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# 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



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**Title**

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

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## ABSTRACT

### Introduction

Patients with a first venous thromboembolism (VTE) are at risk of recurrence. Recurrent VTE can be prevented by extended anticoagulant therapy, but this comes at the cost of an increased risk of bleeding. It is still uncertain whether patients with an intermediate recurrence risk or with a high recurrence and high bleeding risk will benefit from extended anticoagulant treatment, and whether a strategy where anticoagulant duration is tailored on the predicted risks of recurrent VTE and bleeding can improve outcomes. The aim of the Leiden Thrombosis Recurrence Risk Prevention (L-TRRiP) study is to evaluate the outcomes of tailored duration of long-term anticoagulant treatment based on individualised assessment of recurrent VTE and major bleeding risks.

### Methods and analysis

The L-TRRiP study is a multicentre, open-label, cohort-based, randomised controlled trial, in which patients with a first VTE will be included. We classify the risk of recurrent VTE (low, medium, high) and major bleeding (low, high) using the L-TRRiP and VTE-BLEED scores, respectively. After three months of anticoagulant therapy, patients with a low recurrent VTE risk will discontinue anticoagulant treatment, patients with a high recurrent VTE and low bleeding risk will continue anticoagulant treatment, whereas all other patients will be randomised to continue or discontinue anticoagulant treatment. Inclusion will continue until the randomised group consists of 608 patients. The primary outcome is the combined incidence of recurrent VTE and major bleeding in the randomised group after two years of follow-up. Secondary outcomes include the incidence of recurrent VTE and major bleeding, functional outcomes, quality of life and cost-effectiveness in all patients.

### Ethics and dissemination

The protocol was approved by the Medical Research Ethics Committee Leiden – Den Haag – Delft. Results are expected in 2028 and will be disseminated through peer-reviewed journals and during (inter)national conferences.

**Trial registration number**

NL9003, NCTxxxx

**Strengths and limitations of this study**

> This is the first randomised trial using prediction models for both risk of recurrent VTE and major bleeding to guide an individualised decision on treatment duration after a first VTE.

> The models can be applied to all patients with a first VTE event without cancer, irrespective of whether this event was provoked or unprovoked.

> After the regular VTE treatment for three months, we will randomise to continuing or discontinuing anticoagulation in patients for whom the risks and benefits of extended anticoagulation are uncertain.

> This is an open-label trial, which might increase cross-over between treatment groups and hence dilute their contrast.

## INTRODUCTION

Patients with a first venous thromboembolism (VTE) are at risk of a recurrent event, especially when the first event was unprovoked. The estimated risk of recurrence in patients with a first unprovoked VTE was 10% in the first year and 36% after ten years,[1] whereas patients with a first VTE provoked by a transient risk factor have an estimated risk of 1-6% in the first year and 3-15% after five years, depending on whether the provoking factor was a minor or major transient risk factor.[2 3] A recurrent VTE has serious consequences with estimated case fatality rates of 4%.[1 4] In addition, compared with the initial event, recurrent VTE is associated with a higher risk of long-term complications such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension.[5 6] Recurrent VTE can be prevented by prolonged oral anticoagulant therapy, but this comes at the cost of an increased risk of major bleeding compared with ceasing treatment.[7 8] A recent meta-analysis reported an overall major bleeding incidence of 1.7 per 100 person-years during extended use of vitamin K antagonists (VKAs) and 1.1 per 100 person-years during extended use of direct oral anticoagulants (DOACs), with a case fatality rate of 8.4%.[9] Importantly, the same meta-analysis reported limited safety information on long-term anticoagulation in VTE patients, in particular for DOAC recipients where information beyond one year of treatment was sparse. Indeed, indefinite use of anticoagulant therapy may result in a significant lifetime risk of major bleeding, a risk that is still to be quantified.

Consequently, the optimal duration of anticoagulant treatment is still under debate. Previously, patients received oral anticoagulant treatment for a fixed period (i.e., 3-6 months) after a first VTE, whereas current guidelines recommend to base treatment duration, (i.e. either a limited period or indefinite duration), on the balance between the risk of recurrent VTE and major bleeding.[10-15] Indefinite treatment should be considered for patients with a first unprovoked VTE given its higher associated recurrence risk, and it is recommended to discontinue anticoagulant treatment after three months for patients with a provoked VTE. However, the definition of provoked

VTE varies between guidelines, between centres, and over time, highlighting the clinical ambiguity surrounding this decision.[16] In addition, basing the decision on treatment duration solely on the classification of the first event into provoked or unprovoked may be too crude: a study from our group showed that the c-statistic of the (un)provoked status was only 0.61, indicating that the ability to distinguish patients at low and high risk of recurrence is limited. In fact, 15% of patients with a first provoked VTE had a predicted two-years recurrence risk of more than 10%, whereas this risk was below 10% in 45% of the patients with a first unprovoked VTE.[17] This finding indicates that these patient groups would have been under- or overtreated if the current guidelines were strictly followed (without accounting for bleeding risk or patient preferences).[11-15 17] Furthermore, guidelines advise to take the risk of major bleeding into account, but guidance on how to best assess the risk of major bleeding and balance this against the risk of VTE is not available.[11-15 18] Moreover, studies investigating the optimal duration of anticoagulation in relation to patient-relevant outcomes such as quality of life are lacking.[19] Therefore, in current clinical practice the decision to stop or continue treatment indefinitely is based on insufficient information. For these reasons, more elaborate individualised risk stratification in combination with knowledge on the optimal treatment duration, linked to these risks, is expected to reduce both types of serious complications.

Multiple prediction models have been developed to assess the risk of VTE recurrence and major bleeding in VTE patients.[20 21] At the time we started to design the present study (2018), models for the prediction of VTE recurrence included the Men and HERDOO2 rule, Vienna prediction model, DASH score, DAMOVES score, pre- and post D-dimer strategy, Worcester VTE score, and L-TRRiP model.[17 22-27] Of these, the L-TRRiP model is the only externally validated model that predicts long-term recurrence risk after a provoked as well as an unprovoked first VTE, which allows for easier use given the problems related to the distinction between provoked and unprovoked VTE as described above. In addition, it allows for more precise risk stratification by providing an absolute recurrence risk, rather that dichotomising high and low recurrence risk. Another advantage of the L-TRRiP model is that all parameters can be determined *during* anticoagulant treatment, so

interruption or discontinuation of the treatment is not required, in contrast to some other models that include D-dimer, a biomarker predictor that needs to be measured after a short interruption of anticoagulation. Besides being unpractical, such interruption – albeit relatively rare – may lead to early recurrent VTE events shortly after discontinuation.[28] Models to predict major bleeding during anticoagulant therapy have mainly been developed for atrial fibrillation (AF) patients. Examples of such models are the HAS-BLED score and HEMORR$_2$HAGES score.[29 30] Nevertheless, in current clinical practice these models are sometimes also used to predict major bleeding among VTE patients.[12 18] However, patient characteristics differ between AF and VTE patients, and the predictive performance of these models in VTE patients is limited.[20] Therefore, dedicated models for VTE patients have been developed, which include the score developed by Kuijer et al., the ACCP risk table, the RIETE score, and VTE-BLEED score.[11 31-34] Of these, the VTE-BLEED score is among the most externally validated models, has been validated during extended anticoagulant therapy and has shown a good predictive performance in patients using VKAs as well as in those using DOACs.[18 35-38]

In summary, the current strategy to decide on (dis)continuation of anticoagulant treatment after a first VTE is not optimal since 1) the definition of provoked VTE is subject to debate, 2) the insufficient discriminative power of a distinction between provoked and unprovoked VTE is disregarded, and 3) the risk of major bleeding is not properly taken into account. This results in both over- and undertreatment with anticoagulants in a proportion of patients with a first VTE, leading to unnecessary high life-time risks of major bleeding or recurrent VTE, respectively. Therefore, in the Leiden Thrombosis Recurrence Risk Prevention (L-TRRiP) study we aim to evaluate outcomes of tailored duration of anticoagulant treatment based on individualised risk assessment of a patient's recurrent VTE and major bleeding risk, using both the L-TRRiP and VTE-BLEED model.

## METHODS AND ANALYSIS

### Study design

The L-TRRiP study is a multicentre, open-label, cohort-based randomised controlled trial. The L-TRRiP and VTE-BLEED prediction models are used to individually classify patients according to their risk of recurrent VTE (as low, intermediate, or high) and major bleeding (as low or high), respectively. After the initial three months, anticoagulant treatment is stopped in patients with a low recurrent VTE risk, while patients with a high recurrent VTE risk and low major bleeding risk continue treatment. Patients in the other risk groups (i.e., patients with an intermediate recurrent VTE risk or a high recurrent VTE risk and high bleeding risk) are randomised to continue or discontinue anticoagulant treatment (**figure 1**). All patients, both in the non-randomised and randomised arms, are followed for two years, following the same procedures. Academic hospitals, teaching hospitals, and general hospitals from the Netherlands participate in this trial. At this time, the trial has started enrolment in 17 hospitals (see list of collaborators); the first patient was enrolled in June 2021. The L-TRRiP study is registered at the Dutch Trial Registry: NL9003 and ClinicalTrials.gov: NCTxxxx. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines were followed when drafting the study protocol.

**Study population**

Patients with a first confirmed symptomatic distal or proximal deep venous thrombosis (DVT) of the lower extremity or pulmonary embolism (PE) with an indication for anticoagulant treatment for at least three months, aged 18 years or above, who provide informed consent prior to any study specific procedure, are eligible to participate in this trial. Patients with active cancer, known antiphospholipid syndrome, those who have an indication other than VTE for prolonged anticoagulant treatment (e.g., atrial fibrillation) or who have an indication for long-term antiplatelet therapy in addition to the use of oral anticoagulation (e.g., recent acute coronary syndrome ) at the time of enrolment will be excluded. Diagnostic testing for malignancy or antiphospholipid syndrome after the index VTE diagnosis is performed at the discretion of the treating physician. Patients with

VTE related to severe COVID-19 (i.e., requiring hospital admission in three months before the index event) as well as patients with vaccine-induced immune thrombotic thrombocytopenia (VITT) are not eligible to participate in this trial since the effect of these conditions on recurrence is not known, and such patients were not included in derivation of the L-TRRiP model.[17]

**Risk prediction models**

The L-TRRiP model includes sex, type and location of VTE, risk factors for VTE, history of cardiovascular disease as well as blood group non-O and the factor V Leiden mutation to predict the absolute two-year risk of recurrent VTE. A predicted two-year VTE risk below 6% is classified as low, a VTE risk of 6-14% as intermediate and a VTE risk above 14% as high (see **Table 1**).[17] The VTE-BLEED model uses age of 60 years or higher, renal dysfunction, anaemia, history of clinically relevant or major bleeding, active malignancy, and uncontrolled hypertension in male patients to predict major bleeding risk. A score <2 is classified as low bleeding risk and a score ≥2 as high bleeding risk (**Table 2**).[33]

**Procedures**

After providing informed consent, patients are asked to fill in a questionnaire including demographic variables, clinical circumstances and risk factors for the first VTE, and past medical history including previous bleeding. Furthermore, a self-administered buccal swab is taken to assess the factor V Leiden mutation and ABO blood group by DNA analysis. Information is obtained from the electronic health records from the hospital including recent haemoglobin level, renal function, blood pressure, comorbidities, and details regarding the first VTE event (type and location of VTE).

Based on this information, the L-TRRiP and VTE-BLEED scores and corresponding risk categories are calculated in the coordinating centre (Leiden University Medical Center). Depending

on the risk category of the patient, a decision on duration of treatment is either made immediately, or the duration of treatment is randomised (**Figure 1**).

When applicable, randomisation is performed shortly before the routine three month visit in the coordinating centre using the randomisation function in CastorEDC to ensure concealment of treatment allocation.[39] Randomisation is performed in a 1:1 ratio, using variable block randomisation with a block size of two, four, or six stratified by study centre, risk group for recurrent VTE and bleeding to ensure equal distribution of the patients. The treating physician receives the risk classification of recurrent VTE and major bleeding risk, and the corresponding treatment duration or outcome of randomisation shortly before the routine three month visit and discusses this with the patient.

Patients who are allocated to continue anticoagulant treatment can remain on the same anticoagulant or switch anticoagulants at the discretion of their treating physician. In the Netherlands, DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) as well as VKAs (acenocoumarol and phenprocoumon) and low-molecular-weight heparins (LMWHs) are registered for the treatment of VTE. Dose reduction of apixaban or rivaroxaban according to current guidelines after the initial six months is allowed, at the discretion of the treating physician. In case the treating physician and/or patient decides to deviate from the treatment duration, the reasons for deviation are registered, and patients will complete follow-up as usual.

**Follow-up**

All patients (both the randomised and the non-randomised groups) are followed for two years during which they will fill in a standardised questionnaire every three months, which is sent and processed by the coordinating centre. The follow-up starts at the routine three month visit after the first VTE, shortly after randomisation, if applicable. The questionnaire is set up to screen for

recurrent VTE, (major) bleeding events and other (severe) adverse events. In case of a reported recurrent VTE or bleeding event, additional information is retrieved from the medical records of the hospital or general practitioner for adjudication. Adverse events related to the study intervention are registered. All severe adverse events, including death and non-elective hospitalisation, are reported to the institutional review board. The questionnaire is also used to evaluate anticoagulant treatment use and remaining symptoms of VTE. Furthermore, we evaluate quality of life by means of the EQ-5D-5L questionnaire.[40] Also, functional recovery is assessed using the post-VTE functional scale (PVFS).[41 42] In order to perform a cost-effectiveness analysis, we measure healthcare consumption and productivity losses by using Medical Consumption Questionnaire (iMTA MCQ) and Productivity Costs Questionnaire (iMTA PCQ) from the institute for Medical Technology Assessment. All questionnaires are offered digitally (via CastorEDC) or by regular mail as preferred by the participant.

Overall, the study is designed to follow general clinical practice as closely as possible, to optimize generalisability of the results, and to lower the burden for the patients.

**Outcomes**

For the randomised group, the primary outcome is a composite endpoint of recurrent VTE and major bleeding. Recurrent VTE is diagnosed after clinical suspicion is objectively confirmed by diagnostic imaging, according to current guidelines.[43 44] Bleeding events will be classified as major, clinically relevant non-major (CRNMB) or minor according to the current guidelines of the International Society of Thrombosis and Haemostasis (ISTH): major bleeding is defined as fatal bleeding, symptomatic bleeding in a critical area or organ or bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; CRNMB is defined as any bleeding that does not fit the criteria for major bleeding, but

does require medical intervention, lead to hospitalisation or increased care level or prompt face to face evaluation.[45 46]

All clinical outcomes will be evaluated and classified by an independent committee blinded for treatment allocation using discharge letters, radiology reports and other relevant information retrieved from the medical records. In case of a recurrent VTE or (major) bleeding event, patients will be treated according to the local clinical practice, meaning that (dis)continuing anticoagulant treatment at that point is at the discretion of the treating physician.

Secondary outcomes are 1) the combined incidence of recurrent VTE and major bleeding events weighted by the associated loss of quality adjusted life years (QALYs) in the randomised group; 2) cost-effectiveness of prolonged anticoagulant treatment compared to discontinuation in the randomised groups; 3) the incidence of recurrent VTE and major bleeding in the non-randomised groups; 4) the incidence of CRNMB in all groups; 5) the predictive performance (discrimination and calibration) of the L-TRRiP and VTE-BLEED model in the arms that discontinue and continue, respectively and 6) the natural course of recovery from a first acute VTE with regard to long-term functional limitations using the PVFS.

**Data collection**

Data are collected and stored pseudonymised using the web-based data management platform CastorEDC.[39] Personal information of included participants is securely shared with the coordinating centre for them to send the questionnaires and buccal swab and contact the participants if needed. To optimize data quality, the digital data collection forms include checks for important study variables, such as range checks for continuous variables, check of the assigned risk categories, and verification of relevant medical history included in the prediction models by both the study team as well as the patient (via the baseline questionnaire).

**Sample size calculation**

The sample size of this study is based on the randomised part of the study. Based on the estimated risks of recurrent VTE and major bleeding as observed in the derivation studies of both prediction models,[17 33] we assume an overall two-year recurrent VTE risk of 10% in the discontinuation arm of the randomised groups and a major bleeding risk of 0.6%. Assuming a reduction of the recurrent VTE risk of 85% by anticoagulant treatment, the recurrent VTE risk of the group that continues anticoagulant treatment will be 1.5%. Furthermore, we estimate this will lead to an increase in the overall risk of major bleeding to 2.1%. To demonstrate a 7% absolute difference in the combined endpoint (i.e., 10.6% vs 3.6%) with an alpha of 0.05 and a power of 90%, we need a sample size of 552 subjects for the randomised part of the study. Taking into account a drop-out rate of 10%, we aim to include 608 patients in the randomised part of the study. Based on the derivation studies we expect the randomised group to form about 38% of the total included population, in which case we expect to include approximately 1600 patients in total; 848 (53%) in the low VTE recurrence risk group and 144 (9%) in the high recurrence and low bleeding risk group.[17 33] Of note, these numbers may change depending on the final proportion of the randomised group.

**Data analysis plan**

Baseline characteristics will be summarised using descriptive statistics (mean, standard deviation [SD] or medium, interquartile range (IQR); number, percentage). Furthermore, we will present the number of patients who continued anticoagulant treatment while being allocated to discontinuation and vice versa (cross-over), including the reason for switching anticoagulant treatment. In case of missing data we will perform multiple imputation if indicated (depending on the amount and nature of the missingness) and pool the results according to Rubin's rules.[47]

*Randomised group:*

Following an intention-to-treat analysis, the cumulative incidence of the primary outcome in the randomised group will be estimated using the cumulative incidence competing risk method, accounting for the competing risk of death from other causes than VTE or major bleeding. Follow-up will start at the time of the three month visit. We will censor patients when they withdraw informed consent, are lost to follow-up, or reach the end of the study follow-up period. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) will be estimated using a Cox regression model.

As secondary analyses, we will perform a per-protocol analysis, in which patients who did not receive the allocated treatment during the complete follow up will be censored at the time of the protocol deviation. In case of a different distribution of risk factors between the treatment groups due to chance, adjusted HRs and 95% CIs will be estimated. The primary outcome (i.e., recurrent VTE and major bleeding) will be weighted for the impact on quality of life (EQ-5D) and functional limitations (PFVS) (in two separate analyses) using the difference between the measures taken after and the last one before the event as weights. Furthermore, we will estimate the incidence of CRNMB and assess repeated events (e.g. CRNMB followed by major bleeding) using negative binomial regression.

Health-care costs will be calculated using Dutch standard prices for economic evaluations.[48] [49] Absence from work will be valued with friction cost method. QALYs will be assessed using the EQ-5D-5L scores (Dutch tariff[50]) at different timepoints, using the area-under-the-curve approach. The economic evaluation will consist of a cost-effectiveness analysis, comparing costs per event, as well as a cost-utility analysis, comparing costs per QALY. In net-benefit analysis, costs will be related to effectiveness and presented in a cost-effectiveness acceptability curve.

*Non-randomised group:*

The two-years cumulative incidences of recurrent VTE, major bleeding and CRNMB in the non-randomised groups will be calculated, using the same approach as in randomised groups.

*All participants:*

We will assess the difference in recommended treatment duration as allocated in the study to treatment duration according to the guidelines (i.e. continuation in unprovoked and discontinuation in provoked VTE). We will determine the predictive performance of the L-TRRiP model in all patients that discontinued anticoagulant treatment (since the L-TRRiP model is developed to predict the risk of VTE recurrence after discontinuation) by creating a calibration plot containing the observed and predicted two-years risks of recurrent VTE. Likewise, we will determine the predictive performance of the VTE-BLEED model in all patients who continued anticoagulant treatment, although observed risks will be plotted against the total score as absolute predicted risks are not provided by the model. For the analysis of functional recovery, an ordinal logistic regression model will be used.

**Patient and Public Involvement statement**

The L-TRRiP study is investigator initiated. An advisory board, consisting of five patients with a history of VTE, is involved in the practical implementation of the trial, such as patient recruitment and dissemination of study results among patients. In order to make the results of the study accessible to patients, we will publish a Dutch summary.

**ETHICS AND DISSEMINATION**

The L-TRRiP study will be conducted according to the principles of Good Research Practice and in accordance with the applying Dutch laws (the Medical Research Involving Human Subjects Act [WMO] and General Data Protection Regulation [GDPR]). The protocol is approved by the Medical

Research Ethics Committee Leiden – Den Haag - Delft, the Netherlands. Monitoring will be executed by monitors working for the coordinating centre who are independent of the study investigators, to ensure compliance with the protocol, Good Research Practice and legal aspects.

Results are expected in 2028. Our aim is to disseminate the results by publication in peer-reviewed journals, professional societies, and through presentations on (inter)national conferences according to publication standards. After data collection and data cleaning are finished, deidentified data will be registered in a repository and be made available for further research upon reasonable request to the corresponding author.

**DISCUSSION**

The L-TRRiP study aims to optimize the duration of anticoagulant treatment in patients with a first VTE based on an individual assessment of the risk of recurrent VTE as well as major bleeding. The L-TRRiP study will show whether in patients who have an intermediate risk of recurrent VTE or a high risk of both recurrent VTE and major bleeding (i.e., the randomised group), prolonged anticoagulant treatment is beneficial compared with discontinuing regarding the combined incidence of recurrent VTE and major bleeding events, as well as regarding quality of life, cost-effectiveness and functional outcomes, which are all important outcomes in VTE patients.[42] Next to this, we will assess the predictive performance of the L-TRRiP and VTE-BLEED models in all patients who had to stop or continue anticoagulant treatment, respectively, to determine whether the applied strategy was able to correctly classify patients in different risk groups. Furthermore, we will determine (the course of) functional limitations and quality of life after a first VTE for all patients.

Previous attempts have been made to optimize the length of treatment of patients after a first VTE based on individualised assessment of recurrent VTE risk.[28 51] One study showed a clear benefit of prolonged anticoagulant treatment compared with discontinuation on recurrent VTE in

patients with an unprovoked VTE and elevated d-dimer levels one month after ceasing anticoagulant treatment (2.9% vs 15% during 9-18 months follow-up respectively).[51] However, the incidence of recurrent VTE in patients with normal d-dimer levels (in whom anticoagulation was therefore stopped) was still high (6-7% per patient-year).[51 52] This indicates that d-dimer alone does not differentiate well enough between patients who should continue or discontinue anticoagulant therapy. Another study showed that prolonging anticoagulant treatment based on the Vienna score versus routine clinical care did not improve overall clinical outcome in the randomised groups, albeit that the risk of actual recurrent VTE was indeed low in those with a low predicted risk based upon the Vienna score.[28] Likewise, a management study implementing the HERDOO2 rule showed that women with a low predicted recurrence risk had indeed a low risk of VTE recurrence after anticoagulant discontinuation.[53] However, the majority of these women had a VTE during estrogen use, which in contrast to current standards, was classified as unprovoked. As far as we know, these are the only studies in which a form of individualised risk assessment was used to determine treatment duration after a first VTE. However, these studies did not include patients with a first provoked VTE nor take the bleeding risk of patients into account and did not provide a sufficiently effective strategy for a targeted treatment duration based on individual risk assessment.

**Limitations and strengths**

The L-TRRiP study has several strengths. First, treatment continuation will be randomised for risk categories with an unknown balance between harm and benefit of prolonged treatment. Second, we incorporate the predicted risk of bleeding into the decision to (dis)continue anticoagulant therapy. Third, the models can be applied to all patients with a first VTE, irrespective of whether the event was provoked or unprovoked and thereby avoiding the problems associated with the distinction between these events. Fourth, we follow the usual clinical procedures, including those for diagnosis of VTE recurrence and bleeding as much as possible, hence increasing

the generalisability of the results. Last, we incorporate patient-reported outcomes and cost-effectiveness, which enable us to interpret the primary outcomes in the perspective of the patient (impact on quality of life and functional limitations) and society (costs, loss of work productivity).

A potential limitation is that this is an open-label trial, which might increase the number of deviations from the treatment allocation. However, the choice for an open-label design was a deliberate decision, since such deviations will reflect clinical practice. Furthermore, we are not studying a treatment (the efficacy and safety of the used medication is well known) but a treatment strategy. Also, we expect these deviations will not happen at a large scale, given the uncertainty about (dis)continuing anticoagulation in these groups. Another potential limitation of the open-label design is that it might influence the assessment and reporting of study outcomes by the patient or treating physicians. However, we use well defined clinical outcomes (i.e., recurrent VTE and major bleeding) as primary outcome and all events will be evaluated by a blinded outcome assessment committee. A second limitation is that the first indication that a study outcome has occurred is based on questionnaires, which makes outcome detection dependent on the willingness to fill in the questionnaire and on the accuracy of the answers of the participants or of the reporting of the treating physician. However, to stimulate a high response rate, 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. Lastly, it is a limitation that the L-TRRiP model only provides a two-years predicted risk of VTE recurrence, which is a limited prediction horizon given that continued treatment is indefinitely.

**Conclusion**

In summary, the L-TRRIP study is the first open-label, cohort-based, randomised controlled trial that applies individualised risk assessment to determine anticoagulant treatment duration in patients with a first VTE. Thereby, this trial will provide insight on the optimal treatment duration of anticoagulants in patients with a first VTE through which it is expected that eventually, both thrombotic and bleeding complications will be minimised in this large patient group.

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**Authors contributions**

SCC, MVH, FAK, GJG and SM designed the study. EvdA-vM (health-care economics) and SlC (statistics) contributed to the parts in the protocol on their specific disciplines. JLIB wrote the first manuscript draft. All authors revised the manuscript and gave final approval of the version to be published.

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**Collaborators**

The L-TRRiP Investigators: see **Appendix I**.

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**Conflicts of interest statement**

**MC** has received financial support for research from Bayer, CSL Behring, Roche, Novo Nordisk, and UniQure and lees for lecturing or consultancy from Alexion, Bayer, CSL Behring, Daiichi Sankyo, Sobi, and Viatris, all unrelated to the present work and paid to his institution. **NvE** has received a lecture

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**FIGURES**

**Figure 1. Design of the L-TRRiP study**

**TABLES**

**Table 1. L-TRRiP model**

| Factor | Coefficient |
|---|---|
| Male sex | 0.63 |
| Type of first VTE | |
| PE | -0.61 |
| PE + DVT | 0.32 |
| Location of DVT | |
| Popliteal DVT [a] | -0.46 |
| Surgery [b] | -0.51 |
| Pregnancy/puerperium [b] | -1.49 |
| Hormone use [c] | -0.67 |
| Plaster cast [b] | -0.79 |
| Immobility in bed, in hospital [b, d] | -0.31 |
| History of cardiovascular disease [e] | -0.35 |
| Blood group, non-O | 0.24 |
| Factor V Leiden mutation [f] | 0.40 |
| **Calculation of the L-TRRiP score** | |
| Prognostic score | Beta1*x1 + beta2*x2 + beta3*x3 + …. The x1, x2, x3, etc. represent the factors in the model, and beta1, beta2, beta3 etc. represent the corresponding coefficients. |
| Absolute 2-years risk of VTE recurrence | 1- 0.9235595^exp(prognostic score) |
| **Classification of patients with the L-TRRiP score** | |
| Low recurrent VTE risk | 2-years risk < 0.06 |
| Intermediate recurrent VTE risk | 2-years risk 0.06 - 0.14 |
| High recurrent VTE risk | 2-years risk > 0.14 |

Table adapted from Timp et al.[17]

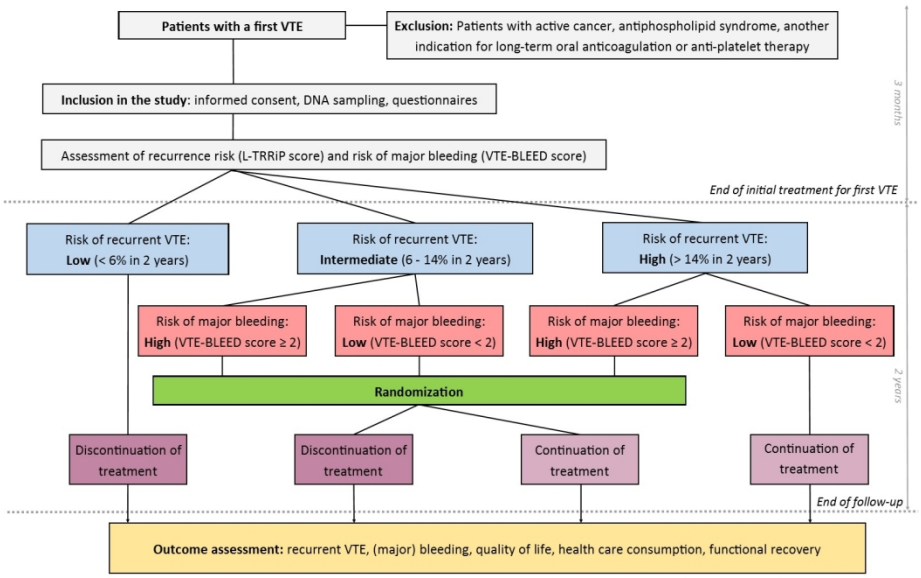
[a] Indicates DVT at the level of the vena poplitea or below. [b] Within three months before VTE. [c] Use of hormonal contraceptives or hormone replacement therapy at the time of VTE. [d] Confinement to bed ≥ 3 days. [e] Including a history of heart failure, angina pectoris, peripheral artery vascular disease (claudication), acute myocardial infarction. [f] Homozygous or heterozygous.

**Table 2. VTE-BLEED model**

| Factor | Score |
|---|---|
| Active cancer [a] | 2 |
| Male with uncontrolled arterial hypertension [b] | 1 |
| Anaemia [c] | 1.5 |
| History of bleeding [d] | 1.5 |
| Age ≥ 60 years old | 1.5 |
| Renal dysfunction [e] | 1.5 |
| **Classification of patients with the VTE-BLEED score** | |
| Low bleeding risk | Total score < 2 |
| High bleeding risk | Total score ≥ 2 |

Table adapted from Klok et al.[35]

[a] Cancer diagnosed within six months before diagnosis of VTE (excluding basal-cell or squamous-cell carcinoma of the skin), recently recurrent or progressive cancer or any cancer that required anti-cancer treatment within six months before the VTE was diagnosed. [b] Value of systolic blood pressure ≥ 140 mmHg at baseline. [c] Haemoglobin < 13 g/dl in men or < 12 g/dl in women. [d] Including prior major or non-major clinically relevant bleeding events, rectal bleeding (more than spotting on toilet paper), frequent nose bleeding or haematuria. [e] Estimated glomerular filtration rate (eGFR) < 60 ml/min at baseline (calculated with Cockcroft-Gault formula).




Design of the L-TRRiP study

297x209mm (150 x 150 DPI)

# Appendix I - Contributors L-TRRiP study; version August 2023

## Participating centres:

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# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 4 and 9 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | See trial register |
| Protocol version | #3 | Date and version identifier | n/a for manuscript, current version of MREC approved protocol is 1.5 (20-10-22) |
| Funding | #4 | Sources and types of financial, material, and other support | 24 |

| | | | |
|---|---|---|---|
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 1, 24 |
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 2 (corresponding author) |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 24 |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | See methods (p9-15) |
| **Introduction** | | | |
| Background and rationale | #6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 6-8 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 6-8 |
| Objectives | #7 | Specific objectives or hypotheses | 8 |

| | | | |
|---|---|---|---|
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 9 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 9 |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 9/10 |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 10/11 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | 10-12 |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | 11,12 |

| | | | |
|---|---|---|---|
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | n/a, no restriction to routine care are made in the trial |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12/13 |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 10-12 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 14 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 9 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce | 11 |

| | | | |
|---|---|---|---|
| | | predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | |
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 11 |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 11 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 13 (only outcome adjudication committee is blinded) |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a, since patient and treating physicians are not blinded |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if | 13 |

| | | | |
|---|---|---|---|
| | | known. Reference to where data collection forms can be found, if not in the protocol | |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 13/19 |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 14-16 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 14-16 |
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 14-16 |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about | 17, monitoring of trial execution is monitored by monitors from the LUMC; since this is a neglectable risk study no data safety monitoring board has been |

| | | | |
|---|---|---|---|
| | | its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | installed (according to Dutch legislation). |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a, since this is a neglectable risk study no data safety monitoring board has been installed (according to Dutch legislation). |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 12 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | n.a. no preplanned audits |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 15 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | 16 all relevant protocol amendments will be reviewed by the MREC |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 10 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data | Included in patient information file |

| | | | |
|---|---|---|---|
| | | and biological specimens in ancillary studies, if applicable | |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 13 |
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 24/25 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 17 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | According to Dutch laws a participant insurance is available; information on compensation for injury is included in the patient information letter (in Dutch) and available upon request |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 17 |
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 17 |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 17 |

**Appendices**

| | | | |
|---|---|---|---|
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | Available upon request (Dutch only) |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 10, detailed information is available upon request |

BMJ Open

# 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



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**Title**

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**

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**ABSTRACT**

**Introduction**

Patients with a first venous thromboembolism (VTE) are at risk of recurrence. Recurrent VTE (rVTE) can be prevented by extended anticoagulant therapy, but this comes at the cost of an increased risk of bleeding. It is still uncertain whether patients with an intermediate recurrence risk or with a high recurrence and high bleeding risk will benefit from extended anticoagulant treatment, and whether a strategy where anticoagulant duration is tailored on the predicted risks of rVTE and bleeding can improve outcomes. The aim of the Leiden Thrombosis Recurrence Risk Prevention (L-TRRiP) study is to evaluate the outcomes of tailored duration of long-term anticoagulant treatment based on individualised assessment of rVTE and major bleeding risks.

**Methods and analysis**

The L-TRRiP study is a multicentre, open-label, cohort-based, randomised controlled trial, including patients with a first VTE. We classify the risk of rVTE and major bleeding using the L-TRRiP and VTE-BLEED scores, respectively. After three months of anticoagulant therapy, patients with a low rVTE risk will discontinue anticoagulant treatment, patients with a high rVTE and low bleeding risk will continue anticoagulant treatment, whereas all other patients will be randomised to continue or discontinue anticoagulant treatment. All patients will be followed for at least two years. Inclusion will continue until the randomised group consists of 608 patients; we estimate to include 1600 patients in total. The primary outcome is the combined incidence of rVTE and major bleeding in the randomised group after two years of follow-up. Secondary outcomes include the incidence of rVTE and major bleeding, functional outcomes, quality of life and cost-effectiveness in all patients.

**Ethics and dissemination**

The protocol was approved by the Medical Research Ethics Committee Leiden – Den Haag – Delft. Results are expected in 2028 and will be disseminated through peer-reviewed journals and during (inter)national conferences.

**Trial registration number**

NL9003, NCT06087952

**Strengths and limitations of this study**

> The models can be applied to all patients with a first VTE without cancer, irrespective of whether this event was provoked or unprovoked.

> The study is designed to follow usual clinical procedures as much as possible to increase the generalisability of the results.

> Primary outcomes will be adjudicated by a committee blinded for treatment.

> The open-label design might increase cross-over between treatment groups and might influence assessment and reporting of study outcomes by the patient or treating physician.

> Questionnaires are used for follow-up which might result in missing outcome data, despite procedures to limit this, such as regular phone contact and collecting information from treating physicians.

## INTRODUCTION

Patients with a first venous thromboembolism (VTE) are at risk of a recurrent event, especially when the first event was unprovoked. The estimated risk of recurrence in patients with a first unprovoked VTE was 10% in the first year and 36% after ten years,(1) whereas patients with a first VTE provoked by a transient risk factor have an estimated risk of 1-6% in the first year and 3-15% after five years, depending on whether the provoking factor was a minor or major transient risk factor.(2,3) A recurrent VTE has serious consequences with estimated case fatality rates of 4%.(1,4) In addition, compared with the initial event, recurrent VTE is associated with a higher risk of long-term complications such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension.(5,6) Recurrent VTE can be prevented by prolonged oral anticoagulant therapy, but this comes at the cost of an increased risk of major bleeding compared with ceasing treatment.(7,8) A recent meta-analysis reported an overall major bleeding incidence of 1.7 per 100 person-years during extended use of vitamin K antagonists (VKAs) and 1.1 per 100 person-years during extended use of direct oral anticoagulants (DOACs), with a case fatality rate of 8.4%.(9) Importantly, the same meta-analysis reported limited safety information on long-term anticoagulation in VTE patients, in particular for DOAC recipients where information beyond one year of treatment was sparse. Indeed, indefinite use of anticoagulant therapy may result in a significant lifetime risk of major bleeding, a risk that is still to be quantified.

Consequently, the optimal duration of anticoagulant treatment is still under debate. Previously, patients received oral anticoagulant treatment for a fixed period (i.e., 3-6 months) after a first VTE, whereas current guidelines recommend to base treatment duration, (i.e. either a limited period or indefinite duration), on the balance between the risk of recurrent VTE and major bleeding.(10-15) Indefinite treatment should be considered for patients with a first unprovoked VTE given its higher associated recurrence risk, and it is recommended to discontinue anticoagulant treatment after three months for patients with a provoked VTE. However, the definition of provoked

VTE varies between guidelines, between centres, and over time, highlighting the clinical ambiguity surrounding this decision.(16) In addition, basing the decision on treatment duration solely on the classification of the first event into provoked or unprovoked may be too crude: a study from our group showed that the c-statistic of the (un)provoked status was only 0.61, indicating that the ability to distinguish patients at low and high risk of recurrence is limited. In fact, 15% of patients with a first provoked VTE had a predicted two-years recurrence risk of more than 10%, whereas this risk was below 10% in 45% of the patients with a first unprovoked VTE.(17) This finding indicates that these patient groups would have been under- or overtreated if the current guidelines were strictly followed (without accounting for bleeding risk or patient preferences).(11-15,17) Furthermore, guidelines advise to take the risk of major bleeding into account, but guidance on how to best assess the risk of major bleeding and balance this against the risk of VTE is not available.(11-15,18) Moreover, studies investigating the optimal duration of anticoagulation in relation to patient-relevant outcomes such as quality of life are lacking.(19) Therefore, in current clinical practice the decision to stop or continue treatment indefinitely is based on insufficient information. For these reasons, more elaborate individualised risk stratification in combination with knowledge on the optimal treatment duration, linked to these risks, is expected to reduce both types of serious complications.

Multiple prediction models have been developed to assess the risk of VTE recurrence and major bleeding in VTE patients.(20) (21) At the time we started to design the present study (2018), models for the prediction of VTE recurrence included the Men and HERDOO2 rule, Vienna prediction model, DASH score, DAMOVES score, pre- and post D-dimer strategy, Worcester VTE score, and L-TRRiP model.(17,22-27) Of these, the L-TRRiP model is the only externally validated model that predicts long-term recurrence risk after a provoked as well as an unprovoked first VTE, which allows for easier use given the problems related to the distinction between provoked and unprovoked VTE as described above. In addition, it allows for more precise risk stratification by providing an absolute recurrence risk, rather that dichotomising high and low recurrence risk. Another advantage of the L-

TRRiP model is that all parameters can be determined *during* anticoagulant treatment, so interruption or discontinuation of the treatment is not required, in contrast to some other models that include D-dimer, a biomarker predictor that needs to be measured after a short interruption of anticoagulation. Besides being unpractical, such interruption – albeit relatively rare – may lead to early recurrent VTE events shortly after discontinuation.(28)

Models to predict major bleeding during anticoagulant therapy have mainly been developed for atrial fibrillation (AF) patients. Examples of such models are the HAS-BLED score and HEMORR$_2$HAGES score.(29,30) Nevertheless, in current clinical practice these models are sometimes also used to predict major bleeding among VTE patients.(12,18) However, patient characteristics differ between AF and VTE patients, and the predictive performance of these models in VTE patients is limited.(20) Therefore, dedicated models for VTE patients have been developed, which include the score developed by Kuijer et al., the ACCP risk table, the RIETE score, and VTE-BLEED score.(11,31-34) Of these, the VTE-BLEED score is among the most externally validated models, has been validated during extended anticoagulant therapy and has shown a good predictive performance in patients using VKAs as well as in those using DOACs.(18,35-38)

Previous attempts have been made to optimize the length of treatment of patients after a first VTE based on individualised assessment of recurrent VTE risk.(28,39) One study showed a clear benefit of prolonged anticoagulant treatment compared with discontinuation on recurrent VTE in patients with an unprovoked VTE and elevated d-dimer levels one month after ceasing anticoagulant treatment (2.9% vs 15% during 9-18 months follow-up respectively).(39) However, the incidence of recurrent VTE in patients with normal d-dimer levels (in whom anticoagulation was therefore stopped) was still high (6-7% per patient-year),(39,40) indicating d-dimer alone cannot be used to guide anticoagulant treatment duration. Another study showed that prolonging anticoagulant treatment based on the Vienna score versus routine clinical care did not improve the clinical outcome in the randomised groups, albeit that the risk of actual recurrent VTE was indeed low in

those with a low predicted risk based upon the Vienna score.(28) Likewise, a management study implementing the HERDOO2 rule showed that women with a low predicted recurrence risk had indeed a low risk of VTE recurrence after anticoagulant discontinuation.(41) However, the benefit of extended anticoagulation in the patients with a high risk of VTE recurrence remains uncertain. Furthermore, none of these studies included patients with a first provoked VTE or applied a bleeding risk model next to the prediction of recurrence risk. Currently, none of these strategies is recommended by the guidelines.

In summary, the current strategy to decide on (dis)continuation of anticoagulant treatment after a first VTE is not optimal since 1) the definition of provoked VTE is subject to debate, 2) the insufficient discriminative power of a distinction between provoked and unprovoked VTE is disregarded, and 3) the risk of major bleeding is not properly taken into account, and 4) patient relevant outcomes such as quality of life are not taken into account. This results in both over- and undertreatment with anticoagulants in a proportion of patients with a first VTE, leading to unnecessary high life-time risks of major bleeding or recurrent VTE, respectively. Although some novel strategies have been studied, this has not resulted in a more tailored strategy to determine optimal treatment duration. Therefore, in the Leiden Thrombosis Recurrence Risk Prevention (L-TRRiP) study we aim to evaluate outcomes of tailored duration of anticoagulant treatment based on individualised risk assessment of a patient's recurrent VTE and major bleeding risk, using both the L-TRRiP and VTE-BLEED model.

## METHODS AND ANALYSIS

### Study design

The L-TRRiP study is a multicentre, open-label, cohort-based randomised controlled trial. The L-TRRiP and VTE-BLEED prediction models are used to individually classify patients according to their risk of recurrent VTE (as low, intermediate, or high) and major bleeding (as low or high), respectively. After the initial three months, anticoagulant treatment is stopped in patients with a low recurrent VTE risk, while patients with a high recurrent VTE risk and low major bleeding risk continue treatment. Patients in the other risk groups (i.e., patients with an intermediate recurrent VTE risk or a high recurrent VTE risk and high bleeding risk) are randomised to continue or discontinue anticoagulant treatment (**figure 1**). All patients, both in the non-randomised and randomised arms, are followed for at least two years, following the same procedures. Academic hospitals, teaching hospitals, and general hospitals from the Netherlands participate in this trial. At this time, the trial has started enrolment in 17 hospitals (see **Appendix I**). Study enrolment started in 2021, the first patient was enrolled in June 2021. The planned end date of the study is 2027, two years after enrolment of the last patient, which is expected to be in 2025. The L-TRRiP study is registered at the Dutch Trial Registry: NL9003 and ClinicalTrials.gov: NCT06087952. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines were followed when drafting the study protocol.

**Study population**

Patients with a first confirmed symptomatic distal or proximal deep venous thrombosis (DVT) of the lower extremity or pulmonary embolism (PE) with an indication for anticoagulant treatment for at least three months, aged 18 years or above, who provide informed consent prior to any study specific procedure, are eligible to participate in this trial. Patients with active cancer, known antiphospholipid syndrome, those who have an indication other than VTE for prolonged anticoagulant treatment (e.g., atrial fibrillation), who have an indication for long-term antiplatelet therapy despite the use of oral anticoagulation (e.g., recent myocardial infarction) or who have an

extremely high bleeding risk necessitating discontinuation of anticoagulant treatment will be excluded. Diagnostic testing for malignancy or antiphospholipid syndrome after the index VTE diagnosis is performed at the discretion of the treating physician. Patients with VTE related to severe COVID-19 (i.e., requiring hospital admission in three months before the index event) as well as patients with vaccine-induced immune thrombotic thrombocytopenia (VITT) are not eligible to participate in this trial since the effect of these conditions on recurrence is not known, and such patients were not included in derivation of the L-TRRiP model.(17)

**Risk prediction models**

The L-TRRiP model includes sex, type and location of VTE, risk factors for VTE, history of cardiovascular disease as well as blood group non-O and the factor V Leiden mutation to predict the absolute two-year risk of recurrent VTE. A predicted two-year VTE risk below 6% is classified as low, a VTE risk of 6-14% as intermediate and a VTE risk above 14% as high (see **Table 1**).(17) The VTE-BLEED model uses age of 60 years or higher, renal dysfunction, anaemia, history of clinically relevant or major bleeding, active malignancy, and uncontrolled hypertension in male patients to predict major bleeding risk. A score <2 is classified as low bleeding risk and a score ≥2 as high bleeding risk (**Table 2**).(33)

**Procedures**

After providing informed consent, patients are asked to fill in a questionnaire including demographic variables, clinical circumstances and risk factors for the first VTE, and past medical history including previous bleeding. Furthermore, a self-administered buccal swab is taken to assess the factor V Leiden mutation and ABO blood group by DNA analysis. Information is obtained from

the electronic health records from the hospital including recent haemoglobin level, renal function, blood pressure, comorbidities, and details regarding the first VTE event (type and location of VTE).

Based on this information, the L-TRRiP and VTE-BLEED scores and corresponding risk categories are calculated in the coordinating centre (Leiden University Medical Center). Depending on the risk category of the patient, a decision on duration of treatment is either made immediately, or the duration of treatment is randomised (**Figure 1**).

When applicable, randomisation is performed shortly before the routine three month visit in the coordinating centre using the randomisation function in CastorEDC to ensure concealment of treatment allocation.(42) Randomisation is performed in a 1:1 ratio, using variable block randomisation with a block size of two, four, or six stratified by study centre, risk group for recurrent VTE and bleeding to ensure equal distribution of the patients. The treating physician receives the risk classification of recurrent VTE and major bleeding risk, and the corresponding treatment duration or outcome of randomisation shortly before the routine three month visit and discusses this with the patient.

Patients who are allocated to continue anticoagulant treatment can remain on the same anticoagulant or switch anticoagulants at the discretion of their treating physician. In the Netherlands, DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) as well as VKAs (acenocoumarol and phenprocoumon) and low-molecular-weight heparins (LMWHs) are registered for the treatment of VTE. Dose reduction of apixaban or rivaroxaban according to current guidelines after the initial six months is allowed, at the discretion of the treating physician. In case the treating physician and/or patient decides to deviate from the treatment duration, the reasons for deviation are registered, and patients will complete follow-up as usual.

**Follow-up**

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.

In case of a reported recurrent VTE or bleeding event, additional information is retrieved from the medical records of the hospital or general practitioner for adjudication. Adverse events related to the study intervention are registered. All severe adverse events, including death and non-elective hospitalisation, are reported to the institutional review board. The questionnaire is also used to evaluate anticoagulant treatment use and remaining symptoms of VTE. Furthermore, we evaluate quality of life by means of the EQ-5D-5L questionnaire.(43) Also, functional recovery is assessed using the post-VTE functional scale (PVFS).(44,45) In order to perform a cost-effectiveness analysis, we measure healthcare consumption and productivity losses during the first two years of follow-up by using Medical Consumption Questionnaire (iMTA MCQ) and Productivity Costs

Questionnaire (iMTA PCQ) from the institute for Medical Technology Assessment. All questionnaires are offered digitally (via CastorEDC) or by regular mail as preferred by the participant.

Overall, the study is designed to follow general clinical practice as closely as possible, to optimize generalisability of the results, and to lower the burden for the patients.

**Outcomes**

For the randomised group, the primary outcome is a composite endpoint of recurrent VTE and major bleeding at two years. Recurrent VTE is diagnosed after clinical suspicion is objectively confirmed by diagnostic imaging, according to current guidelines.(46,47) Bleeding events will be classified as major, clinically relevant non-major (CRNMB) or minor according to the current guidelines of the International Society of Thrombosis and Haemostasis (ISTH): major bleeding is defined as fatal bleeding, symptomatic bleeding in a critical area or organ or bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; CRNMB is defined as any bleeding that does not fit the criteria for major bleeding, but does require medical intervention, lead to hospitalisation or increased care level or prompt face to face evaluation.(48,49)

All clinical outcomes will be evaluated and classified by an independent committee blinded for treatment allocation using discharge letters, radiology reports and other relevant information retrieved from the medical records. In case of a recurrent VTE or (major) bleeding event, patients will be treated according to the local clinical practice, meaning that (dis)continuing anticoagulant treatment at that point is at the discretion of the treating physician.

Secondary outcomes are 1) the combined incidence of recurrent VTE and major bleeding events (primary outcome) weighted by the associated loss of quality adjusted life years (QALYs) and functional limitations (PFVS) in the randomised group; 2) cost-effectiveness of prolonged

anticoagulant treatment compared to discontinuation in the randomised groups; 3) the incidence of recurrent VTE and major bleeding and CRNMB at two years and during entire follow-up in in all groups; 4) the predictive performance (discrimination and calibration) of the L-TRRiP and VTE-BLEED model in the arms that discontinue and continue, respectively and 5) the natural course of recovery from a first acute VTE with regard to long-term functional limitations using the PVFS.

**Data collection**

Data are collected and stored pseudonymised using the web-based data management platform CastorEDC.(42) Personal information of included participants is securely shared with the coordinating centre for them to send the questionnaires and buccal swab and contact the participants if needed. To optimize data quality, the digital data collection forms include checks for important study variables, such as range checks for continuous variables, check of the assigned risk categories, and verification of relevant medical history included in the prediction models by both the study team as well as the patient (via the baseline questionnaire).

**Sample size calculation**

The sample size of this study is based on the randomised part of the study. Based on the estimated risks of recurrent VTE and major bleeding as observed in the derivation studies of both prediction models,(17,33) we assume an overall two-year recurrent VTE risk of 10% in the discontinuation arm of the randomised groups and a major bleeding risk of 0.6%. Assuming a reduction of the recurrent VTE risk of 85% by anticoagulant treatment, the recurrent VTE risk of the group that continues anticoagulant treatment will be 1.5%. Furthermore, we estimate this will lead to an increase in the overall risk of major bleeding to 2.1%. To demonstrate a 7% absolute difference in the combined endpoint (i.e., 10.6% vs 3.6%) with an alpha of 0.05 and a power of 90%, we need a

sample size of 552 subjects for the randomised part of the study. Taking into account a drop-out rate of 10%, we aim to include 608 patients in the randomised part of the study. Based on the derivation studies we expect the randomised group to form about 38% of the total included population, in which case we expect to include approximately 1600 patients in total; 848 (53%) in the low VTE recurrence risk group and 144 (9%) in the high recurrence and low bleeding risk group.(17,33) Of note, these numbers may change depending on the final proportion of the randomised group.

**Data analysis plan**

Baseline characteristics will be summarised using descriptive statistics (mean, standard deviation [SD] or medium, interquartile range (IQR); number, percentage). Furthermore, we will present the number of patients who continued anticoagulant treatment while being allocated to discontinuation and vice versa (cross-over), including the reason for switching anticoagulant treatment. In case of missing data, we will perform multiple imputation if indicated (depending on the amount and nature of the missingness) and pool the results according to Rubin's rules.(50)

*Randomised group:*

Following an intention-to-treat analysis, the cumulative incidence of the primary outcome in the randomised group at two years will be estimated using the cumulative incidence competing risk method, accounting for the competing risk of death from other causes than VTE or major bleeding. Follow-up will start at the time of the three month visit. We will censor patients when they withdraw informed consent, are lost to follow-up, or reach the end of the study follow-up period. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) will be estimated using a Cox regression model.

As secondary analyses, we will perform a per-protocol analysis, in which patients who did not receive the allocated treatment during the complete follow up will be censored at the time of

the protocol deviation. In case of a different distribution of risk factors between the treatment groups due to chance, adjusted HRs and 95% CIs will be estimated. The primary outcome (i.e., recurrent VTE and major bleeding) will be weighted for the impact on quality of life (EQ-5D) and functional limitations (PFVS) (in two separate analyses) using the difference between the measures taken after and the last one before the event as weights. Furthermore, we will estimate the incidence of recurrent VTE and major bleeding during the entire follow-up, estimate the cumulative incidence of CRNMB and assess repeated events (e.g., CRNMB followed by major bleeding) using negative binomial regression.

Health-care costs will be calculated using Dutch standard prices for economic evaluations.(51,52) Absence from work will be valued with friction cost method. QALYs will be assessed using the EQ-5D-5L scores (Dutch tariff(53)) at different timepoints, using the area-under-the-curve approach. The economic evaluation will consist of a cost-effectiveness analysis, comparing costs per event, as well as a cost-utility analysis, comparing costs per QALY. In net-benefit analysis, costs will be related to effectiveness and presented in a cost-effectiveness acceptability curve.

*Non-randomised group:*

The cumulative incidences of recurrent VTE, major bleeding and CRNMB at two years and during the entire follow-up in the non-randomised groups will be calculated, using the same approach as in the randomised groups.

*All participants:*

We will assess the difference in recommended treatment duration as allocated in the study to treatment duration according to the guidelines (i.e., continuation in unprovoked and discontinuation in provoked VTE). We will determine the predictive performance of the L-TRRiP model in all patients that discontinued anticoagulant treatment (since the L-TRRiP model is developed to predict the risk of VTE recurrence after discontinuation) by creating a calibration plot

containing the observed and predicted two-years risks of recurrent VTE. Likewise, we will determine the predictive performance of the VTE-BLEED model in all patients who continued anticoagulant treatment, although observed risks will be plotted against the total score as absolute predicted risks are not provided by the model. For the analysis of functional recovery, an ordinal logistic regression model will be used.

**Patient and Public Involvement statement**

The L-TRRiP study is investigator initiated. An advisory board, consisting of five patients with a history of VTE, is involved in the practical implementation of the trial, such as patient recruitment and dissemination of study results among patients. In order to make the results of the study accessible to patients, we will publish a Dutch summary.

**ETHICS AND DISSEMINATION**

The L-TRRiP study will be conducted according to the principles of Good Research Practice and in accordance with the applying Dutch laws (the Medical Research Involving Human Subjects Act [WMO] and General Data Protection Regulation [GDPR]). The protocol is approved by the Medical Research Ethics Committee Leiden – Den Haag - Delft, the Netherlands. Monitoring will be executed by monitors working for the coordinating centre who are independent of the study investigators, to ensure compliance with the protocol, Good Research Practice and legal aspects.

Results are expected in 2028. Our aim is to disseminate the results by publication in peer-reviewed journals, professional societies, and through presentations on (inter)national conferences according to publication standards. After data collection and data cleaning are finished, deidentified data will be registered in a repository and be made available for further research upon reasonable request to the corresponding author.

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**Authors contributions**

SCC, MVH, FAK, GJG and SM designed the study. MEvdA-vM (health-care economics) and SlC (statistics) contributed to the parts in the protocol on their specific disciplines. JLIB-vD wrote the first manuscript draft, supervised by NvR and SCC. RHHB, JWKvdB, CYB, MC-vB, MC, ME, YE-V, NvE, CvG, WKdJ, FK, TK, CK, SK, JL, DL, ATAM, KM, MAvdR, RR, IS, JSH, AWGvdV are involved in the trial conduct in their affiliations and revised the manuscript. All authors gave final approval of the version to be published.

**Acknowledgements**

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**Collaborators**

The L-TRRiP Investigators: see **Appendix I**.

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**Conflicts of interest statement**

**MC** has received financial support for research from Bayer, CSL Behring, Roche, Novo Nordisk, and UniQure and lees for lecturing or consultancy from Alexion, Bayer, CSL Behring, Daiichi Sankyo, Sobi, and Viatris, all unrelated to the present work and paid to his institution. **NvE** has received a lecture

fee from Bristol Myers Squibb, which was unrelated to this work and paid to his institution. **JL** reports grants or contracts from BMS-Pfizer, Viatris, AstraZeneca en Synapse, all unrelated to this work and paid to her institution. **KM** reports speaker fees from Alexion, Bayer and CSL Behring, participation in trial steering committees for Bayer and Astra Zeneca, consulting fees from Uniqure, participation in data monitoring and endpoint adjudication committee for Octapharma. All payments are made to her institution. **SM** reports grants and personal fees from Daiichi-Sankyo, Bayer, Pfizer, and Boehringer-Ingelheim, personal fees from Portola/Alexion, Abbvie, Pfizer/ Bristol-Meyers Squibb, Norgine, Viatris, and Sanofi, all paid to her institution and outside the submitted work. **MVH** reports grants from Dutch Heart Foundation, Netherlands Organisation for Health Research and Development, Bayer Health Care, Pfizer-BMS Leo Pharma Boehringer-Ingelheim, all outside this work. **FAK** reports grants or contracts from Bayer, BMS, BSCI, MSD, Leo Pharma, Actelion, Farm-X, The Netherlands Organisation for Health Research and Development, the Dutch Thrombosis Association, The Dutch Heart Foundation and the Horizon Europe Program, all unrelated to this work and paid to his institution. All others report no conflicts of interest related to this project.

**FIGURES**

**Figure 1. Design of the L-TRRiP study**

**TABLES**

**Table 1. L-TRRiP model**

| Factor | Coefficient |
|---|---|
| Male sex | 0.63 |
| Type of first VTE | |
| PE | -0.61 |
| PE + DVT | 0.32 |
| Location of DVT | |
| Popliteal DVT [a] | -0.46 |
| Surgery [b] | -0.51 |
| Pregnancy/puerperium [b] | -1.49 |
| Hormone use [c] | -0.67 |
| Plaster cast [b] | -0.79 |
| Immobility in bed, in hospital [b, d] | -0.31 |
| History of cardiovascular disease [e] | -0.35 |
| Blood group, non-O | 0.24 |
| Factor V Leiden mutation [f] | 0.40 |
| **Calculation of the L-TRRiP score** | |
| Prognostic score | Beta1*x1 + beta2*x2 + beta3*x3 + …. The x1, x2, x3, etc. represent the factors in the model, and beta1, beta2, beta3 etc. represent the corresponding coefficients. |
| Absolute 2-years risk of VTE recurrence | 1- 0.9235595^exp(prognostic score) |
| **Classification of patients with the L-TRRiP score** | |
| Low recurrent VTE risk | 2-years risk < 0.06 |
| Intermediate recurrent VTE risk | 2-years risk 0.06 - 0.14 |
| High recurrent VTE risk | 2-years risk > 0.14 |

Table adapted from Timp et al.(17)

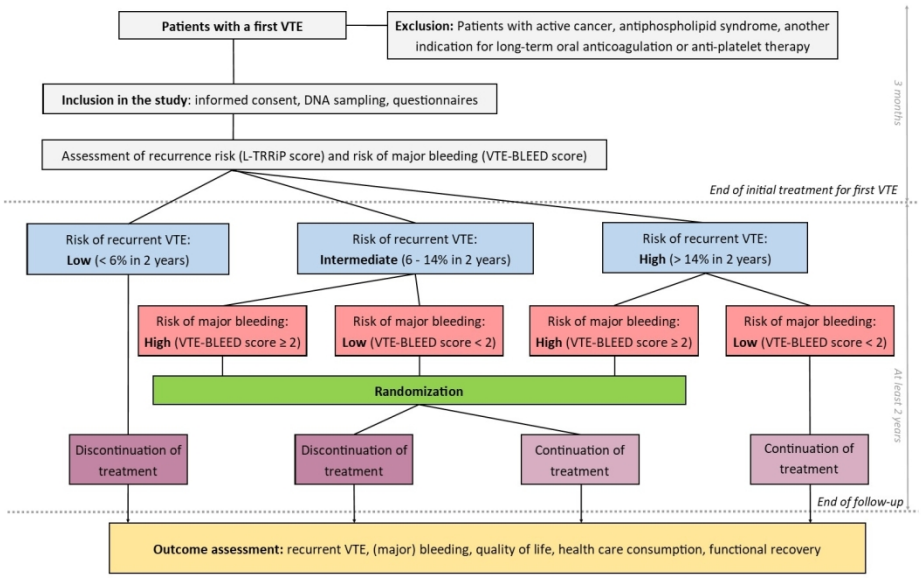
[a] Indicates DVT at the level of the vena poplitea or below. [b] Within three months before VTE. [c] Use of hormonal contraceptives or hormone replacement therapy at the time of VTE. [d] Confinement to bed ≥ 3 days. [e] Including a history of heart failure, angina pectoris, peripheral artery vascular disease (claudication), acute myocardial infarction. [f] Homozygous or heterozygous.

**Table 2. VTE-BLEED model**

| Factor | Score |
|---|---|
| Active cancer [a] | 2 |
| Male with uncontrolled arterial hypertension [b] | 1 |
| Anaemia [c] | 1.5 |
| History of bleeding [d] | 1.5 |
| Age ≥ 60 years old | 1.5 |
| Renal dysfunction [e] | 1.5 |
| **Classification of patients with the VTE-BLEED score** | |
| Low bleeding risk | Total score < 2 |
| High bleeding risk | Total score ≥ 2 |

Table adapted from Klok et al.(35)

[a] Cancer diagnosed within six months before diagnosis of VTE (excluding basal-cell or squamous-cell carcinoma of the skin), recently recurrent or progressive cancer or any cancer that required anti-cancer treatment within six months before the VTE was diagnosed. [b] Value of systolic blood pressure ≥ 140 mmHg at baseline. [c] Haemoglobin < 13 g/dl in men or < 12 g/dl in women. [d] Including prior major or non-major clinically relevant bleeding events, rectal bleeding (more than spotting on toilet paper), frequent nose bleeding or haematuria. [e] Estimated glomerular filtration rate (eGFR) < 60 ml/min at baseline (calculated with Cockcroft-Gault formula).




Design of the L-TRRiP study

297x209mm (150 x 150 DPI)

# Appendix I - Contributors L-TRRiP study; version December 2023

## Participating centres:

**Adrz, Goes**

- Yavuz Bilgin
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- Marja A J Voskuilen
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- Aline van de Vendel

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- Ellis S. van Etten, department of neurology, Leiden university Medical Center

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 4 and 10 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | See trial register |
| Protocol version | #3 | Date and version identifier | n/a for manuscript, current version of MREC approved protocol is 1.6 (21-09-2023) |
| Funding | #4 | Sources and types of financial, material, and other support | 23 |

| | | | |
|---|---|---|---|
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 1, 23 |
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 2 (corresponding author) |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 23 |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | See methods (p9-15) |
| **Introduction** | | | |
| Background and rationale | #6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 6-9 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 6-9 |
| Objectives | #7 | Specific objectives or hypotheses | 9 |

| | | | |
|---|---|---|---|
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 9-10 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 9-10 |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 10-11 |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 11-12 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | 11-12 |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | 12-13 |

| | | | |
|---|---|---|---|
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | n/a, no restriction to routine care are made in the trial |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 14-15 |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 11-13 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 15-16 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 9 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce | 12 |

| | | | |
|---|---|---|---|
| | | predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | |
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 12 |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 12 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 14 (only outcome adjudication committee is blinded) |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a, since patient and treating physicians are not blinded |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if | 14-15 |

| | | | |
|---|---|---|---|
| | | known. Reference to where data collection forms can be found, if not in the protocol | |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 12-13 |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 15 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 16-18 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 16-18 |
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 16-18 |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about | 18, monitoring of trial execution is monitored by monitors from the LUMC; since this is a neglectable risk study no data safety monitoring board has been |

| | | | |
|---|---|---|---|
| | | its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | installed (according to Dutch legislation). |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a, since this is a neglectable risk study no data safety monitoring board has been installed (according to Dutch legislation). |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 13 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | n.a. no preplanned audits |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 18 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | 18 all relevant protocol amendments will be reviewed by the MREC |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 11 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data | Included in patient information file |

| | | | |
|---|---|---|---|
| | | and biological specimens in ancillary studies, if applicable | |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 15 |
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 23-24 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 18 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | According to Dutch laws a participant insurance is available; information on compensation for injury is included in the patient information letter (in Dutch) and available upon request |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 18 |
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 18 |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 18 |

**Appendices**

| | | | |
|---|---|---|---|
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | See enclosed Subject information |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | See enclosed subject information |