PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The CATERPILLAR-study protocol: an assessor-blinded randomized controlled trial comparing taurolidine-citrate-heparin to heparin-only lock solutions for the prevention of central-line associated bloodstream infections in paediatric oncology patients
AUTHORS	van den Bosch, Ceder; Loeffen, Yvette; van der Steeg, Alida; van der Bruggen, Jan-Tom; Frakking, Florine; Fiocco, Marta; van de Ven, Cornelis; Wijnen, Marc; van de Wetering, Marianne

VERSION 1 – REVIEW

REVIEWER	Dydak, Karolina Wroclaw Medical University
REVIEW RETURNED	05-Dec-2022

GENERAL COMMENTS	One thing I miss is a description of how the results of the TCHL-study arm patients will be analyzed if in the shared care centers or at home a regular heparin lock is instilled after the TCHL is used. Authors wrote that patients will not be excluded from the study in such a case. in my opinion, it will be valuable to describe how the results will be classified in this case - what if CLABSI occurs after changing TCHL to HL? Will be the HL changed immediately after the patient arrives to the Princess Máxima Centre or after 1 or 3 weeks? If TCHL is changed to HL, will the patient still be classified in the TCHL- study group or will be transferred to the HL-group and subsequent locks also be HL? I am guessing that completely avoiding TCHL being replaced with HL will be logistically difficult or impossible, so I believe that if patients are not excluded for this reason, a more detailed description of the procedure in such a situation should be included in the protocol.

REVIEWER	Sinha, Arpan The University of Oklahoma Health Sciences Center, Pediatrics
REVIEW RETURNED	24-Jan-2023

GENERAL COMMENTS	The authors present a study protocol for a randomized control trial to evaluate efficacy of taurolidine containing lock solutions for the prevention of CLABSI in pediatric oncology patients. This study protocol has potential benefit if the trial is successful. The protocol is overall comprehensive and well-written. Comments - Specific - Some sentences in the abstract are difficult to follow. The abstract will benefit from language editing. - Tunneled CVAD/CVAD/Tunneled external CVAD are used interchangeably at places, it will be helpful to keep them distinct especially since tunneled catheters are a subgroup within all

	CVAD. For e.g. – In introduction (page 5 -line 80) – CVAD might be more appropriate than tunneled CVAD. It might also help the reader to add a few introductory sentences on types of CVADs to help clear the distinction between the types/subgroups. - As the rates of infections/complications may vary between tunneled catheters vs others - subgroup analyses between the two groups will be very relevant. - Similarly, as complication rates may vary between different oncology diagnosis – e.g. leukemia/lymphoma vs solid tumors and often the diagnosis guides type of CVAD; inpatient vs outpatient treatment; and incidence of complications - it will be helpful to keep the groups similar to eliminate confounding factors as much as possible.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer 1 Karolina Dydak, Wroclaw Medical University	**Reply**	**Page**
One thing I miss is a description of how the results of the TCHL-study arm patients will be analysed if in the shared care centres or at home a regular heparin lock is instilled after the TCHL is used. Authors wrote that patients will not be excluded from the study in such a case. in my opinion, it will be valuable to describe how the results will be classified in this case - what if CLABSI occurs after changing TCHL to HL? Will be the HL changed immediately after the patient arrives to the Princess Máxima Centre or after 1 or 3 weeks? If TCHL is changed to HL, will the patient still be classified in the TCHL- study group or will be transferred to the HL-group and subsequent locks also be HL? I am guessing that completely avoiding TCHL being replaced with HL will be logistically difficult or impossible, so I believe that if patients are not excluded for this reason, a more detailed description of the procedure in such a situation should be included in the protocol.	Thank you for your review and feedback. This was indeed not thoroughly described in the method section, we added more information in the “Design and setting” part of the manuscript. Furthermore, all patients will be analysed in the intervention group they were initially randomized in, this note is added to the statistical analysis part of the manuscript.	Page 5-6, line 149-162 Page 14, line 410-411

Reviewer 2 Dr. Arpan Sinha, The University of Oklahoma Health Sciences Center	**Reply**	**Page**
The authors present a study protocol for a randomized control trial to evaluate efficacy of taurolidine containing lock solutions for the prevention of CLABSI in pediatric oncology patients. This study protocol has potential benefit if the trial is successful. The protocol is overall comprehensive and well-written.	Thank you for these kind comments.	
Some sentences in the abstract are difficult to follow. The abstract will benefit from language editing.	Thank you, we revised the language in the abstract.	Page 2, line 32-50
Tunneled CVAD/CVAD/Tunneled external CVAD are used interchangeably at places, it will be helpful to keep them distinct especially since tunneled catheters are a subgroup within all CVAD. For e.g. – In introduction (page 5 -line 80) – CVAD might be more appropriate than tunneled CVAD. It might also help the reader to add a few introductory sentences on types of CVADs to help clear the distinction between the types/subgroups.	Thank you for this comment, we added an extra sentence to the introduction and design and setting section. Also, we checked/corrected all sentences with CVAD in it.	Page 4, line 100-101
As the rates of infections/complications may vary between tunneled catheters vs others - subgroup analyses between the two groups will be very relevant. Similarly, as complication rates may vary between different oncology diagnosis – e.g. leukemia/lymphoma vs solid tumours and often the diagnosis guides type of CVAD; inpatient vs outpatient treatment; and incidence of complications - it will be helpful to keep the groups similar to eliminate confounding factors as much as possible.	Thank you for this comment. This was indeed not yet described in the statistical method section. A sentence has now been added.	Page 15, 437-438

VERSION 2 – REVIEW

REVIEWER	Dydak, Karolina Wroclaw Medical University
REVIEW RETURNED	09-Mar-2023

GENERAL COMMENTS	I have no remarks on the revised version of the manuscript.