PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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 multicenter, non-randomized, open label cohort trial, the OPTI-CLOT: To WiN study
AUTHORS	Heijdra, Jessica; Al Arashi, Wala; de Jager, Nico; Cloesmeijer, Michael; Bukkems, Laura; Zwaan, Christian; Leebeek, Frank; Mathôt, Ron; Cnossen, Marjon

VERSION 1 – REVIEW

REVIEWER	Roy, Debabrata Drug Safety Research Unit
REVIEW RETURNED	18-Mar-2021

GENERAL COMMENTS	The protocol is very well written and clearly presented. Please find minor comments on the manuscript below to aid clarity: - Please could VWF be expanded in the title? - Could the title incorporate "in von Willebrand disease and in cases of reduced von Willebrand Factor levels". - I am unsure whether the study can be described as (inter)national. I would recommend removing this and stating as a multicenter study conducted in the Netherlands. - Could 'precision medicine' be added to the keywords? Abstract: - Line 5 : please could details be added as to what levels are being referred to? - Line 12/13 : please could the description of the predictive performance be placed in brackets? - Line 15 and 17 : could the semi-colon be replaced for 70: 30 and 20:10 as this may be confused with a ratio? - Line 8 of strengths and limitations: could 'with less levels below or above target' be reworded please as not currently reading well? - Line 9 of strengths and limitations: Should 'von' be added to Willebrand? Introduction Page 7 - Line 3 and 9, and throughout manuscript: Please could a different word be used instead of qualitative? e.g. "which can either be an issue with quantitative levels or a physical defect"? - Line 8 - please could a semi-colon be added after respectively? - Line 10 - please could associated be used in place of combined? - Line 14 (and throughout manuscript): could procedure be used in place of intervention?

	- Line 21 - please consider removing the word 'unnecessarily'? - Line 23 - please consider removing the word 'global'? Page 8 - Line 5: could further details on the source of the retrospective data be provided? - Have other groups conducted similar work on population PK models which can be mentioned and referenced? - Line 7: Please could Bayesian forecasting be briefly described and a reference provided? Line 13: Please could safety also be added after efficacy? Methods: Page 9, Line 2 - Could it be made clear that these are medical events that the patient would normally undergo? Page 9 - line 11 - could further details on type 2N VWD be included. Page 9 - line 21 - just to clarify that patients between 12 years and over and under 18 years) require informed consent only even though this is a paediatric population? Could ethics information regarding this be included? Page 10 - line 10 - could 2B VWD be described further? Page 15 - line 15 - please could you clarify 'at least' at 1 hour please? Page 5 - line 22 - please could you clarify the meaning of when indicated please? Table 1 mentioned VWF:RCo - would this require further describing as not mentioned elsewhere? Page 12 - line 17 - is this referring to blood group type, could this be clarified please? Page 12 - line 21 - is this correct use of the term concomitant as unclear what this is referring to? Page 13 - line 22 - could you clarify the definition of re-operation please? Page 13 - line 24 - does this refer to the number of clinical visits? Data analysis plan - Page 15, line 17 - could a reference be added to the Bland Altman analysis? - Page 16 - line 10 - please could examples of health care costs be provided?

REVIEWER	Sylvester, Katelyn Brigham and Women's Hospital, Pharmacy
REVIEW RETURNED	20-Mar-2021

GENERAL COMMENTS	Thank you for your submission describing your protocol for investigating the clinical and economic impact of PK-guided dosing of desmopressin and VWF containing products in patients with VWD and low VWF. If validated, this will help optimize dosing for many VWD patients. Some suggestions or points of clarification: - The sample size in all groups is relatively small but it would be helpful to know if the PK modeling is accurate in VWD/low VWF as a whole and based on the individual subtypes of VWD. Unclear from the paper if individual group level data will be collected and reported even though it likely wont be possible to do statistics on the small sample. - My understanding is that the dosing will be based on the PK model vs the current standard of practice. It would be helpful to know what the standard dosing would have been compared to the

	PK-guided dose to see if it results in a clinically (and economically) significant difference in dose. Introduction - The last sentence of the 1st paragraph could be reworded for readability such as "The low VWF group was defined as individuals with VWF levels between 30-50 IU/mL in combination with a bleeding tendency." - Introduction line 15 may want to clarify delivery as childbirth - Introduction lines 18-20 may be helpful to list the % reported with higher and lower than targeted levels and note what population this study was reporting on. - Methods / Study Population - page 9, lines 2-6 may want to say this is specifically hereditary VWD since the exclusion criteria state that acquired VWD was excluded - Methods - confirming that urgent / non-elective procedures were not included. - Sample size - for groups C and D the sample anticipated seems like it would be more hypothesis generating vs validating the model based on the sample size. Considering making this explicit. - Data analysis plan, secondary study parameters, page 16, line 4-5; will blood loss in the peri-operative group also be compared to historical groups? - Data analysis plan, economic evaluation - will the costs also include the cost of PK software, training of clinicians on the model and time comparison of calulating doses based on traditional model vs the PK-dosing

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Debabrata Roy, Drug Safety Research Unit

Comments to the Author:
The protocol is very well written and clearly presented. Please find minor comments on the manuscript below to aid clarity:
Thank you, we are very pleased that you value the quality of our protocol. Please find the answers to your comments below.

- Please could VWF be expanded in the title?
We have done so accordingly.

- Could the title incorporate "in von Willebrand disease and in cases of reduced von Willebrand Factor levels".
As ‘low VWF’ or ‘low von Willebrand factor’ are commonly used in literature to describe individuals with low VWF levels, we have chosen to rephrase this sentence as follows: ‘in individuals with von Willebrand disease or low von Willebrand factor’.

- I am unsure whether the study can be described as (inter)national. I would recommend removing this and stating as a multicenter study conducted in the Netherlands.
This part is about the complete OPTI-CLOT research programme. For the development of some of the PK-models, data from different centers from the Netherlands as well as the UK are included.

- Could 'precision medicine' be added to the keywords?
We have done so accordingly.

Abstract:
- Line 5 : please could details be added as to what levels are being referred to?
We have changed ‘levels’ into ‘factor levels’ to make it more clear that we are referring to von Willebrand factor and factor VIII levels.

- Line 12/13 : please could the description of the predictive performance be placed in brackets?
We have done so accordingly.

- Line 15 and 17 : could the semi-colon be replaced for 70: 30 and 20:10 as this may be confused with a ratio?
We have done so accordingly.

- Line 8 of strengths and limitations: could 'with less levels below or above target' be reworded please as not currently reading well?
We have removed this entire sentence from the strengths and limitations sections.

- Line 9 of strengths and limitations: Should 'von' be added to Willebrand?
Yes, thank you, we have added this to the sentence.

Introduction
Page 7
- Line 3 and 9, and throughout manuscript: Please could a different word be used instead of qualitative? e.g. "which can either be an issue with quantitative levels or a physical defect"?
We have accordingly altered these lines.
Line 3 now reads ‘It is caused by low or absent von Willebrand factor (VWF), or by a functional defect of VWF.’
Line 9 reads: 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.

- Line 8 - please could a semi-colon be added after respectively?
- Line 10 - please could associated be used in place of combined?
- Line 14 (and throughout manuscript): could procedure be used in place of intervention?
- Line 21 - please consider removing the word 'unnecessarily'?
- Line 23 - please consider removing the word 'global'?
We have changed or removed these words accordingly.

Page 6
- Line 5: could further details on the source of the retrospective data be provided?
We have added some extra information to this sentence, it now reads:
‘Population PK models that describe plasma VWF activity (VWF:Act) and FVIII after administration of desmopressin or VWF-containing concentrates, based on retrospective DDAVP-testing data and VWF-containing concentrate treatment data from multiple hemophilia treatment centers in the Netherlands and in the United Kingdom, have been constructed by our group (however not all models have been published yet).

- Have other groups conducted similar work on population PK models which can be mentioned and referenced?
No other groups have yet published work on population PK models in VWD or low VWF

- Line 7: Please could Bayesian forecasting be briefly described and a reference provided?
We have added a sentence before and after this sentence, and have added 2 references to explain more clearly:
In a population PK model, the typical PK parameters and their corresponding variability are estimated, Subsequently, covariate relationships, e.g. 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 uncertaininty are combined into a predictive distribution for the future values, after which point and interval forecasts can be obtained.[12]

Line 13: Please could safety also be added after efficacy?
We have done so accordingly.

Methods:
Page 9, Line 2 - Could it be made clear that these are medical events that the patient would normally undergo?
We have adjusted this sentence:
After obtaining informed consent, individuals with VWD or low VWF who will, for medical reasons, have to undergo a desmopressin test,……

Page 9 - line 21 - just to clarify that patients between 12 years and over and under 18 years) require informed consent only even though this is a paediatric population? Could ethics information regarding this be included?
This sentence wasn't correct. We have adjusted this into:
informed patient consent if patient is ≥12 years and (also) parental informed consent if patient is <16 years

Page 9 - line 11 - could further details on type 2N VWD be included.
Page 10 - line 10 - could 2B VWD be described further?
Details on the subtypes have been added to the introduction:
In type 2A, binding of VWF to platelets is decreased, while in type 2B, affinity of VWF for platelets is increased. In both type 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.

Page 15 - line 15 - please could you clarify 'at least' at 1 hour please?
We have removed 'at least' from this sentence.

Page 5 - line 22 - please could you clarify the meaning of when indicated please?
We have changed 'when indicated' into 'if needed' to provide more clarity.

Table 1 mentioned VWF:RCo - would this require further describing as not mentioned elsewhere?
We have changed VWF:RCo into VWF:Act.

Page 12 - line 17 - is this referring to blood group type, could this be clarified please?
Yes, we have added 'group' to blood type.

Page 12 - line 21 - is this correct use of the term concomitant as unclear what this is referring to?
We have removed 'the concomitant' from this sentence.

Page 13 - line 22 - could you clarify the definition of re-operation please?
We have added to this sentence: re-operation because of bleeding.

Page 13 - line 24 - does this refer to the number of clinical visits?

We have adjusted this sentence into: duration of hospitalization (days), number of clinical visits.

Data analysis plan
- Page 15, line 17 - could a reference be added to the Bland Altman analysis?
We have added a reference accordingly.

- Page 16 - line 10 - please could examples of health care costs be provided?
We have added to this sentence: … taking all health care costs (a.o. costs of medication, hospitalization costs) into account.

Reviewer: 2
Dr. Katelyn Sylvester, Brigham and Women's Hospital

Comments to the Author:
Thank you for your submission describing your protocol for investigating the clinical and economic impact of PK-guided dosing of desmopressin and VWF containing products in patients with VWD and low VWF. If validated, this will help optimize dosing for many VWD patients.
Thank you very much for your careful assessment of our study protocol. Please find below our answers to your suggestions.

Some suggestions or points of clarification:

- The sample size in all groups is relatively small but it would be helpful to know if the PK modeling is accurate in VWD/low VWF as a whole and based on the individual subtypes of VWD. Unclear from the paper if individual group level data will be collected and reported even though it likely wont be possible to do statistics on the small sample.
Analysis of the different study arms will be done separately. VWD subtype is not a significant covariate in most of the developed PK models, suspectedly because of the relatively small numbers of especially type 2 subtypes in these populations. Significant covariates included, for example, age and sex.

- My understanding is that the dosing will be based on the PK model vs the current standard of practice. It would be helpful to know what the standard dosing would have been compared to the PK-guided dose to see if it results in a clinically (and economically) significant difference in dose.
This would indeed be very interesting to study. However, to do this in the best way, we would have to randomize patients between PK-guided and standard dosing. In the earlier OPTI-CLOT trial on perioperative PK-guided factor concentrate in hemophilia A, we have chosen this approach. The results of the OPTI-CLOT trial in hemophilia A will be published very soon. The experience from the hemophilia A trial has led us to the conclusion that for VWD, in which we wanted to study the different treatment options in different disease types, this would make the study too complicated and the number of patients we would need to include in the study would be too high.

Introduction
- The last sentence of the 1st paragraph could be reworded for readability such as "The low VWF group was defined as individuals with VWF levels between 30-50 IU/mL in combination with a bleeding tendency."
We have adjusted this sentence into: individuals with low VWF have a bleeding tendency associated with VWF levels between 0.30-0.60 IU/mL.

- Introduction line 15 may want to clarify delivery as childbirth
We have adjusted this accordingly.

- Introduction lines 18-20 may be helpful to list the % reported with higher and lower than targeted levels and note what population this study was reporting on.
We have adjusted this sentence into:
However it has been previously reported in a study on perioperative treatment of VWD patients with Haemate P, that a majority (65%, 53% and 57% in type 1, type 2 and type 3 respectively) of patients achieves higher VWF:Act levels than aimed for, and a minority (16%, 38% and 29% in type 1, type 2 and type 3 respectively) does not reach sufficient levels for adequate hemostasis.

- Methods / Study Population - page 9, lines 2-6 may want to say this is specifically hereditary VWD since the exclusion criteria state that acquired VWD was excluded
We have added ‘congenital’ before VWD.

- Methods - confirming that urgent / non-elective procedures were not included.
We have added ‘elective’ at bullet point 3.

- Sample size - for groups C and D the sample anticipated seems like it would be more hypothesis generating vs validating the model based on the sample size. Considering making this explicit.
Thank you, however in the last paragraph of the ‘sample size’ part, it is explained that we will extrapolate the models to in order to see if the predictive performance of the models is acceptable in these situations, and if it is feasible to use the models in these situations.

- Data analysis plan, secondary study parameters, page 16, line 4-5; will blood loss in the peri-operative group also be compared to historical groups?
Unfortunately, as in our retrospective data sets data on the exact amount of blood loss is lacking in a lot of cases, we will not be able to compare this.

- Data analysis plan, economic evaluation - will the costs also include the cost of PK software, training of clinicians on the model and time comparison of calculating doses based on traditional model vs the PK-dosing
Yes, this will also be calculated. However we are currently working on making the PK models available through a web site with a user friendly interface, so that clinicians can easily calculate the required doses. This will make PK guided dosing more cost efficient in the future.

VERSION 2 – REVIEW

REVIEWER	Roy, Debabrata Drug Safety Research Unit
REVIEW RETURNED	28-Jul-2021

GENERAL COMMENTS	The protocol has been comprehensively and clearly written. I have suggested some minor revisions: Strengths and Limitations: - von Willebrand factor-containing concentrate would need abbreviation. - please state that a non-interventional approach would be used for treatment choice and brand of medication Introduction: Page 7: - Line 16 - please could commas or brackets be used instead of hyphens - Line 24 - VWF: Act would need defining here rather than later in the manuscript Page 8: -Line 11 - please define DDAVP testing - Line 19 - please could point and interval forecasts be explained further? Methods: Page 9: Study population: - please could the enrolment criteria be reviewed as it may be interpreted as patients have to undergo a desmopressin test and hemostatic treatment? - Please could the inclusion criteria be reviewed as it is unclear which criteria are individual and which criteria are together (and/or)? Exclusion criteria: - would children less than 12 years of age be part of the exclusion criteria? Intervention: - please could it be explained why feasibility of PK-guided dosing cannot be tested in arm A - please could a reference for Table 1 be provided? Individual PK profiling: - please change to 'a procedure' rather than 'an procedure' - Blood sampling period of 2-6 hours is a long time window. Could an explanation be provided why this time window has be chosen?

	Population PK models: - Please check 'in a population individuals' - Would it be possible to explain inter-individual and intra-individual variability further? Primary endpoints: - Should Arm C be bleeding episode requiring treatment with desmopressin 'and/or' VWF-containing concentrate? Secondary endpoints: - please replace '&' with 'and' - please could study arms be added for 'only in cases of desmopressin testing or desmopressin treatment) Sample size: - please could the effect of the low sample sizes in arms C and D on the primary endpoints be described? Secondary study parameters: - please could a reference be added where 'of which the data have already been published'? - unsure as to the meaning of the abbreviation a.o.?

REVIEWER	Sylvester, Katelyn Brigham and Women's Hospital, Pharmacy
REVIEW RETURNED	16-Jul-2021

GENERAL COMMENTS	Thank you for the revisions to the manuscript. The current manuscript reads well and addressed the majority of the suggested edits. A few minor suggested edits / clarification remain: 1. Consider putting examples in parantheses throughout the manuscript to make long sentences easier to read. This happens about 5-10 places throughout the manuscript. Examples include intro page 5, line19-20, page 6, line 16-18. 2. Delivery was changed to "in-hospital childbirth" on page 8, but not on page 5 line 20. 3. Page 5 lines 18 and 21, the sentences should start with "the" or be re-worded. 4. Intro line 25, I believe the word "higher" or "above" is missing from this sentence. 5. Page 6 - consider removing the word "usually" from line 1 since "frequent" is already included at the beginning of the sentence. Consider removing the word "strongly" from line 28 unless the stats is going to be able to assess the strength of improvement in efficacy and safety. 6. Page 10, line 19 - When weight based doses are calculated for the patient, will this be based on actual or ideal body weight?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Dr. Katelyn Sylvester, Brigham and Women's Hospital

Comments to the Author:
Thank you for the revisions to the manuscript. The current manuscript reads well and addressed the majority of the suggested edits. A few minor suggested edits / clarification remain:
Thank you for your suggestions, we have incorporated the suggested changes into the manuscript.

1. Consider putting examples in parantheses throughout the manuscript to make long sentences easier to read. This happens about 5-10 places throughout the manuscript. Examples include intro page 5, line19-20, page 6, line 16-18.
2. Delivery was changed to "in-hospital childbirth" on page 8, but not on page 5 line 20.
3. Page 5 lines 18 and 21, the sentences should start with "the" or be re-worded.
4. Intro line 25, I believe the word "higher" or "above" is missing from this sentence.
5. Page 6 - consider removing the word "usually" from line 1 since "frequent" is already included at the beginning of the sentence. Consider removing the word "strongly" from line 28 unless the stats is going to be able to assess the strength of improvement in efficacy and safety.
6. Page 10, line 19 - When weight based doses are calculated for the patient, will this be based on actual or ideal body weight?

Reviewer: 1
Dr. Debabrata Roy, Drug Safety Research Unit

Comments to the Author:
The protocol has been comprehensively and clearly written. I have suggested some minor revisions:
Thank you for your suggestions, we have incorporated the suggested changes into the manuscript. For two of your queries, we have added some extra explanation below.
Strengths and Limitations:
- von Willebrand factor-containing concentrate would need abbreviation.
- please state that a non-interventional approach would be used for treatment choice and brand of medication
Introduction:
Page 7:
- Line 16 - please could commas or brackets be used instead of hyphens
- Line 24 - VWF: Act would need defining here rather than later in the manuscript Page 8:
-Line 11 - please define DDAVP testing
- Line 19 - please could point and interval forecasts be explained further?
Methods:
Page 9:
Study population:
- please could the enrolment criteria be reviewed as it may be interpreted as patients have to undergo a desmopressin test and hemostatic treatment?
- Please could the inclusion criteria be reviewed as it is unclear which criteria are individual and which criteria are together (and/or)?
Exclusion criteria:
- would children less than 12 years of age be part of the exclusion criteria?
Intervention:
- please could it be explained why feasibility of PK-guided dosing cannot be tested in arm A
PK-guided dosing cannot be tested in arm A, as this arm will only contain desmopressin testing (making an individual PK profile for desmopressin) and not treatment.
- please could a reference for Table 1 be provided?

Individual PK profiling:
- please change to 'a procedure' rather than 'an procedure'
- Blood sampling period of 2-6 hours is a long time window. Could an explanation be provided why this time window has be chosen?

This time window has been chosen because a time point within this window will usually reflect VWF or FVIII between peak level and t1/2. The most important thing is that the exact time of the measurement is registered, so the time-concentration curve will reflect the true values. The reason why we have given a time window instead of an exact time point is that it is more convenient for the patient, as the patient may wish to stay in the hospital and wait for two hours before the next measurement, or may leave the hospital and come back at the end of the day.

Population PK models:
- Please check 'in a population individuals'
- Would it be possible to explain inter-individual and intra-individual variability further?

Primary endpoints:
- Should Arm C be bleeding episode requiring treatment with desmopressin 'and/or' VWF-containing concentrate?

Secondary endpoints:
- please replace '&' with 'and'
- please could study arms be added for 'only in cases of desmopressin testing or desmopressin treatment)

Sample size:
- please could the effect of the low sample sizes in arms C and D on the primary endpoints be described?

Secondary study parameters:
- please could a reference be added where 'of which the data have already been published'?
- unsure as to the meaning of the abbreviation a.o.?