PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A Randomized Controlled Trial Protocol to Evaluate a Fixed Dose Prothrombin Complex Concentrate against the Variable Dose in Vitamin K Antagonist Related Bleeding (PROPER3)
AUTHORS	Abdoellakhan, Rahat ; Khorsand, Nakisa; Van Hest, Reinier; Veeger, Nic; Ter Avest, Ewoud; Ypma, Paula; Faber, Laura; Meijer, Karina

VERSION 1 – REVIEW

REVIEWER	Mike Makris University of Sheffield Sheffield UK
REVIEW RETURNED	18-Dec-2017

GENERAL COMMENTS	The authors are to be congratulated in designing and performing a randomised trial in the field of emergency anticoagulation reversal. The deferred consent approach is a good way to allow the study to be conducted without impairing immediate clinical care. My main comment is that this study will likely show non-inferiority by the way it is designed rather than because the two doses are equivalent in every setting studied. By not specifically having inclusion criteria other than the physician wants to use PCC, patients of all bleeding severity including many that probably do not need PCC will be entered. If enough patients with relatively low INR elevations and moderate bleeding are entered then the low dose PCC will be sufficient and non-inferiority will be concluded. If there is any superiority of dosing based on the INR, this is likely to be seen in the high INR patients. Since 50% of the patients have already been recruited, the protocol can not change but I would encourage the authors to analyse their results by severity of bleeding and by prolongation of the INR (in particular analyse separately the group with INR of >4.5). The inpatient stay and survival should be compared to patients with the complication but not on anticoagulants as this will give an indication if patients with milder severity were recruited eg after gastrointestinal bleeding the survival would be expected not to exceed that of patients not on anticoagulants. One critical issue that needs to be clarified is the vitamin K administration - the dose, route and timing should be precisely recorded. Also the pre-PCC INR timing in relation to PCC and Vitamin K administration should be accurately recorded. Also accurately recorded should be the timing of the post-PCC INR.

	When analysing their results the authors should specifically address two points: a) Was the PCC justified in every case? ie could just vitamin K have been sufficient b) Was the response due to the PCC or due to the vitamin K that was co-administered since after vitamin K alone you get a reasonable correction of the coagulopathy at 6 hours (if given intravenously) and a complete correction at 24hours.

REVIEWER	Sean G. Yates, MD Assistant Professor, Pathology Associate Medical Director, Transfusion Medicine University of Texas Medical Branch Galveston, TX United States
REVIEW RETURNED	29-Dec-2017

GENERAL COMMENTS	This protocol focuses on an interesting and relevant area of healthcare. I find the protocol to be well written and easy to comprehend. Overall, the proposed study is practical, and no ethical obstacles were identified. Moreover, it has practice altering potential, as demonstration of the non-inferiority of a fixed PCC dosing strategy vs. a variable dosing strategy in VKA-associated extracranial bleeding emergencies may potentially improve the logistics of VKA reversal, reduce thromboembolic events associated with PCC administration and lead to a reduction in the overall cost of managing VKA associated bleeding events. However, this protocol may be improved addressing elements that need to be refined or require further clarification. Study Setting – Patient enrollment in the study is contingent on the treating physician deciding to order PCC. Could the authors comment on the rate at which physicians elect to utilize other treatments for VKA related bleeding events at their respective institutions? Is this a potential source of selection bias? Intervention – The variable dosing strategy differs with the brand of PCC that is being utilized. Is there a provision to analyze the results separately for both PCCs? Does composition matter? Intervention – The author's mention, "All treatment aspects other than the PCC dosing strategy, such as the use of vitamin K or packed cells, should agree with routine clinical practice." Would it be possible to define the accepted definition of routine clinical practice at their respective institutions? Data Collection and Management – Would it be possible to include the specific date and patient characteristics that will be collected by case report forms? This information is essential to determine risk factors or potential risk factors that may affect the efficacy of the interventions and influence study outcomes. It is also needed to assess the generalizability of the study findings. Recognizing that blinding of treating physicians in a study such as this is difficult if not impossible, efforts should be made to limit or standardize co-interventions (medications, therapies or behaviors) that may impact the primary outcome of hemostatic efficacy. Could

	the authors of the proposal provide what efforts if any were implemented to minimize or standardize potential co-interventions?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

The authors are to be congratulated in designing and performing a randomised trial in the field of emergency anticoagulation reversal. The deferred consent approach is a good way to allow the study to be conducted without impairing immediate clinical care.

My main comment is that this study will likely show non-inferiority by the way it is designed rather than because the two doses are equivalent in every setting studied.
By not specifically having inclusion criteria other than the physician wants to use PCC, patients of all bleeding severity including many that probably do not need PCC will be entered. If enough patients with relatively low INR elevations and moderate bleeding are entered then the low dose PCC will be sufficient and non-inferiority will be concluded. If there is any superiority of dosing based on the INR, this is likely to be seen in the high INR patients.

[response]
First of all, thank you very much for taking the time to review our manuscript and your valuable and thorough comments.

We understand that our inclusion criteria could be interpreted as physicians having full liberty to use PCC in this study, also in patients with moderate bleeding. However in Dutch clinical practice the use of PCC is highly regulated, both by a national guideline [1] and by local treatment protocols. The PCC is given as standard medical care in bleeds necessitating PCC in this study and therefore paid from the regular hospital budget. There is therefore no incentive to use PCC more often than strictly necessary. To test this assumption, as a sensitivity analysis, we will perform a subgroup analysis for the higher versus the lower presenting INRs.

Considering we understand that the inclusion criteria might lead to this interpretation from the manuscript, we now have added further clarification in the manuscript under 'Study setting' and 'Intervention'.

[1] Nederlandse Internisten Vereniging. Richtlijn Antitrombotisch beleid, published 21 april 2016. https://internisten.nl/files/Richtlijn%20Antitrombotisch%20beleid_def.pdf. Date accessed: January 2018.
[/response]

Since 50% of the patients have already been recruited, the protocol can not change but I would encourage the authors to analyse their results by severity of bleeding and by prolongation of the INR (in particular analyse separately the group with INR of >4.5).

[response]
We share the concern about homogeneity of the effect in specific subgroups of patients, especially in patients with high baseline INR. This is therefore one of the planned subgroup analyses that will be conducted in the analysis phase, as well as analysis by type of bleeding and/or severity of bleed, brand of PCC, type of VKA, etcetera. These will be elaborated in the statistical analysis plan before locking of the database.

We have now added the intention to perform these subgroup analyses to the manuscript under 'Statistical methods'. Thank you for pointing out the importance of this.
[/response]

The inpatient stay and survival should be compared to patients with the complication but not on anticoagulants as this will give an indication if patients with milder severity were recruited eg after gastrointestinal bleeding the survival would be expected not to exceed that of patients not on anticoagulants.

[response]
In our study we focus on a possible benefit of a fixed dose regime versus variable dosing PCC to convert anticoagulant therapy. In that respect, a comparison with patients not on anticoagulants is beyond the scope of this RCT. However, it is a very valuable suggestion, especially for the subgroup of patients with milder severity, and we will consider this research question as a substudy.
[/response]

One critical issue that needs to be clarified is the vitamin K administration - the dose, route and timing should be precisely recorded. Also the pre-PCC INR timing in relation to PCC and Vitamin K administration should be accurately recorded. Also accurately recorded should be the timing of the post-PCC INR.

[response]
We agree that the characteristics of PCC and vitamin K administration are critical. The case report forms record all appointed factors (i.e. vitamin k administration, dose, route and timing, timing of pre- and post-PCC INR and time of PCC dose). We have updated the manuscript under 'Data collection and management' to be clearer about this.
[/response]

When analysing their results the authors should specifically address two points:
a) Was the PCC justified in every case? ie could just vitamin K have been sufficient

[response]
We will look into this, and describe this as accurately as possible in the final report of the study. Thank you for pointing out its importance. As explained above, we are confident that the complete cohort will accurately represent clinical practice. We see however that clinical practice might vary worldwide and thus will look into this.
[/response]

b) Was the response due to the PCC or due to the vitamin K that was co-administered since after vitamin K alone you get a reasonable correction of the coagulopathy at 6 hours (if given intravenously) and a complete correction at 24hours.

[response]
Another valuable point that we take into account by asking to order the INR 60 minutes after PCC administration (defined in the manuscript as secondary parameter). When analyzing the results we will examine the time between PCC and vitamin K administration.

Again, thank you for reviewing our manuscript and your valuable comments, highly appreciated.
[/response]

Reviewer: 2

This protocol focuses on an interesting and relevant area of healthcare. I find the protocol to be well written and easy to comprehend. Overall, the proposed study is practical, and no ethical obstacles were identified. Moreover, it has practice altering potential, as demonstration of the non-inferiority of a fixed PCC dosing strategy vs. a variable dosing strategy in VKA-associated extracranial bleeding emergencies may potentially improve the logistics of VKA reversal, reduce thromboembolic events associated with PCC administration and lead to a reduction in the overall cost of managing VKA associated bleeding events. However, this protocol may be improved addressing elements that need to be refined or require further clarification.

Study Setting – Patient enrollment in the study is contingent on the treating physician deciding to order PCC. Could the authors comment on the rate at which physicians elect to utilize other treatments for VKA related bleeding events at their respective institutions? Is this a potential source of selection bias?

[response]
Firstly we like to thank the reviewer very much for reviewing the manuscript and taking the time to provide helpful and detailed input.

We do not see this as a potential source of bias since 4F-PCC is well implemented in Dutch clinical practice with over 50 years of market access and experience as reversal agent for VKA related bleeds. Its place in treatment of VKA-related bleeds is well-known and Dutch practice guidelines, as well as local hospital guidelines highly regulate 4F-PCC as the preferred and only reversal agent for VKA-related bleeds. 3F-PCC is not available on the Dutch market, while activated PCC is not available nor used for this indication as it is far more expensive (approx. factor 10) and thus reserved for hemophilia treatment and in a rare NOAC bleeding emergency. Furthermore national guidelines advise against the use of plasma or other factor concentrates for this indication.

Therefore we are not afraid that other treatments such as those previously mentioned will cloud our study and/or introduce selection bias. However we will absolutely keep this in mind when analyzing and discussing the final results. To improve the manuscript, we now have elaborated this under 'Study setting'.
[/response]

Intervention – The variable dosing strategy differs with the brand of PCC that is being utilized. Is there a provision to analyze the results separately for both PCCs? Does composition matter?

[response]
Sharply noticed, thank you for that. The variable dose does indeed differ with PCC brand. As mentioned in the study protocol two brands of PCC are used in the Netherlands, Beriplex (KCentra, CSL Behring), and Cofact (Sanquin). The variable dose varies between brands because both brands vary in target-INR to achieve. For example, Beriplex strives to achieve an INR < 1.3 while Cofact is dosed to achieve either INR < 2.1 or INR < 1.5. Regarding composition, both PCC brands are considered to contain the same approximate amounts constituents and are therefore used interchangeably in clinical practice. We are however documenting the PCC brand and intend to do subgroup analyses for the different PCC brands to check on homogeneity of haemostatic effect. This is now added to the manuscript under 'Statistical methods'.
[/response]

Intervention – The author's mention, "All treatment aspects other than the PCC dosing strategy, such as the use of vitamin K or packed cells, should agree with routine clinical practice." Would it be possible to define the accepted definition of routine clinical practice at their respective institutions?

[response]
What we can do is describe in detail the protocols that the hospitals use, in the final study report. At this stage, we cannot prescribe the hospitals what they should do: one of the strengths of this study is that it fits with normal practice, both in terms of feasibility in performing the study as in external validity once the results are available.

To add more clarity, we have updated the manuscript under 'Intervention' mentioning why we chose this approach.
[/response]

Data Collection and Management – Would it be possible to include the specific date and patient characteristics that will be collected by case report forms? This information is essential to determine risk factors or potential risk factors that may affect the efficacy of the interventions and influence study outcomes. It is also needed to assess the generalizability of the study findings.

[response]
Of course, the CRFs are added as supplementary files.
[/response]

Recognizing that blinding of treating physicians in a study such as this is difficult if not impossible, efforts should be made to limit or standardize co-interventions (medications, therapies or behaviors) that may impact the primary outcome of hemostatic efficacy. Could the authors of the proposal provide what efforts if any were implemented to minimize or standardize potential co-interventions?

[response]
Blinding is indeed practically impossible, but as mentioned before, the fact that clinical care around this type of bleeding is highly regulated in guidelines and protocols, already limits and standardizes co-interventions. We will perform subgroup analyses to verify this. Of note, endpoint assessments vulnerable to information bias will be evaluated without knowledge on the allocated strategy by the independent endpoint adjudication board (EAB).

VERSION 2 – REVIEW

REVIEWER	Mike Makris University of Sheffield UK
REVIEW RETURNED	03-Feb-2018

GENERAL COMMENTS	The authors have adequately addressed my comments.

REVIEWER	Sean G. Yates, MD University of Texas Medical Branch, Galveston TX, USA
REVIEW RETURNED	12-Feb-2018

GENERAL COMMENTS	The authors have adequately addressed all questions and concerns in the revised manuscript. This should prove to be a valuable addition to the literature.