PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Tailored anticoagulant treatment after a first venous thromboembolism: Protocol of the Leiden Thrombosis Recurrence Risk Prevention (L-TRRiP) study, a cohort-based randomised controlled trial
AUTHORS	Burggraaf - van Delft, Louise; van Rein, Nienke; Bemelmans, Remy; van den Berg, Jan-Willem; Bruggeman, Coty; Cloos - van Balen, Marissa; Coppens, Michiel; Eefting, Matthijs; Ende - Verhaar, Yvonne; van Es, Nick; van Guldener, Coen; de Jong, Wouter; Kleijwegt, Fleur; Koster, Ted; Kroon, Cees; Kuipers, Saskia; Leentjens, Jenneke; Luijten, Dieuwke; Mairuhu, Albert; Meijer, Karina; van de Ree, Marcel; Roos, Rick; Schrover, Ilse; Swart, Janneke; van der Velden, Annette; van den Akker-van Marle, Elske; le Cessie, S; Geersing, Geert-Jan; Middeldorp, Saskia; Huisman, Menno; Klok, Frederikus; Cannegieter, Suzanne; L-TRRiP investigators, .

VERSION 1 – REVIEW

REVIEWER	Rodger, Marc First author of HERDOO2 derivation and validation studies.
REVIEW RETURNED	05-Sep-2023

GENERAL COMMENTS	Important area of research- duration of anticoagulation after VTE is most vexing problem in the area. Concerns: 2 year-endpoint: should be justified. Since this is an indefinite treatment decision why are you only studying outcomes at 2 years? Why not longer horizon to capture more time in "less risky (bleed and recurrent)" longer-term interval where the trade-off may be diferent? Minor: Pg 20 line 8- who says estrogen associated VTE are "provoked"? They have a similar risk of recurrence of VTE if age matched. High risk HERDOO2 women with estrogen associated VTE had high recurrence risk- you are making similar argument by including provoked VTE in your study i.e. there may be a sub-group with high recurrence risk...

REVIEWER	Kopec, Grzegorz Jagiellonian University Medical College
REVIEW RETURNED	07-Dec-2023

GENERAL COMMENTS	Great project within very experienced group. Congratulations. More international approach could be considered if feasible.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Marc Rodger
Comments to the Author:
Important area of research- duration of anticoagulation after VTE is most vexing problem in the area.

Concerns:

2 year-endpoint: should be justified. Since this is an indefinite treatment decision why are you only studying outcomes at 2 years? Why not longer horizon to capture more time in "less risky (bleed and recurrent)" longer-term interval where the trade-off may be different?
This follow-up duration was chosen since the L-TRRiP prediction model used to determine the risk of VTE recurrence predicts the absolute risk of a VTE recurrence within two years. However, we fully agree with your concern that the follow-up of 2 years is short given the indefinite nature of the treatment decision. Therefore, we have indeed recently decided to extend follow-up duration of all participants until 2027/2028, providing a follow-up duration up to 6 or 7 years for the participants that have been recruited early in the trial. Since the trial was originally set up to have enough power for our primary outcome (the combined incidence of recurrent VTE and major bleeding after two years) this will remain our primary outcome. The incidence of recurrent VTE and major bleeding during the entire follow-up duration will be a secondary outcome. An amendment for this extended follow-up duration was submitted to the METC in September 2023 and approved in October 2023. We have changed the manuscript (abstract, Methods and analysis – Follow-up) according to this amendment.

*Abstract: we added the following sentence: '*All patients will be followed for at least two years.'

Methods and analysis – Follow-up: This paragraph is now reads as follows:
*'*All patients (both the randomised and the non-randomised groups) are followed for at least two years. The follow-up starts at the routine three month visit after the first VTE, shortly after randomisation, if applicable. During the first two years they will fill in a standardised questionnaire every three months, which is sent and processed by the coordinating centre. After the first two years of follow-up patients will fill in a questionnaire once every year for the remaining study duration (i.e., as expected until 2027), implying that the total duration of follow-up is expected to vary between two (patients enrolled in 2025) and six years (patients enrolled in 2021). Since the follow-up beyond two years was not originally planned, but added to the protocol in an amendment which was approved in October 2023, patients enrolled before this time will be asked separately for informed consent for the additional follow-up period.
The follow-up questionnaires are set up to screen for recurrent VTE, (major) bleeding events and other (severe) adverse events. To prevent missing outcome information, we will contact patients by telephone when they do not return the questionnaire. In addition, at the time of inclusion patients provide consent to request information on recurrent VTE and bleeding from their treating physician and general practitioner, which allows us to collect information from them and detect the primary outcomes even if a patient does not respond to the questionnaires. […]'

Minor:
Pg 20 line 8- who says estrogen associated VTE are "provoked"? They have a similar risk of recurrence of VTE if age matched. High risk HERDOO2 women with estrogen

associated VTE had high recurrence risk- you are making similar argument by including provoked VTE in your study i.e. there may be a sub-group with high recurrence risk...
According to the editor's comments the paragraph containing this sentences was moved to the introduction in a modified format, in which this sentence was removed.

Reviewer: 2
Dr. Grzegorz Kopec, Jagiellonian University Medical College
Comments to the Author:
Great project within very experienced group. Congratulations. More international approach could be considered if feasible.
Thank you for comment. For logistic and financial reasons we decided to set up the trial in the Netherlands. However, we are open to international collaboration.

VERSION 2 – REVIEW

REVIEWER	Kopec, Grzegorz Jagiellonian University Medical College
REVIEW RETURNED	06-Feb-2024

GENERAL COMMENTS	Very nice study- look forward to the results.