Author’s response to reviews

Title: NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): evaluation of a national guideline on management of neonatal catheter-related thrombosis

Authors:

Jeanine Sol (jeanine.sol@ghz.nl)

Moniek van de Loo (m.vandeloo@amc.uva.nl)

Marit Boerma (381864mb@student.eur.nl)

Klasien Bergman (k.a.bergman@umcg.nl)

Albertine Donker (a.donker@mmc.nl)

Mark van der Hoeven (m.vander.hoeven@mumc.nl)

Christiaan Hulzebos (c.v.hulzebos@umcg.nl)

Ronny Knol (r.knol@erasmusmc.nl)

K.Djien Liem (d.liem@cukz.umcn.nl)

Richard van Lingen (r.a.van.ingen@isala.nl)

Enrico Lopiore (e.lopriore@lumc.nl)

Monique Suijker (m.h.suijker@amc.nl)

Daniël Vijlbrief (d.vijlbrieuf@umcutrecht.nl)

Remco Visser (r.visser@lumc.nl)

Mirjam van Weissenbruch (m.vanweissenbruch@vumc.nl)

Margreet Veening (ma.veening@vumc.nl)

Heleen van Ommen (c.vanommen@erasmusmc.nl)

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Author’s response to reviews:

Dear Nawsheen Boodhun, Editor BMC Pediatrics,
We are very pleased our manuscript "NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): evaluation of a national guideline on management of neonatal catheter-related thrombosis" (BPED-D-16-00696R1) is potentially acceptable for publication in BMC pediatrics.

We would like to thank you and the reviewers for the positive feedback and suggestions.

In this response letter, we will provide a point-by-point detailed response to each reviewer/editorial point raised and we describe what amendments have been made to the manuscript text and where these can be found in the revised manuscript.(marked yellow)

We hope our revised version of the manuscript is acceptable for publication.

Yours sincerely,

Heleen van Ommen

Reviewer 1

I do not believe one year will be good enough to assess for this complication in neonates. Extended duration >5 years will give additional information regarding this complication.

We completely agree with the reviewer. Many children will have follow up at 1, 2 and 5 years. We will ask the participating centers to perform additional assessment of PTS after 2 and 5 years with MVS. After 5 years the new developed CAPTSureTM will be used as well.

Page 16 and 17
Suggest adding ratio catheter to vein neonate and number of attempted CVC insertions as additional risks factors for thrombosis.

To add ratio catheter vein will be difficult as we do not know the exact size of the vein. That is why we collect data about the size of the catheter.

Attempted CVC insertions is a good suggestion. However, we have started our study already in 2014, so we are half way. We will only have results of half of the patients. But we added it to the collected data.

Page 16

Consider family history of thrombophilia, other thrombosis risk factors such as maternal diabetes, maternal APS as other potential risk factors for CVC related thrombosis.

These risk factors will be additionally collected in the study.

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Reviewer 2

150 neonates will be recruited over a 5 year period (i.e. 150/5 years = 30 patients per year/10 NICU = 3 patients with CVC-related DVT per NICU per year).

Looking at these numbers, this reviewer suspects that a different recruitment rate will occur between NICUs according to team awareness, study engagement, and overall patient disease severity. The study will report the efficacy and safety of the proposed consensus-based management of CVC-related DVT in neonates, stating that "violations to the protocol" will be noted and that neonates and infants without a signed consent will be excluded. Therefore, a potential for patient selection bias may hamper the study findings if, for example, only NICUs with the sickest patients, where DVTs are more likely, include patients. Conversely, because mothers from severely ill neonates may also be still hospitalized, maybe such patients would be less likely to be included if a consent cannot be obtained. With these examples, this reviewer suggests that the authors consider reporting the population included according to disease severity (examples: PELOD, NEOMOD), which may address some of the points raised herein. Secondly, it would also be important to report the rates of thrombosis (clinically noted), bleeding, and death in the population of patients excluded, to improve the interpretation of the study findings and address the study's generalizability (i.e. intracranial bleeds in anticoagulated vs. non-anticoagulated subjects).
The chance of selection bias, especially for not very sick kids, will be very small. The neonatologists in all centers, participating in this study are very aware of the study and include all patients. As we have a waiver from the MEC, informed consent is not necessary and all neonates are included.

We will report the patients who do not participate for any reason, as well. At this moment, there are none.

Diagnosis of CVC-related thrombosis: a) the clinical recognition of DVT relies on experience. Because the body of nurses working in NICUs rotates, the authors may consider having a horizontal person per NICU to review the patients included to ensure that some type of "clinical adjudication" exists; b) the same applies to imaging (i.e. imaging adjudication vs. imaging performed could be reviewed by local expert in vascular imaging in neonates and infants).

We agree with the reviewer that clinical recognition of DVT relies on experience, as well as imaging. Therefore, at all NICUs at least one neonatologist is responsible for this. That is just how it goes “in the real world” as well. So, this study is a copy of how it usually goes on the NICUs in the Netherlands. So probably some DVT will be missed, but they would not be treated anyway.

On the topic of DVT recurrence: a) the DVT-risk stratification of NEOCLOT encompasses either a vein within the deep venous system or the right atrium. A third potential category of CVC-related thrombotic events that may also be considered separately in the neonatal population would be the portal vein.

The portal vein in included in the catheter-related VTE in the vein.

Some of the DVTs detected in neonates are identified when the thrombus is already in a sub-acute/chronic state and this has not been taken into consideration in the risk stratification algorithm (i.e. calcification). This will be important, particularly in the "wait and see" patient category.

It will be difficult to define whether a thrombus is new or old. We will probably treat all thrombi as new as we cannot make a differentiation. However, if we will find calcification,
which will be very scarce, we will follow wait and see protocol. In the database one can explain why one followed that regime.

For DVT recurrence and lab. monitoring, the anti-Xa kit used amongst the 10 NICUs may differ; this may need to be addressed in the evaluation of the DVT recurrence results, particularly if the recurrence rates differ amongst the NICUs.

This might be true. However, the target anti Xa level which is used for all neonates is the same in all hospitals. This is the most important item we need to know for recurrence. This is an observational study, adjustments for anti Xa will be done based on the results of anti Xa performed in the various hospitals, with their own antiXa kits. We will note every anti-Xa and adjustment and control- anti Xa measurements in the database.

For DVT risk factors and DIC, I would bring to the authors' attention that ISTH has DIC criteria available, which they may consider as an alternative to the one provided.

We used the DIC criteria of the ISTH. To our knowledge, there are no specific pediatric ISTH DIC criteria available. The score mentioned in the article of Levi et al. is the ISTH score. But to make it clearer we changed the reference.

Page 16

Regarding bleeding, while ISTH has standardized criteria for bleeding secondary to anticoagulation in children, there may be additional bleeding scores that could be seen as more suitable for patients in an intensive care unit setting. For example, the authors may consider the one published in the Arch Dis Child Fetal Neonatal Ed. 2013 May;98(3):F260-3. doi: 10.1136/archdischild-2012-302443. Epub 2012 Nov 9.

Thank you very much for this suggestion.

The NeoBat is not used very often in other neonatal studies, so we prefer to use the bleeding definitions as given by the ISTH for use of anticoagulants in children.
As in neonates cerebral hemorrhages might be an important complication, we used the definition of the PLANET study to define these bleedings and to divide them in major and non major clinical relevant and minor bleeding complications..

For post-thrombotic syndrome (PTS): neonates and infants will be followed for at least 1 year. It is very likely that at the time of their PTS evaluation, the report will only be feasible by proxy. Currently, both pediatric PTS tools, the modified Villalta and the Manco-Johnson Scale, have limitations particularly in this age range. Hence, the authors may consider using a scale already validated, when obtained by proxy.

When we started this study only the two mentioned scales were available. We have chosen to use the Modified Villalta scale as this is the most often used scale in the Netherlands and it is easy to use, also for neonatologists. Furthermore, it is advised as one of the scores which can be used by the ISTH (Goldenberg NA JTH 2012).

We are going to assess the PTS after 5 years as well and will use the new scale (CAPTSure TM) Avila et al. JTH 2016 14:2376-2385 in addition.

Reviewer 3

Page 10. Lines 26-31 and 46. Not clear why a project that was not considered Human Subjects or requiring IRB review, does require written or oral consent from families? The reviewer is completely right. No informed consent is needed. We deleted this exclusion criterion.

Page 14. Lines 19-22. When do these ultrasounds take place? 4 weeks? 6 weeks? Ideally these ultrasounds are performed at 6 weeks. However, when a child is discharged after 4 weeks, an ultrasound will be performed before discharge. So these ultrasound are usually made between 4 to 6 weeks.

We added this to the manuscript. Page 14
Page 16. Will data collection be actively performed by research assistants at the bedside? Or will there be reliance only on what already appears in the medical record?

There is a data-sheet which will be filled in at the bedside. But probably some of the data will be extracted from the medical record.

Page 16. Lines 27-37. Where will these follow-up visits take place? Hematology clinics? At what specified time points?

All neonates on the NICU will be followed at the NICU outpatient clinic. Regular controls are after 1 year, 2 years and 5 years. At the same time development of the child will be checked. We added that to the manuscript.

Page 16

Page 17 Table 3 could be deleted - not a main focus of the paper and the reference is provided.

We deleted table 3.

Page 17 Lines 46-51. How can this logistic regression be performed when only patients with CVC-thrombosis are included in the study? No control population is described. The reviewer is right. We can only show percentages of risk factors in neonates with thrombosis.

We changed that in the manuscript.

Page 17

Page 25. Figure 1. In the occlusive column, when does that ultrasound take place? If a patient with high risk thrombosis has complete resolution after 24 hours of tPA, anticoaguation would really be stopped completely?

Thanks for the comment.
During thrombolysis ultrasonography will be performed at least once daily (see protocol thrombolysis, table 1)

When thrombolysis is stopped, LMWH will be started, even as the clot has disappeared.(see figure 1 and 2: thrombolysis max of 72 hours followed by LMWH)

After 4 to 6 weeks, ultrasonography will be performed.

If the clot is still not there, LMWH will be stopped.

We added this to the manuscript.

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