleeding and surgery, we will aim for VWF:Act and FVIII target trough levels (defined as 100%–125% of VWF:Act and FVIII target trough level as stated by the treating physician and according to the national guidelines).

It is not common practice to calculate a sample size for prognostic models, and to our knowledge, it is not possible to calculate a sample size for the determination of predictive performance, our primary outcome. However, as characteristics such as age, sex and disease type are not part of the inclusion criteria or exclusion criteria, the study population will be a reflection of the heterogeneous 'real life' VWD and low VWF population. Consequently, this will increase the 'effective sample size' of our study population.

To be able to provide an estimation of the sample size needed, we have calculated sample sizes for outcomes that may be seen as surrogates for the primary outcome. Based on a random sample (n=100) of our retrospective cohort of patients whom underwent a desmopressin test, we have constructed an average VWF:Act-after-desmopressin curve with 25% percentiles. In 81% of individual desmopressin tests, one or more time points fall outside of the 50% CI of this average curve. Data from our retrospective cohort study on perioperative treatment with a VWF-containing concentrate (Haemate P) show that in the total study population, 81% of FVIII trough levels in the

first 36 hours was >0.20 IU/mL higher than targeted.[4] Using adaptive Bayesian dosing, we estimate that we can decrease the percentage in both groups from 81% to <50%. To determine this with an alpha of 0.02 and a power of 90%, we will have to include at least 25 patients in the desmopressin test group and at least 25 patients in the perioperative VWF-containing concentrate group. To allow for dropouts, at least 30 patients will be included in the desmopressin test group, and 30 patients will be included in the perioperative VWF-containing concentrate group. For desmopressin treatment during medical procedures, scarce data are available on factor levels during the periprocedural period. However, as we will also use the desmopressin test PK model in this setting, we assume similarity to the desmopressin test group and will also include 30 patients.

To explore the applicability of the currently available population PK models in other settings, predictive performance of the population PK models and PK-guided dose adjustments in groups for which no retrospective data are available, will be tested. Only small numbers of patients are currently treated with desmopressin in combination with VWF-containing concentrate, and it is expected that inclusion of patients with acute bleeding will be logistically challenging. Therefore, we aim to include 10 patients who will receive a combination of desmopressin and VWF-containing concentrate during a medical procedure, 10 patients with a bleeding episode receiving treatment with desmopressin and 10 patients with a bleeding episode receiving treatment with VWF-containing concentrate. As very few patients in the Netherlands receive prophylaxis, we aim to include 3–5 patients in arm D. In these settings, the population PK models for treatment with desmopressin and VWF-containing concentrate will be combined, and we will extrapolate the perioperative PK models to bleeding and prophylaxis. Due to the low sample sizes in arms C and D, predictive performance of the models (the primary endpoint) in these arms can only be assessed on an individual level, giving a rough idea of the accuracy of the models in these settings.

### Data analysis plan
#### Primary study parameters
Predictive performance of the population PK models (defined as difference between predicted and actual FVIII and VWF:Act levels achieved after dosing) will be analysed using Bland Altman analysis.[14] Mean relative error will be calculated to determine accuracy, and root mean squared error will be calculated to determine precision.

#### Secondary study parameters
1. In case of perioperative treatment with VWF-containing concentrate (n=30): concentrate consumption (IU/kg) from 24 hours before surgery until stop of VWF-containing concentrate infusions will be compared with consumption in the retrospective treatment cohort, of which the data have already been published.[4] If patients underwent >1 surgical procedure, only the

first one will be used for analysis. The distribution of outcomes for the prospectively studied group will be tested for normality using the Shapiro-Wilk test. In case of a non-significant (p>0.05) result of this test, the t-test will be used for the comparison of the primary endpoint. In case the resulting p-value for the Shapiro-Wilk test is equal or less than 0.05, the Wilcoxon-rank sum test will be used. The level for significance for this analysis will be set at two-sided p<0.05. Number and timing of desmopressin infusions will be defined quantitatively.
2. In the perioperative group, haemostasis will be quantified by amount of blood loss (mL). Bleeding complications or thrombotic complications will be defined quantitatively.
3. In the perioperative group, duration of hospitalisation (days) will be defined quantitatively.
4. Feasibility of the procedure: patient and physician satisfaction during PK-guided treatment during surgery and bleeding will be measured using a 10-point VAS (visual-analogue scale) questionnaire and will be defined quantitatively. Economic evaluation will be performed from a healthcare perspective taking all healthcare costs (i.a, costs of medication, hospitalisation costs) into account.
5. To test the correlation between desmopressin concentrations and relative increase in FVIII and VWF levels during desmopressin tests, and during desmopressin treatment during surgery or bleeding, the Pearson correlation coefficient will be calculated.

### Patient and public involvement
During development of all OPTI-CLOT studies, we work closely together with The Netherlands Hemophilia Patient Society (NVHP). A member of the NVHP is also a member of the OPTI-CLOT study group and plays an advisory role in developing the studies within the consortium. The final results of the study will be communicated through international scientific journals and at international conferences. In addition, a layman summary of the results of this study will be published in the NVHP magazine. Finally, the results of the study will be implemented in treatment guidelines and patient information will be adjusted accordingly.

### Ethics and dissemination
The trial protocol was approved by the Medical Ethics Committee of the Erasmus MC, University Medical Centre Rotterdam, the Netherlands. The study will be conducted according to good clinical practice guidelines and the Declaration of Helsinki, and in accordance with the Dutch Medical Research Involving Humans Act. Written informed consent will be obtained from all participants by the investigator. Also, see online supplemental data 1 for our regulations for data storage, amendments and compensation for injury. Results of the study will be communicated to the (inter)national medical and scientific community through publication in high-ranking

peer-reviewed international journals and at (inter)national conferences. Results of the study will be implemented in the Dutch Haemophilia Treatment Guidelines and may also be adopted by international Haemophilia Treatment Societies.

## Data monitoring committee and serious adverse events

Safety risks for participants are minimal as the VWF-containing concentrates and desmopressin used in this study are registered therapeutics for treatment of von Willebrand disease. To guarantee safety for participants in this study, VWF and FVIII levels will be monitored closely to prevent any additional bleeding risk. Therefore, a data safety monitoring board is not needed.

Serious adverse events (SAE) will be communicated to the sponsor within 24 hours. The sponsor will register the SAE within 15 days on ToetsingOnline, the Dutch registration system for SAEs.

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## REFERENCES

1 Leebeek FWG, Eikenboom JCJ. Von Willebrand's disease. *N Engl J Med* 2016;375:2067–80.
2 Sadler JE, Budde U, Eikenboom JCJ, *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.
3 Lavin M, Aguila S, Schneppenheim S, *et al*. Novel insights into the clinical phenotype and pathophysiology underlying low vWF levels. *Blood* 2017;130:2344–53.
4 Hazendonk HCAM, Heijdra JM, de Jager NCB, *et al*. Analysis of current perioperative management with Haemate® P/Humate P® in von Willebrand disease: Identifying the need for personalized treatment. *Haemophilia* 2018;24:460-470.
5 Heijdra JM, Cnossen MH, Leebeek FWG. Current and emerging options for the management of inherited von Willebrand disease. *Drugs* 2017;77:1531–47.
6 Castaman G, Lethagen S, Federici AB, *et al*. Response to desmopressin is influenced by the genotype and phenotype in type 1 von Willebrand disease (vWD): results from the European study MCMDM-1VWD. *Blood* 2008;111:3531–9.
7 Federici AB, Mazurier C, Berntorp E, *et al*. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. *Blood* 2004;103:2032–8.
8 Lethagen S, Kyrle PA, Castaman G, *et al*. Von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. *J Thromb Haemost* 2007;5:1420–30.
9 de Jager NCB, Bukkems LH, Heijdra JM, *et al*. One piece of the puzzle: Population pharmacokinetics of FVIII during perioperative Haemate P® /Humate P® treatment in von Willebrand disease patients. *J Thromb Haemost* 2020;18:295–305.
10 de Jager NCB, Heijdra JM, Kieboom Q, *et al*. Population pharmacokinetic modeling of von Willebrand factor activity in von Willebrand disease patients after desmopressin administration. *Thromb Haemost* 2020;120:1407–16.
11 Mentré F, Mallet A. Handling covariates in population pharmacokinetics. *Int J Biomed Comput* 1994;36:25–33.
12 Dargaud Y, Delavenne X, Hart DP, *et al*. Individualized PK-based prophylaxis in severe haemophilia. *Haemophilia* 2018;24 Suppl 2:3–17.
13 de Wee EM, Leebeek FWG, Eikenboom JCJ. Diagnosis and management of von Willebrand disease in the Netherlands. *Semin Thromb Hemost* 2011;37:480–7.
14 Myles PS, Cui J. Using the Bland-Altman method to measure agreement with repeated measures. *Br J Anaesth* 2007;99:309–11.