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Title:

Thromboembolic Risk Stratification by TRiP(cast) Score to Rationalize Thromboprophylaxis in Patients with Lower Leg Trauma Requiring Immobilization: Study Protocol of the CASTING Stepped-wedge Cluster Randomized Trial.

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Conflict of interest statement The authors that they declare to have no competing interests.

‘Strengths and limitations of this study’

- The CASTING Study will be the first prospective, evaluating the implementation of a risk-stratification model for thromboprophylaxis in patients with lower limb trauma and orthopaedic immobilization.
- The CASTING trial will be a prospective stepped-wedge randomized clinical trial in 15 Emergency Departments in France and Belgium.
- A medico-economic analysis will be carried out to demonstrate the efficiency of this strategy.
- Due to the design, the study staff and participating investigators are not blinded to the period which is a limitation.

Abstract

Introduction

Patients with lower limb trauma requiring orthopedic immobilization may be at risk of venous thromboembolism but controversy persists about whom may benefit from thromboprophylactic anticoagulant treatment.

The aim of the CASTING study is to demonstrate the safety of a thromboprophylaxis decision strategy based on the TRiP(cast) score with regards to the three-month rate of symptomatic VTE in low-risk patients not receiving thromboprophylaxis, as well as the usefulness of this strategy on the rate of patients receiving anticoagulant treatment in comparison to current practice.

Methods and analysis

CASTING will be a stepped-wedge cluster randomized controlled clinical trial, performed in 15 emergency departments in France and Belgium. With their informed consent, consecutive outpatients admitted to one of the participating emergency department for a lower limb trauma requiring orthopaedic immobilization without surgery will be included. All centres will begin the trial on the "observational period" and, every two weeks, one centre will randomly be assigned to switch to the "interventional period" and to apply the TRiP(cast) score, in which only patients with a score ≥ 7 will receive thromboprophylactic anticoagulant treatment. The primary endpoint is the rate of clinical thromboembolic event within 90 days following the inclusion of low-risk patients not receiving thromboprophylaxis.

Ethics and dissemination The protocol has been approved by the Comité de Protection des Personnes Sud I (Ethics Review ID-RCB: ID-RCB: 2019-A01829-48) and is carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The findings of this study will be disseminated in peer-reviewed journals and at scientific conferences.

Discussion Presenting a high level of evidence, it will be possible to confirm the safety and reliability of the TRiP(cast) score in guiding decisions on thromboprophylaxis, indicating that the CASTING study will have a major impact on medical practices and on public health.

Trial registration NCT04064489.

INTRODUCTION

Lower limb traumas requiring orthopaedic immobilization (plaster or splint) without surgery are a common reason for admission to the Emergency Department (ED) admission. Ankle and foot injuries are among the most common reasons for presentation in the ED. For example, in Australian, over 90,000 ankle and/or foot soft tissue injuries were recorded in 2014-2015 [1]. Due to venous stasis caused by immobilization, hypercoagulable states and vascular injuries brought on by the trauma, these patients are at risk of developing venous thromboembolism (VTE)[2]. The odds-ratio (OR) of developing deep venous thrombosis (DVT) or pulmonary embolism (PE) following immobilization with a cast boot is estimated to be 8.3 (95% confidence interval (CI): 5.3-12.9) after adjusting for age, gender, body mass index (BMI) and regular physical activity [3]. Moreover, in patients immobilized using cast boots, the risk is higher if the indication is traumatic rather than non-traumatic: OR 12.7 (95% CI 6.6-24.6) vs 7.6 (95% CI 0.9-66.4)[3]. For this reason, the current practice in many countries, and especially in France and Belgium to prescribe a thromboprophylaxis for the majority of patients with lower limb trauma and orthopaedic immobilization [4,5]. Indeed, the efficacy (including asymptomatic thromboembolism and distal deep venous thrombosis) of low molecular weight heparin (LMWH) and fondaparinux has been shown in selected patient populations [6–8]. However, the benefit/risk ratio of this treatment is still controversial. Moreover, the cost of this therapy is considerable. Studies evaluating the cost-effectiveness of thromboprophylaxis in this indication are contradictory [9,10]. The largest randomized controlled study on the subject did not show any benefit of LMWH on the rate of symptomatic VTE among 1,435 non-selected patients. Venous thromboembolism occurred in 10 of the 719 patients (1.4%) in the treated group and in 13 of the 716 patients (1.8%) in the control group (absolute difference in risk −0.4%; 95% CI, −1.8 to 1.0%) [5]. Therefore, in 2017, the Cochrane meta-analysis concluded that a stratification of thromboembolism risk was required [1] in order to identify high-risk patients with lower leg cast immobilization who may benefit from thromboprophylaxis and low-risk patients who will not [11–13].

We recently developed and validated a risk stratification model: the TRiP(cast) score [14] (Table 1). This includes 14 items; one item for trauma severity, one for the kind of immobilization and 12 items related to the patient's characteristics. The TRiP(cast) score is easy to calculate thanks to a digital application developed for IOS (https://apps.apple.com/us/app/trip-cast-score/id1438610930) and the Android mobile plat-form (https://play.google.com/store/apps/details?id=com.everywhereim.tripcast&hl=nl). In external validation on the POT-CAST database, it exhibited an Area Under the Curve (AUC) of 0.74 (95%CI 0.61-0.87). The calibration plot confirmed a good correspondance between the observed and predicted risks (intercept 0.0016 and slope 0.0933). Using a cut-off score of 7, the sensitivity, specificity, positive and negative predictive values were 76.1%, 51.2%, 2.5%, and 99.2%, respectively. With this cut-off, it is possible to identify a large group of patients at very low risk of

developing VTE. In a monocentric prospective study, this subgroup corresponded to 70% of patients with lower limb trauma and orthopaedic immobilization [5].

Aim and hypothesis

The aim of the CASTING study is to demonstrate, in patients with lower limb trauma requiring orthopaedic immobilization admitted to the ED, the safety of a thromboprophylaxis decision strategy based on the TRiP(cast) score with regards to the three-month rate of symptomatic VTE in low-risk patients not receiving thromboprophylaxis, as well as the usefulness of this strategy on the rate of patients receiving anticoagulant treatment as compared to current practice.

METHODS AND ANALYSIS

Study design

The CASTING trial (NCT04064489) will be a prospective stepped-wedge randomized clinical trial in France and Belgium [15].

Trial objectives and outcomes

Primary objective and outcome

The main objective will be to demonstrate the reliability and the safety of a TRiP(cast) score <7 in order to not consider thromboprophylaxis for emergency patients with lower limb trauma requiring orthopaedic immobilization without surgery. The primary outcome will be the rate of symptomatic venous thromboembolism (DVT or PE) during the three-month follow-up period among patients with a TRiP(cast) score <7 without thromboprophylaxis. The TRiP(cast) score will be considered reliable if the rate of VTE is lower than or equal to 1%, with an upper limit of the 95% confidence interval lower than or equal to 2% (non-inferiority hypothesis). An independent adjudication committee will centrally assess all potential clinical events centrally, confirm or deny their occurrence and decide on their severity. Members of the adjudication committee are experienced clinicians independent from the investigators and the sponsor.

Secondary objectives

The first secondary objective will be to demonstrate that the implementation of the TRiP(cast) score during the interventional period significantly reduces the rate of patients receiving thromboprophylaxis compared to current practices during the observational period.

The other secondary objectives will be to compare between current practices (observational period) and thromboprophylaxis based on the TRiP(cast) score (interventional period):

1) The rate of symptomatic VTE at 90 days;

2) The rate of major bleeding according to the criteria proposed by the International Society on Thrombosis and Haemostasis [16];

3) The rate of non-major clinically relevant bleeding as defined as any bleeding requiring hospitalization or a medical intervention including temporary withholding of anticoagulant treatment to stop the bleeding at 90 days.

Finally, we will perform a medico-economic analysis between current practices (observational period) and thromboprophylaxis based on the TRiP(cast) score (interventional period) within 90 days of inclusion, focusing on the cost-utility ratio in terms of cost per quality-adjusted life year (QALY) gained (primary analysis), and the cost-effectiveness ratio in terms of cost per symptomatic VTE avoided (secondary analysis).

Experimental plan for the stepped-wedge design

In this stepped-wedge clinical trial, patients will be recruited in 15 EDs in France and in Belgium, academic and non-academic, and rural and urban centres (Table 2). All centres will begin the trial on the "observational period" and every two weeks one centre will randomly be assigned to switch to the "interventional period" and to apply the TRiP(cast) score. After 32 weeks, all centres will be in the "interventional period" for the seven remaining months of the trial (Table 3). The order of centre changes to the interventional phase will be developed using non-stratified list randomization. This randomization will be carried out by the methodological managers of the Research and Innovation Department of Angers University Hospital (including the data management). The inclusion rate will be closely monitored during the trial, and time periods will be adjusted if the number of patients included differs substantially from the expectations in order to respect the number of subjects required in the observational phase [17]. No data monitoring committee has been set up, as this is not a drug study but an implemented strategy. A monitoring grade is defined according to the risk of the study according to the promoter's procedures (i.e. grade 1: low level of risk).

This design was chosen for the following reasons:

- The comparison with current practice was chosen because of the lack of recent recommendation and consensus guidelines on thromboprophylaxis in patients with lower limb trauma and orthopaedic immobilization. Indeed, the 2012 American recommendations advised against systematic preventative treatment if the patient does not require surgery whereas the 2011 French guidelines suggest thromboprophylaxis for all patients without possible foot support if there is not a high risk of bleeding [18,19]. Therefore, the decision to introduce thromboprophylaxis varies from country to country, from centre to centre and even from doctor to doctor [4].

– Comparison to current practice precludes randomization at the patient level or a crossover design that would induce bias through contamination. The implementation of the score will change healthcare practices and an emergency physician who would have already used the TRiP(cast) score during the study will be influenced by the score criteria and will change his/her "standard of care" in deciding on thromboprophylaxis.

- A cluster, stepped-wedge design prevents such contamination and also prevents a potential "period effect" that could have resulted from a simple before/after design.
- This design is especially suitable for inclusion in the emergency departments because it is less time-consuming than randomization at the patient level, as the physician knows, prior to patient inclusion, what he/she will do if the patient agrees to participate in the study.
- The robustness of the stepped-wedge design is widely recognized [20,21] and this methodology is increasingly used in studies aimed at implementing modification in care practices [17].

Study settings and population

The CASTING Trial will involve patients with isolated lower limb trauma requiring rigid (plaster or resin) or semi-rigid immobilization for an anticipated duration of at least seven days. It will be a continuous recruitment. Therefore, consecutive adult patients who are admitted for this reason to one of the participating emergency departments will be assessed for inclusion. They must have up-to-date health insurance coverage and express in writing their consent to participate in the study after verbal and written explanations of the procedure, as recommended in clinical and research good practices (Additional file 1). If the patient is unable to consent, then the physician will seek consent from a trustworthy person, family member or close relative. If none is available, the physician can proceed to an "emergency inclusion" without prior consent. Therefore and as soon as possible, a written informed consent to pursue study participation will be requested of the patient or a trustworthy person as soon as possible. In case of refusal, the patient will be excluded from the trial (L1122-1-2 article of the French Public Health Code).

Patients will be excluded if they have any of the followings:

- Current anticoagulant treatment at time of trauma,
- Trauma requiring surgery or hospitalization for more than two days (excluding short-term hospital stay) at time of inclusion,
- Comorbidity or comorbidities requiring hospitalization at time of inclusion,
- Any factor that makes 90-day follow-up impossible,
- Legal protection measures (tutorship or curatorship) or detainee status.

Description of the intervention

In both study periods, consecutive patients admitted for lower limb trauma requiring rigid or semi-rigid immobilization without surgery will be evaluated for potential inclusion. After verifying eligibility and obtaining patient consent, the investigator will proceed to the inclusion. The patient's characteristics including thromboembolism risk factors, the kind of trauma and the type of immobilization, as well as the anticipated duration of immobilization will be collected. The data will be recorded in an electronic case report form (e-CRF), available on smartphones, tablets and computers and secured by a personal password. All personal data will be subsequently

anonymized. All patients included will receive a study participation card including emergency phone numbers and the phone number of the local principal investigator of the trial (Additional file 2). Participants may not participate in any other intervention trial during the CASTING study participation period

Observational control period

During this period, the TRiP(cast) score will not be calculated. Physicians will be free to decide whether or not to prescribe thromboprophylactic treatment with LMWH or fondaparinux depending on local practices.

Interventional period

During this period, the TRiP(cast) score will be prospectively calculated and thromboprophylactic treatment will be based on its result. When the emergency physician will record the patient's data on the e-CRF, the TRiP(cast) score will be automatically calculated. The physician will be advised to prescribe LMWH or Fondaparinux if the score is 7 or higher, and otherwise to not introduce thromboprophylaxis otherwise (score<7).

Follow-up

In both periods, the patients included will receive a follow-up consultation by phone at 30 days and 90 days after inclusion, in order to collect data on potential clinical events (thromboembolic events, haemorrhages, thrombocytopenia or other adverse effects), and on the use of healthcare resources linked to thromboprophylaxis (anticoagulant treatments, biological examinations, medical consultations or subsequent hospitalizations). The phone interviews will be performed using a standardized follow-up form in each centre.

An independent adjudication committee will assess all potential clinical events in order to confirm or deny their occurrence and decide on their severity.

Statistical analysis

Descriptive analysis

Quantitative variables will be described in terms of mean +/- standard deviation in cases of Gaussian distribution. Otherwise, they will be described in terms of median and inter-quartile range. Qualitative variables will be described in terms of numbers and frequencies. A comparison of patient characteristics between the two referral strategies will be evaluated using Student, Mann-Whitney, or Fisher's exact test depending on the context.

Main objective

The main analysis will be conducted on patients enrolled during the interventional period and who will not receive a thromboprophylactic anticoagulant treatment because of a TRiP(cast) score below 7. The rate of symptomatic VTE that occurred between emergency department discharge and

three-month follow-up and its 95% confidence interval will be estimated, using a logistic mixed model with a random effect on centre. The TRiP(cast) score will be considered as reliable if the upper 95% confidence limit of VTE rate is less than 2%. A sensitivity analysis will be performed as an intention-to-treat analysis taking into account all patients with a TRiP(cast) score <7.

Secondary objectives

The first secondary outcome will be analysed on the "intention-to-treat" population, meaning all evaluable patients included in the observational period versus all evaluable patients included in the interventional period. A logistic mixed model with a random effect on centre will be conducted which allowed to take into account the intra- inter-cluster correlations. A two-sided test with a type I error rate of 5% will be conducted.

The 90-day rates of symptomatic VTE, major bleeding and non-major clinically relevant bleeding will be compared between the control period and the interventional period using the same method. The results will be presented as the absolute difference in rates between the two periods and their 95% confidence interval.

Sensitivity analyses

Sensitivity analyses will be performed excluding patients from centres with a mean rate of inclusion by month below 5.

All the analyses will be conducted using R software (R Foundation for Statistical Computing; 2008/. http://www.R-project.org).

Missing Data

No imputation of missing data is planned. However, missing data will be analysed to determine whether they are informative and whether they are likely to lead to potential selection or information bias.

Multiple testing

A hierarchical management of objectives will be carried out, making it possible to limit the problem of multiplicity. Moreover, when necessary, a correction will be made allowing a control of the FWER at a risk of 5%.

Trial results will be reported in accordance with the extended SPIRIT guidance for cluster randomized trials.

Sample size calculation

Taking into consideration a 1% rate of symptomatic VTE in the low-risk group of patients [2], 753 patients would be required to obtain a higher limit of the 95% confidence interval that is lower than or equal to 2%. In a monocentric study conducted in Angers, the proportion of low-risk patients according to the TRiP(cast) score (score <7) was 67%. Considering that this rate would be ≥60% in the population included in the CASTING study and the possibility of patients lost to follow-up or patients who cannot be analysed at 5%, the number of patients to include has been set at 1,400 in the interventional period with a type-I error rate of 5% and a power of 80%.

The number of patients to include in the observational period has been established from the first secondary objective. Considering a 15% difference in the rate of patients receiving prophylactic anticoagulant treatment during the interventional period versus the control period, participation of 15 centres and an intra-class correlation coefficient (centre effect) of 0.1, 540 patients would be needed at each stage to demonstrate a significant difference with a 5% alpha risk and power of 80%. Taking into account the possibility of patients lost to follow-up and patients who cannot be analysed, the number of patients to be included in the control observational period was set at 600. The total number of participants in the study has thus been set at 2,000 patients across 15 centres.

Patient and Public Involvement

The current trial will be conducted without direct patient involvement. The ethics committee (Comité de Protection des Personnes Sud I) includes patient representatives, charged with the responsibility to protect patient rights; thus, the CASTING trial protocol was reviewed by a patient representative. Besides the above review process, patients will not be invited to comment on the study design and interpretation of the study results. Patients were not involved in the writing of this manuscript.

ETHICS AND DISSEMINATION

Informed consent will be obtained from all study participants whenever possible. If the patient is unable to consent, informed consent from a relative will be obtained. An Institutional Review Board authorized the study (Comité de Protection des Personnes Sud I, ID-RCB: 2019-A01829-48 the October 16th, 2020) for all participating centres and authorization was granted by the ethics committee of the participating hospital for Belgium. The trial has been designed on the basis of the SPIRIT guidelines and a Standard Protocol Items [22]. A SPIRIT checklist file is attached (Additional file 3).

The results of this study will be published in peer-reviewed manuscripts and will be presented to local community groups and stakeholders, as well as at national and international conferences as applicable. The authorship guidelines [23] will be followed for all relevant publications and presentations. Open access publication of this protocol will facilitate full public access to our protocol.

Discussion

To our knowledge, this study protocol describes the first prospective, multi-centric study evaluating the implementation of a risk-stratification model for thromboprophylaxis in patients with lower limb trauma and orthopaedic immobilization.

It is based on a well validated model, the TRiP(cast) score, exhibiting good performance especially in defining low-risk patients that would not benefit from prophylactic anticoagulant treatment. If our

hypotheses are confirmed, the CASTING trial will confirm that a large number of patients with lower limb trauma requiring orthopaedic immobilization without surgery could safely not receive any thromboprophylaxis, and conversely that some patients not receiving treatment in current practice could benefit from thromboprophylaxis. Indeed, in a monocentric, observational pilot study, 35.5% (11/30) of patients classified as being at high risk of VTE according to the TRiP(cast) score did not receive preventative treatment. Among them, one patient developed a deep venous thromboembolism. On the other hand, 31.5% of patients classified as being low risk (52/165) (63.3% of all patients) received thromboprophylactic anticoagulant treatment [5]. The cost of this treatment and its impact on the day-to-day lives of patients, due to its subcutaneous administration, are significant. Pandor et al. suggest that risk-based strategies are potentially more cost-effective to limit thromboprophylaxis [9]. Due to the high frequency of lower limb trauma, this represents high healthcare costs [24,25]. By presenting a high level of evidence due to the stepped-wedge design, it is possible to confirm that the implementation of the TRiP(cast) score leads to a significant decrease in the rate of patients receiving anticoagulant treatment and an improvement on the cost-utility ratio, indicating that the CASTING study will have an important impact on patients care and public health.

The CASTING study results are particularly anticipated and after the protocol was reviewed and approved by the French and Belgian Ethics Committees, recruitment began on June 22, 2020. The results are anticipated for the end of 2021.

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Declarations

Ethics approval and consent to participate

All participants invited will provide informed consent prior to gaining access to the online survey. On the consent form, participants will be asked if they agree to use of their data and are aware of the option to withdraw from the trial at a later date. Participants will also be asked for permission for the research team to share relevant data with people from the Universities taking part in the research or from regulatory authorities, where relevant. This trial does not involve collecting biological specimens for storage. There is no anticipated harm and no compensation provided for trial participation.

Authors' contributions

DD, PMR, AP conceived the overarching study. DD, PMR, AP participated in the elaboration of the study design and writing of the protocol. JR is responsible for the statistical analysis. MT and TM made substantial contributions to the protocol and this article. All authors take responsibility for this paper as a whole. All authors contributed critical analysis, interpretation and writing within all drafts and approved the final draft for submission.

Funding

The trial is funded by a grant from the French Ministry of Health (PHRCI-18-056). The funding body agreed to the design of the study and has no role in the collection, analysis, and interpretation of the data, nor in the writing of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not Applicable.

Availability of data and materials

The dataset from this study will be safely stored following the principles of research ethics. Upon completion of the study, data may be made available by the corresponding author upon request with justification. The results of this study will be disseminated through publications in journals, presentation of abstracts in scientific conferences.

Acknowledgements

We would like to thank the financial support of the HUGO network and the support of the Department of Innovation and Research of Angers University Hospital. We would like to thank all the partner centres that agreed to participate in this study.

Additional files

Additional file 1. Consent

Additional file 2. Study participation card

Additional file 3. SPIRIT checklist

Abbreviations

AUC: Area Under the Curve, BMI: Body Mass Index; eCRF: Electronic Case Report Form; ED: Emergency Department; ICEC : Independent Clinical Events Committee; LMWH: Low Molecular Weight Heparin; OR Odds Ratio; QALY: Quality Adjusted Life Year; TRiP(cast): Thrombosis Risk Prediction for patients with cast immobilization score; VTE: Venous thromboembolism.

Table 1. TRiP(cast) score*

Trauma †	Points
High-risk trauma	
Fibula and/or tibia shaft fracture	**3**
Tibial plateau fracture	
Achilles tendon rupture	
Intermediate-risk trauma	
Bi or tri-malleolar ankle fracture	
Patellar fracture	**2**
Ankle dislocation, Lisfranc injury	
Severe knee sprain (with oedema / haemarthrosis)	
Severe ankle sprain (grade 3)	
Low-risk trauma	
Single malleolar ankle fracture	
Patellar dislocation	**1**
(Meta)Tarsal bone(s) or forefoot fracture	
Non-severe knee sprain or ankle sprain (grade 1 or 2)	
Significant muscle injury	
Immobilization ‡	
Upper-leg cast	**3**
Lower-leg cast	**2**
Foot cast (ankle free) or any semi-rigid without plantar support	**1**
Other cast or bracing with plantar support	**0**
Patient characteristics §	
Age <35 years	**0**
Age ≥ 35 and <55 years	**1**
Age ≥ 55 and <75 years	**2**
Age ≥ 75 years	**3**
Male sex	**1**
Body Mass Index BMI ≥25 and <35 kg/m^2	**1**
Body Mass Index BMI ≥35kg/m^2	**2**
Family history of VTE (first-degree relative)	**2**
Personal history of VTE or known major thrombophilia	**4**
Current use of oral contraceptives or Estrogenic hormone therapy	**4**
Cancer diagnosis within the past 5 years	**3**
Pregnancy or puerperium	**3**
Immobilization (other) within the past 3 months ||	**2**
Hospital admission, bedridden or flight > 6 hours, Lower limb paralysis	
Surgery within the past 3 months	**2**
Comorbidity	**1**
Heart failure, rheumatoid arthritis, chronic kidney disease, COPD, IBD	
Chronic venous insufficiency *(varicose veins)*	**1**

* Thrombosis Risk Prediction in patients with cast immobilization score
TRiP(cast) score is the sum of the Trauma, Immobilization and Patient components
† Trauma: Choose one, (the most severe trauma)
‡ Immobilization: Choose one
§ Patient: multiple points can be scored
|| Other immobility next to cast immobilization

Table 2. List of the principal investigators of participating centers

Name	First Name	Country	Hospital
Baudin	Laure	France	CH Cholet
Brice	Christian	France	CH St Brieuc
Casalino	Enrique	France	APHP Paris, Bichat
Douillet	Delphine	France	CHU Angers
Dumas	Florence	France	APHP Paris, Cochin
Lecoules	Nathalie	France	CHU Toulouse
Maignan	Maxime	France	CHU Grenoble
Malet	Anne	France	CHRU Orléans
Marjanovic	Nicolas	France	CHU Poitiers
Montassier	Emmanuel	France	CHU Nantes
Penaloza	Andrea	Belgium	Bruxelles, Universités cliniques Saint-Luc
Polisset	Nathalie	France	CHU Tours
Schotté	Thibault	France	CH Le Mans
Soulat	Louis	France	CHU Rennes
Vives	Philippe	France	CH Agen

Table 3. Experimental design of the stepped-wedge methodology

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Step 9	Step 10	Step 11	Step 12	Step 13	Step 14	Step 15	Step 16
Center 1	C	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Center 2	C	C	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Center 3	C	C	C	I	I	I	I	I	I	I	I	I	I	I	I	I
Center 4	C	C	C	C	I	I	I	I	I	I	I	I	I	I	I	I
Center 5	C	C	C	C	C	I	I	I	I	I	I	I	I	I	I	I
Center 6	C	C	C	C	C	C	I	I	I	I	I	I	I	I	I	I
Center 7	C	C	C	C	C	C	C	I	I	I	I	I	I	I	I	I
Center 8	C	C	C	C	C	C	C	C	I	I	I	I	I	I	I	I
Center 9	C	C	C	C	C	C	C	C	C	I	I	I	I	I	I	I
Center 10	C	C	C	C	C	C	C	C	C	C	I	I	I	I	I	I
Center 11	C	C	C	C	C	C	C	C	C	C	C	I	I	I	I	I
Center 12	C	C	C	C	C	C	C	C	C	C	C	C	I	I	I	I
Center 13	C	C	C	C	C	C	C	C	C	C	C	C	C	I	I	I
Center 14	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I	I
Center 15	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I

Each step lasts for 2 weeks, except for step 1 which last for 4 weeks and the step 16 which last 7 months. I Intervention, C Control.

PARTICIPANT INFORMATION LETTER

Stratification of the thromboembolic risk using the TRriP(cast) score to guide preventive care decisions in patients having suffered isolated leg trauma requiring rigid or semi-rigid orthopedic immobilization: prospective multicenter interventional trial.

Sponsor
CHU d'Angers
4, rue Larrey
49933 Angers cedex 9

Coordinating Investigator
Dr. Douillet Delphine
Department of Emergency Medicine, CHU Angers
Tel.: 02 41 35 66 50
Fax: 02 41 35 66 51

Principal Investigator
Name: .....
Department: .....
Telephone: .....
Fax: .....

To Whom It May Concern:

You are invited to participate in a clinical trial entitled **CASTING**. The CHU d'Angers is the sponsor of this trial: it assumes responsibility for the trial, its organization, and data management.
Data processing within the scope of the trial is necessary to fulfill a mission of public interest that the CHU d'Angers has invested in.

Before deciding to participate in this trial, it is important that you understand its objective and the implications of your involvement. Please take the time to carefully read through the following information. If you have questions or require further information, please do not hesitate to speak with your physician. You may take as much time as necessary to decide whether or not to participate in the trial.

If you agree to participate, we will ask you to sign a consent form.

1. OBJECTIVE OF THE TRIAL

This trial seeks to assess the interest of screening risk factors for thrombosis (phlebitis or pulmonary embolism) in patients whose leg must be immobilized following trauma.
In fact, having suffered leg trauma exposes you to a risk of phlebitis, i.e. the formation of blood clots in the leg veins, and to the risk of pulmonary embolism (formation of blood clots in a lung artery). In usual practice, a preventative (low) dose of anticoagulant treatment (which reduces the risk of forming a blood clot) is prescribed. However, if you exhibit few or no factors increasing the risk of phlebitis, this treatment would not be useful. This trial aims to confirm this.

This trial will consist of two phases at each participating center: an initial "neutral" phase during which the decision to prescribe a preventative treatment for phlebitis shall be made according to the prescribing physician's usual practices, and a second "interventional" stage during which this decision depends on a score known as TRiP(cast). The TriP(cast) score takes into consideration the characteristics of the trauma, the prescribed immobilization, and the patient. All of these criteria are collected on a daily basis in the usual manner.

The objective of this trial is to demonstrate that this score allows patients to be identified for whom preventative treatment is necessary (significant risk factors) and those for whom it is not useful.

This trial shall take place in France at 15 hospitals and anticipates the participation of approximately 2100 patients.

2. TRIAL PROCESS

If you chose to participate in this trial, the study doctor will fill out an information form to calculate your TRiP(cast) score. Preventative treatment for phlebitis will then be prescribed if applicable according to the conditions corresponding to the respective phase at the center where you are receiving care.

After your visit to the ER, all information regarding you will be sent in a completely secure manner to an assistant to the study doctors, all of whom are bound to patient confidentiality. This assistant will consult your medical records to complete the data gathered for the trial, if necessary. Either the assistant or one of the center's study doctors will contact you twice by telephone approximately 30 and 90 days after your ER visit. You will be asked about the potential onset of a clinical event (phlebitis or pulmonary embolism, bleeding, etc.) as well as the use of healthcare resources related to your care (medications, tests, medical visits, possible hospitalizations). In case you cannot be reached, your primary care physician and/or a healthcare proxy will be asked instead. You may also be contacted by mail. After this phone conversation, access to personal information allowing you to be identified will be deleted, giving you complete anonymity.

Your participation is voluntary and you will not be compensated.

During your participation in this trial, you are forbidden from participating in another interventional trial taking place at the same time. Furthermore, you may not participate in another interventional trial for 3 months after your participation in this trial.

3. ALTERNATIVES TO THE TRIAL PRODUCTS OR THE PROPOSED TRIAL

With the exception of the decision to prescribe (or not) preventative care based on your TRiP(cast) score calculated in the interventional phase, your participation in this trial will not affect the conditions of your care.

4. POTENTIAL RISKS OF THE TRIAL

Adverse events expected in patients included in the trial are the occurrence of thromboembolic events (phlebitis, pulmonary embolism) or bleeding. In the short term, phlebitis causes pain, edema of the leg, involves treatment that thins your blood for several weeks, and may in rare cases lead to long-term complications: postphlebitic syndrome involving feelings of heaviness, cramping, pain, or even a pins and needles sensation in your leg. In the short term, a pulmonary embolism can lead to difficulty breathing, chest pain, or malaise. In very rare cases, pulmonary embolisms can be fatal. In the long term, a pulmonary embolism can in rare cases lead to persistent difficulty breathing related to effort or everyday actions. A low occurrence rate is expected, less than 2%, in the target population of this trial, and participation in the interventional phase of the trial does not seem to pose an increased risk compared to usual practices. In fact, data from previous studies on the TRiP(cast) score show that prescribing a preventative anticoagulant to the sub-group of low-risk patients (score<7) does not yield benefits.

5. POTENTIAL BENEFITS OF THE TRIAL

If the trial hypotheses are confirmed, this study will have a direct impact on future patients receiving care for leg trauma requiring immobilization (reducing prescription rates with no increased risk of thromboembolism) and for insurance agencies (avoiding unnecessary treatment).

6. VOLUNTARY PARTICIPATION

Your participation in this trial is completely volunteer.

You are free to refuse to participate as well as to withdraw your consent at any time without need for justification and without any consequences regarding the quality of care that you will receive. In this case, you must inform the study doctor of your decision.

During the trial, the study doctor will inform you of anything that may influence your willingness to continue participating in the trial.

The Healthcare Authorities, the study doctor, or the sponsor may decide to end your participation in the trial at any time without your prior consent. If this should happen, you would be informed and the justification would be explained to you.

7. RECEIVING ADDITIONAL INFORMATION

A study doctor can respond to your questions concerning this trial and your medical care.

At the end of the trial, you may request to be informed of the overall results of the trial by a study doctor.

8. CONFIDENTIALITY AND MEDICAL DATA USAGE

The objective of processing your data is to carry out this trial, which is compliant with the public interest criteria defined by law. They will be processed pursuant to European

regulations (no. 2016/679 of April 27, 2016) on personal data protection and the French Data Protection Act.

The people who will have access to your medical records for this trial are the team providing care, the clinical research technicians responsible for collecting data under the supervision of the center investigator, and the clinical research associates selected by the CHU d'Angers to ensure the quality of the trial data. All of these individuals are bound to total confidentiality.

The data collected will be sent to the CHU d'Angers. The investigator agrees to never disclose your name and to encode your data before sending it to the database manager. Your data will be associated with a code consisting of the center number and a rank number. Your initials as well as the month and year you were born will also be collected.

The encoded trial data may also be sent to the French Healthcare Authorities.

In compliance with the current legislation for this type of trial, your encoded data will be saved for 15 years after the end of the trial (starting at the end of the final participant's participation). After this time, you will no longer be able to exercise your rights regarding the data processed.

You have the right to access, amend, delete, and limit the processing of your data. These rights may be exercised with the physician performing follow-up as part of the trial and who knows your identity.

If you withdraw your consent during the trial, the data already collected will be processed unless you object thereto. However, this right may not be exercised if the deletion of your data would compromise the analysis of the trial data or make it impossible.

Barring your opposition, research projects on the same subject could be conducted using the data collected for this study. The data that will be used are the anonymized data, preventing you from being identified. If necessary, these data will be sent to other teams of the sponsor and/or other public or private partners, nationally or internationally. The CHU d'Angers will send these data under conditions compliant with the demands of European regulations and will ensure that the destination countries offer a level of data protection considered to be adequate by the European Community.

Before transmission to a third party, including for data analysis, the data will be anonymized by the database manager in the following manner:

- month and year of birth will be replaced by age,
- initials will be deleted,
- all dated related to your care will be replaced by durations.

Data processing in this trial meets the criteria for "Reference Methodology" (MR-001) in accordance with the regulations of the French Act on Data Processing, Data Files and Individual Liberties. The CHU d'Angers, sponsor of the trial, has signed a compliance undertaking regarding this "Reference Methodology."

If you have questions, comments, or complaints regarding the management of your personal data, please contact the physician providing follow-up as part of the trial or the principal investigator of the center. If you have questions regarding data protection in the scope of the trial, you may contact the Data Protection Delegate of the CHU d'Angers (dpo@chu-angers.fr).

The French National Commission on Informatics and Liberty (https://www.cnil.fr) is the French authority authorized to receive all official complaints regarding the processing of your data.

9. PROTECTION OF PEOPLE

This trial is being conducted in compliance with Law No. 2012-300 of March 5, 2012 as well as the regulatory texts concerning research involving human subjects.

Participation in this trial requires that you be affiliated with or a beneficiary of the Social Security system.

10. INSURANCE

The Sponsor has taken insurance guaranteeing its own civil responsibility as well as that of any physician or collaborator involved in conducting the trial for the duration thereof from SHAM (Société Hospitalière d'Assurances Mutuelles, 18 rue Edouard Rochet, 69372 Lyon Cédex 08), SHAM insurance agreement number 147412. It will also ensure complete compensation for any damages resulting from the trial for the person affected and their successors-in-interest unless there is evidence that the damage cannot be attributed to its fault or to that of any contributor and barring any opposition to third-party acts or the voluntary withdrawal of the person who had initially consented to participate in the trial.

11. IRB APPROVAL

The Institutional Review Board CPP Sud-Méditerrannée I has reviewed this research project and granted its approval on October 16, 2019.

If you agree to participate in this trial, please complete and sign the data collection form drawn up in duplicate. You will keep this information letter and a copy of the consent form.

CONSENT FORM

Stratification of the thromboembolic risk using the TRriP(cast) score to guide preventive care decisions in patients having suffered isolated leg trauma requiring rigid or semi-rigid orthopedic immobilization : prospective multicenter interventional trial.

To be filled out by the investigation team

Sponsor
CHU d'Angers
4, rue Larrey
49933 Angers cedex 9

Coordinating Investigator
Delphine DOUILLET

Department of Emergency Medicine
Telephone: 02 41 35 66 50
Fax: 02 41 35 66 51

***Center No.:**|__|__| **Participant No.:**|__|__|__| **Participant Initials:**|__|__|

LAST NAME First Name

**This number will be recorded at least on the investigator copy*

Participant

Last Name:.....

First Name:.....

Date of birth: |__|__|/|__|__|/|__|__|__|__|

My physician has suggested that I participate in the CASTING trial.

I have read and understood the information letter that I received. I have understood the information provided to me orally and in writing. The physician has responded to my questions concerning the trial. I am aware that I may ask questions or request additional information from the physician who informed me of the trial.

I am aware that my participation is completely voluntary. I understand that I will not be responsible for the costs associated with the trial.

I can decide at any time to withdraw from the trial without need for justification and without any consequences regarding the quality of my care.

I understand that the data processed during the trial will be managed in accordance with confidentiality. They will only be consulted by people bound to complete confidentiality belonging to the study doctor's team, the team selected by the sponsor, or by representatives of the French Healthcare Authorities.

I agree to the computer processing of my personal data in accordance with the conditions set forth by the General Data Protection Regulation and by the French Data Protection Data. I was informed of my right to access, amend, and erase my data upon request to the study doctor.
I agree to the computer processing of my encoded data for other subsequent research projects that may be conducted by the sponsor's researchers and/or other public or private partners, nationally or internationally. I was informed of my right to object to this data processing at any time.

I certify that I am affiliated with the Social Security system.

I freely and voluntarily agree to participate in the **CASTING** trial under the conditions set forth by law, as indicated in the information letter I was given.

I was informed that, pursuant to the regulation on trials involving human subjects, the CPP Sud-Méditerranée I granted its authorization to conduct this trial on October 16, 2019.

My consent does not release the trial organizers from their responsibilities. I reserve all my rights guaranteed by law.

Investigator *(To be filled out by the investigator himself)*		**Participant** *(To be filled out by the participant himself/herself)*	
Last name, first name		Last name, first name	
Date		Date	
Signature		Signature	

Made in two original copies, one for the investigator and one for the participant.

Participant letter for the "CASTING" clinical trial

Last Name: _____ **First Name:** _____

Date of Birth: __ __/__ __/__ __ __ __ Date of End of Treatment: __ __/__ __/__ __ __ __

Study Doctor: _____

Telephone: ____ ____ ____ ____ ____

Clinical Research Technician: _____

Telephone: ____ ____ ____ ____ ____

CHU ANGERS CENTRE HOSPITALIER UNIVERSITAIRE

This trial is being carried out by the CHU d'Angers *version 1*
from 09/27/2019

Contact us as well as your primary care physician / center 15 in case of the following symptoms:

- Symptoms and signs of phlebitis
  - Swollen leg and/or leg pain and/or appearance of localized redness and heat
- Symptoms and signs of pulmonary embolism
  - Difficulty breathing, shortness of breath
  - Chest pain
  - Malaise, loss of consciousness
  - Coughing up blood

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract Page 4
	2b	All items from the World Health Organization Trial Registration Data Set	Page 4
Protocol version	3	Date and version identifier	Title
Funding	4	Sources and types of financial, material, and other support	Page 10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page Page 10 Page 11
	5b	Name and contact information for the trial sponsor	Title page
	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	Page 10

	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)	Page 5 Acknowlegment Page 10
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	Page 3
	6b	Explanation for choice of comparators	Page 5
Objectives	7	Specific objectives or hypotheses	Page 4
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, noninferiority, exploratory)	Page 5
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	Page 5
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)	Page 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 6
	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)	NA

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 6
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	Page 4
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)	Page 5 Table 3
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	Page 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 6
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 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	Page 5
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	Page 5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 5

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	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 known. Reference to where data collection forms can be found, if not in the protocol	Page 6
	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	Page 7
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	Page 5
Statistical methods	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	Page 7-8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 7-8
	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)	Page 7-8
Methods: Monitoring			

Data monitoring	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 its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 5
	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	NA
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	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 5
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 9
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)	Abstract Page 4
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	Page 6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
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	NA
Dissemination policy	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	Page 11
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 1
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	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Thromboembolic Risk Stratification by TRiP(cast) Score to Rationalise Thromboprophylaxis in Patients with Lower Leg Trauma Requiring Immobilisation: Study Protocol of the CASTING Stepped-wedge Cluster Randomised Trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045905.R1
Article Type:	Protocol
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Title:

Thromboembolic Risk Stratification by TRiP(cast) Score to Rationalise Thromboprophylaxis in Patients with Lower Leg Trauma Requiring Immobilisation: Study Protocol of the CASTING Stepped-wedge Cluster Randomised Trial.

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Abstract

Introduction

Patients with lower limb trauma requiring orthopaedic immobilisation may be at risk of venous thromboembolism but opinions differ about who may benefit from thromboprophylactic anticoagulant treatment.

The aim of this CASTING study is to demonstrate the safety of thromboprophylaxis based on the TRiP(cast) score with regards to the three-month incidence of symptomatic venous thrombo-embolism events (VTE) in low-risk patients not receiving thromboprophylaxis, as well as the usefulness of this strategy on the rate of patients receiving anticoagulant treatment in comparison to current practice.

Methods and analysis

CASTING will be a stepped-wedge cluster randomised controlled clinical trial, performed in 15 emergency departments in France and Belgium. With their informed consent, outpatients admitted to one of the participating emergency departments for a lower limb trauma requiring orthopaedic immobilisation without surgery will be included. All centres will begin the trial with the "observational period" and, every two weeks, one centre will be randomly assigned to switch to the "interventional period" and to apply the TRiP(cast) score, in which only patients with a score ≥ 7 will receive thromboprophylactic anticoagulant treatment. The primary endpoint is the rate of clinical thromboembolic events within 90 days following the inclusion of low-risk patients not receiving thromboprophylaxis.

Ethics and dissemination

The protocol has been approved by the Comité de Protection des Personnes Sud I (Ethics Review ID-RCB: 2019-A01829-48) for France and the Comité d'éthique hôpital-facultaire Saint Luc (N° B403201941338) for Belgium. It is carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The findings of this study will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration NCT04064489.

'Strengths and limitations of this study'

- The CASTING Study will be the first prospective study evaluating the implementation of a risk-stratification model for thromboprophylaxis in patients with lower limb trauma and orthopaedic immobilisation.
- The CASTING trial will be a prospective stepped-wedge randomised clinical trial in 15 emergency departments in France and Belgium.
- A medico-economic analysis will be carried out to demonstrate the efficiency of this strategy.
- Due to the design, the study staff and participating investigators are not blinded to the period which is a limitation.

INTRODUCTION

Lower limb traumas requiring orthopaedic immobilisation (plaster or splint) without surgery are a common reason for admission to the emergency department (ED). In Australia for example, over 90,000 ankle and/or foot soft tissue injuries were recorded in 2014-2015 [1]. Due to venous stasis caused by immobilisation, hypercoagulable states and vascular injuries brought on by the trauma, these patients are at risk of developing venous thromboembolism (VTE)[2]. The odds-ratio (OR) of developing deep venous thrombosis (DVT) or pulmonary embolism (PE) following immobilisation with a cast boot is estimated to be 8.3 (95% confidence interval (CI): 5.3-12.9) after adjusting for age, gender, body mass index (BMI) and levels of regular physical activity [3]. Moreover, in patients immobilised using cast boots, the risk is higher if the indication is traumatic rather than non-traumatic: OR 12.7 (95% CI 6.6-24.6) vs 7.6 (95% CI 0.9-66.4)[3]. For this reason, the current practice in many countries, and especially in France and Belgium, is to prescribe thromboprophylaxis for the majority of patients with lower limb trauma and orthopaedic immobilisation [4,5]. Indeed, the efficacy (including asymptomatic thromboembolism and distal deep venous thrombosis) of low molecular weight heparin (LMWH) and fondaparinux has been shown in selected patient populations [6–8]. However, the risk/benefit ratio of this treatment is still controversial [9,10]. The largest randomised controlled study on the subject did not show any benefit of LMWH on the rate of symptomatic VTE among 1,435 non-selected patients. Venous thromboembolism occurred in 10 of the 719 patients (1.4%) in the treated group and in 13 of the 716 patients (1.8%) in the control group (absolute difference in risk −0.4%; 95% CI, −1.8 to 1.0%) [11]. Moreover, the cost of this therapy is considerable. Therefore, in 2017, the Cochrane meta-analysis concluded that a stratification of thromboembolism risk was required [1] in order to identify high-risk patients with lower leg cast immobilisation who may benefit from thromboprophylaxis and low-risk patients who will not [12–14].

Risk assessment models have been developed to establish the individual VTE risk of each patient [5,15,16]. The Leiden-TRiP(cast) (Leiden-Thrombosis Risk Prediction for patients with cast immobilisation score) was developed in the Netherlands, using data from a large population-based case-control study [15]. It was retrospectively validated in two independent datasets. The TIP score was developed using a very different approach, i.e., via an international panel of experts and professionals using the Delphi consensus method and validated in a large case-control cohort (MEGA-study) [5]. Thanks to an international collaboration, we recently developed and validated a combined and simplified version of the two earlier prediction models developed for VTE risk following lower-limb immobilisation: the TRiP(cast) score (Thrombosis Risk Prediction in patients with cast immobilisation score) [16] (Table 1). This is made up of 14 variables; the trauma severity, the kind of immobilisation and 12 variables related to the patient's characteristics. The TRiP(cast) score is easy to calculate thanks to a digital application developed for IOS and the Android mobile platform (14). In external validation on the POT-CAST database, it exhibited an Area Under the

Curve (AUC) of 0.74 (95%CI 0.61-0.87). The calibration plot confirmed a good correspondence between the observed and predicted risks (intercept 0.0016 and slope 0.0933). Using a cut-off score of 7, the sensitivity, specificity, positive and negative predictive values were 76.1%, 51.2%, 2.5%, and 99.2%, respectively. With this cut-off, it is possible to identify a large group of patients at very low risk of developing VTE. In the validation dataset, low-risk patients (score < 7) represented 50.7% (n=728/1435) of the total patients and their observed symptomatic VTE risk was 0.8% (95% CI 0.3 – 1.7). Conversely, high-risk patients (score ≥ 7) represented 49.3% (n=707/1435) of the total patients and their observed symptomatic VTE risk was 2.5% (95% CI 1.6 – 4.0). Among low-risk patients treated with LMWH, 0.4% (1.3/360) developed symptomatic VTE as compared to 1.1% (4.2/367.8) in untreated patients: relative risk (RR) 0.30 (95%CI 0.03-2.60) [16]. In a French monocentric prospective study, this subgroup corresponded to 70% of patients with lower limb trauma and orthopaedic immobilisation [5].

Aim and hypothesis

The aim of the CASTING study is to demonstrate, in patients with lower limb trauma requiring orthopaedic immobilisation and admitted to the ED, the safety of thromboprophylaxis based on the TRiP(cast) score with regards to the three-month rate of symptomatic VTE in low-risk patients not receiving thromboprophylaxis, as well as the usefulness of this strategy on the rate of patients receiving anticoagulant treatment as compared to current practice.

METHODS AND ANALYSIS

Study design

The CASTING trial (NCT04064489) will be a prospective stepped-wedge randomised clinical trial in France and Belgium [17].

Trial objectives and outcomes

Primary objective and outcome

The main objective will be to demonstrate the reliability and the safety of a TRiP(cast) score <7 in order to not consider thromboprophylaxis for emergency patients with lower limb trauma requiring orthopaedic immobilisation without surgery. The primary outcome will be the rate of symptomatic venous thromboembolism events (objectively confirmed DVT or PE, fatal PE and unexplained sudden death) during the three-month follow-up period among patients with a TRiP(cast) score <7 without thromboprophylaxis. The TRiP(cast) score will be considered reliable if the rate of VTE is lower than or equal to 1%, with an upper limit of the 95% confidence interval lower than or equal to 2% (non-inferiority hypothesis). An independent adjudication committee will assess all potential clinical events centrally, confirm or deny their occurrence and decide on their severity. Final assignments of the suspected symptomatic VTE, suspected major bleeding or suspected non-major clinically relevant bleeding will be based on the consensus of the Independent Adjudication

Committee of Clinical Events [18]. Members of the adjudication committee are experienced clinicians independent from the investigators and the sponsor.

Secondary objectives

The first secondary objective will be to demonstrate that the implementation of the TRiP(cast) score during the interventional period significantly reduces the rate of patients receiving thromboprophylaxis compared to current practice during the observational period.

The other secondary objectives will be to compare current practice (observational period) and thromboprophylaxis based on the TRiP(cast) score (interventional period):

1) The rate of symptomatic VTE at 90 days;

2) The rate of major bleeding according to the criteria proposed by the International Society on Thrombosis and Haemostasis [19]:

1. Fatal bleeding, and/or

2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or

3. Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells.

3) The rate of non-major clinically relevant bleeding is defined as any bleeding requiring hospitalisation or a medical intervention including temporary withholding of anticoagulant treatment to stop the bleeding at 90 days.

Finally, we will perform a medico-economic analysis between current practice (observational period) and thromboprophylaxis based on the TRiP(cast) score (interventional period) within 90 days of inclusion, focusing on the cost-utility ratio in terms of cost per quality-adjusted life year (QALY) gained (primary analysis), and the cost-effectiveness ratio in terms of cost per symptomatic VTE avoided (secondary analysis).

Experimental plan for the stepped-wedge design

In this stepped-wedge clinical trial, patients will be recruited in 15 EDs in France and Belgium, from academic and non-academic centres, and from rural and urban communities (Table 2). All centres will begin the trial with the “observational period” and every two weeks one centre will be randomly assigned to switch to the “interventional period” and to apply the TRiP(cast) score. After 32 weeks, all centres will be in the “interventional period” for the seven months of the trial remaining (Table 3). The order of centres changing to the interventional phase will be developed using non-stratified list randomisation. This randomisation will be carried out by the methodological managers of the Research and Innovation Department of Angers University Hospital (including the data management). The inclusion rate will be closely monitored during the trial, and time periods will be adjusted if the number of patients included differs substantially from expectation in order to respect the number of subjects required in the observational phase [20]. No data monitoring committee has been set up as this is not a drug study but an implemented strategy. A monitoring grade has been

defined according to the risk of the study according to the promoter's procedures (i.e. grade 1: low level of risk).

This design was chosen for the following reasons:

- The comparison with current practice was chosen because of the lack of updated recommendation and consensus guidelines on thromboprophylaxis in patients with lower limb trauma and orthopaedic immobilisation. Indeed, the 2012 US recommendations advised against systematic preventative treatment if the patient does not require surgery whereas the 2011 French guidelines suggest thromboprophylaxis for all patients without possible foot support if there is not a high risk of bleeding [21,22]. Therefore, the decision to introduce thromboprophylaxis varies from country to country, from centre to centre and even from doctor to doctor [4].

– Comparison to current practice precludes randomisation at the patient level or a crossover design that would induce bias through contamination. The implementation of the score will change healthcare practices and an emergency physician who would have used the TRiP(cast) score during the study will be influenced by the score criteria and will change his/her “standard of care” in deciding on thromboprophylaxis.

- A cluster, stepped-wedge design prevents such contamination and also prevents a potential “period effect” that could have resulted from a simple before/after design.

- This design is especially suited for emergency departments because it is less time-consuming than randomisation at the patient level, as the physician knows, prior to patient inclusion, what he/she will do if the patient agrees to participate in the study.

- The robustness of the stepped-wedge design is widely recognised [23,24] and this methodology is increasingly used in studies aimed at implementing changes in care practices [17].

Study settings and population

The CASTING Trial will involve patients with isolated lower limb trauma requiring rigid (plaster or resin) or semi-rigid immobilisation for an anticipated duration of at least seven days. It will be a continuous recruitment process. Therefore, consecutive adult patients who are admitted for this reason to one of the participating emergency departments will be assessed for inclusion. They must have up-to-date health insurance coverage and express in writing their consent to participate in the study after verbal and written explanations of the procedure, as recommended in clinical and research good practices (Additional file 1). If the patient is unable to consent, then the physician will seek consent from a trusted person, family member or close relative. If none is available, the physician can proceed to an “emergency inclusion” without prior consent. Therefore and as soon as possible, a written informed consent to pursue study participation will be requested of the patient or a trustworthy person as soon as possible. In case of refusal, the patient will be excluded from the trial (L1122-1-2 article of the French Public Health Code).

Patients will be excluded if they have any of the following:

- Current anticoagulant treatment at time of trauma,
- Trauma requiring surgery or hospitalisation for more than two days (excluding short-term hospital stay) at time of inclusion,
- Comorbidity or comorbidities requiring hospitalisation at time of inclusion,
- Any factor that makes 90-day follow-up impossible,
- Legal protection measures (tutorship or curatorship) or detainee status.

Description of the intervention

In both study periods, patients admitted for lower limb trauma requiring rigid or semi-rigid immobilisation without surgery will be evaluated for potential inclusion. After verifying eligibility and obtaining patient consent, the investigator will proceed to inclusion. The patient's characteristics including thromboembolism risk factors, the kind of trauma and the type of immobilisation, as well as the anticipated duration of immobilisation will be collected. The data will be recorded in an electronic case report form (e-CRF), available on smartphones, tablets and computers and secured by a personal password. All personal data will be subsequently anonymised. All patients included will receive a study participation card including emergency phone numbers and the phone number of the local principal investigator of the trial (Additional file 2). Participants may not participate in any other intervention trial during the CASTING study participation period.

Observational control period

During this period, the TRiP(cast) score will not be calculated. Physicians will be free to decide whether or not to prescribe thromboprophylactic treatment with LMWH or fondaparinux depending on local practice. To avoid contamination bias, the first question of the CRF is whether or not the physician-in-charge has considered preventive anticoagulation. They can fill the TRiP(cast) score variables into the CRF only when they have answered this question.

Interventional period

During this period, the TRiP(cast) score will be prospectively calculated and the use of thromboprophylactic treatment will be based on its result. When the emergency physician records the patient's data on the e-CRF, the TRiP(cast) score will be automatically calculated. The physician will be advised to prescribe LMWH or Fondaparinux if the score is 7 or higher, otherwise not to introduce thromboprophylaxis (score<7). According to the preference of individual hospitals and national recommendations, the following 4 treatments could be used, all as one daily subcutaneous injection: Enoxaparin 40mg, Nadroparin 2850 IU, Dalteparin 2500 IU or Fondaparinux 2.5mg.

Follow-up

In both periods, the patients included will receive a follow-up consultation by phone at 30 days and 90 days after inclusion, in order to collect data on potential clinical events (thromboembolic events, haemorrhages, thrombocytopenia or other adverse effects), and on the use of healthcare resources linked to thromboprophylaxis (anticoagulant treatments, biological examinations, medical consultations or subsequent hospitalisations). The phone interviews will be performed using a standardised follow-up form at each centre.

An independent adjudication committee will assess all potential clinical events in order to confirm their occurrence and decide on their severity.

Statistical analysis

Descriptive analysis

Quantitative variables will be described in terms of mean +/- standard deviation in cases of Gaussian distribution. Otherwise, they will be described in terms of median and inter-quartile range. Qualitative variables will be described in terms of numbers and frequencies. A comparison of patient characteristics between the two referral strategies will be evaluated using the Student, Mann-Whitney, or Fisher's exact test, depending on the context.

Main objective

The main analysis will be conducted on patients enrolled during the interventional period and who will not receive a thromboprophylactic anticoagulant treatment because of a TRiP(cast) score below 7. The rate of symptomatic VTE that occurred between emergency department discharge and the three-month follow-up and its 95% confidence interval will be estimated using a logistic mixed model with a random effect on centre. The TRiP(cast) score will be considered reliable if the upper 95% confidence limit of VTE rate is less than 2%. A sensitivity analysis will be performed as an intention-to-treat analysis taking into account all patients with a TRiP(cast) score <7.

Secondary objectives

The first secondary outcome will be analysed on the “intention-to-treat” population, meaning all evaluable patients included in the observational period versus all evaluable patients included in the interventional period. A logistic mixed model with a random effect on centre will be conducted which will allow the intra- inter-cluster correlations to be taken into account. A two-sided test with a type I error rate of 5% will be conducted.

The 90-day incidence of symptomatic VTE (including fatal PE and unexplained sudden deaths), major bleeding (including fatal bleeding) and non-major clinically relevant bleeding during the control period and the interventional period will be compared using the same method.

The results will be presented as the absolute difference in rates between the two periods and their 95% confidence interval.

Sensitivity analyses

Sensitivity analyses will be performed excluding patients from centres with a mean rate of inclusion by month below 5.

All the analyses will be conducted using R software R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Missing Data

No imputation of missing data is planned. However, missing data will be analysed to determine whether they are informative and whether they are likely to lead to potential selection or information bias.

Multiple testing

A hierarchical management of objectives will be carried out, making it possible to limit the problem of multiplicity. Moreover, when necessary, a correction will be made allowing a control of the FWER at a risk of 5%.

Trial results will be reported in accordance with the extended SPIRIT guidance for cluster randomised trials.

Sample size calculation

Taking a 1% rate of symptomatic VTE in the low-risk group of patients [2], 753 patients would be required to obtain a higher limit of the 95% confidence interval that is lower than or equal to 2%. In the POT-CAST trial the proportion of low-risk patients according to the TRiP(cast) score (score <7) was 51%. However, only patients with rigid immobilisation were included [11]. In the CASTING study, we will include immobilised patients with either a rigid or semi-rigid splint or brace, and, conversely, patients requiring surgery at inclusion will be excluded. In a monocentric study conducted in Angers, the proportion of low-risk patients according to the TRiP(cast) score (score <7) was 67% [5]. Considering that this rate would be ≥60% in the population included in the CASTING study and the possibility of patients lost to follow-up or patients who cannot be analysed at 5%, the number of patients to include in the trial has been set at 1,400 in the interventional period with a type-I error rate of 5% and a power of 80%.

The number of patients to be included in the observational period has been established from the first secondary objective. Considering a 15% difference in the rate of patients receiving prophylactic anticoagulant treatment during the interventional period versus the control period, participation of 15 centres and an intra-class correlation coefficient (centre effect) of 0.1, 540 patients would be needed at each stage to demonstrate a significant difference with a 5% alpha risk and power of 80%. Taking into account the possibility of patients lost to follow-up and patients who cannot be analysed, the number of patients to be included in the control observational period was set at 600. The total number of participants in the study has thus been set at 2,000 patients across 15 centres.

Patient and Public Involvement

The current trial will be conducted without direct patient involvement. The ethics committee (Comité de Protection des Personnes Sud I) includes patient representatives, charged with the responsibility of protecting patient rights; thus, the CASTING trial protocol was reviewed by a

patient representative. Besides the above review process, patients will not be invited to comment on the study design and interpretation of the study results. Patients were not involved in the writing of this manuscript.

ETHICS AND DISSEMINATION

Informed consent will be obtained from all study participants whenever possible. If the patient is unable to consent, informed consent from a relative will be obtained. An Institutional Review Board has authorised the study (Comité de Protection des Personnes Sud I, ID-RCB: 2019-A01829-48 the October 16th, 2020) for all participating centres and authorisation was granted by the ethics committee of the participating hospital in Belgium (Comité d'éthique hôpital-facultaire Saint Luc, N° B403201941338). The trial has been designed on the basis of the SPIRIT guidelines and Standard Protocol Items [25]. A SPIRIT checklist file is attached (Additional file 3).

The results of this study will be published in peer-reviewed manuscripts and will be presented to local community groups and stakeholders, as well as at national and international conferences as applicable. The authorship guidelines [26] will be followed for all relevant publications and presentations. Open access publication of this protocol will facilitate full public access.

Discussion

To our knowledge, this study protocol describes the first prospective, multi-centric study evaluating the implementation of a risk-stratification model for thromboprophylaxis in patients with lower limb trauma and orthopaedic immobilisation.

It is based on a well-validated model, the TRiP(cast) score, which has been effective in defining low-risk patients that would not benefit from prophylactic anticoagulant treatment. If our hypotheses are confirmed, the CASTING trial will confirm that a large number of patients with lower limb trauma requiring orthopaedic immobilisation without surgery could safely not receive any thromboprophylaxis, and conversely that some patients not receiving treatment in current practice could benefit from thromboprophylaxis. Indeed, in a monocentric, observational pilot study, 35.5% (11/30) of patients classified as being at high risk of VTE according to the TRiP(cast) score did not receive preventative treatment. Among them, one patient developed a deep venous thromboembolism. On the other hand, 31.5% of patients classified as being low risk (52/165) (63.3% of all patients) received thromboprophylactic anticoagulant treatment [5]. The cost of this treatment and its impact on the day-to-day lives of patients, due to its subcutaneous administration, are significant. Pandor et al. suggest that risk-based strategies are potentially more cost-effective in limiting thromboprophylaxis [9]. Due to the high frequency of lower limb trauma, this represents significant healthcare costs [27,28]. By presenting a high level of evidence thanks to the stepped-wedge design, it is possible to confirm that the implementation of the TRiP(cast) score leads to a significant decrease in the rate of patients receiving anticoagulant treatment and an improvement

on the cost-utility ratio, indicating that the CASTING study will have an important impact on patient care and public health.

The results of the CASTING study are particularly highly anticipated and after the protocol was reviewed and approved by the French and Belgian ethics committees, recruitment began on 22 June 2020. The results are anticipated by the end of 2021.

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Declarations

Ethics approval and consent to participate

All participants invited will provide informed consent prior to gaining access to the online survey. On the consent form, participants will be asked if they agree to use of their data and asked to confirm that they are aware of the option of withdrawing from the trial at a later date. Participants will also be asked for permission for the research team to share relevant data with people from the universities taking part in the research or from regulatory authorities, where relevant. This trial does

not involve collecting biological specimens for storage. There is no risk of harm anticipated and no compensation provided for trial participation.

Authors' contributions

DD, PMR, AP conceived the overarching study. DD, PMR, AP participated in the elaboration of the study design and writing of the protocol. JR is responsible for the statistical analysis. AD is responsible for the medico-economic analysis. AC, OH, ATD, MT and TM made substantial contributions to the protocol and this article. All authors take responsibility for this paper as a whole. All authors contributed critical analysis, interpretation and writing within all drafts and approved the final draft for submission.

Funding

The trial is funded by a grant from the French Ministry of Health (PHRCI-18-056). The funding body agreed to the design of the study and has no role in the collection, analysis, or interpretation of the data, nor in the writing of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not Applicable.

Availability of data and materials

The dataset from this study will be safely stored following the principles of research ethics. Upon completion of the study, data may be made available by the corresponding author upon request and with justification. The results of this study will be disseminated through publications in journals and presentation of abstracts in scientific conferences.

Acknowledgements

We would like to thank the HUGO network for their financial support and the support of the Department of Innovation and Research of Angers University Hospital. We would like to thank all the partner centres that agreed to participate in this study.

Additional files

Additional file 1. Consent

Additional file 2. Study participation card

Additional file 3. SPIRIT checklist

Abbreviations

AUC: Area Under the Curve, BMI: Body Mass Index; eCRF: Electronic Case Report Form; ED: Emergency Department; ICEC : Independent Clinical Events Committee; LMWH: Low Molecular Weight Heparin; OR Odds Ratio; QALY: Quality Adjusted Life Year; TRiP(cast): Thrombosis Risk Prediction for patients with cast immobilisation score; VTE: Venous thromboembolism.

Table 1. TRiP(cast) score*

Trauma †	Points
High-risk trauma	
Fibula and/or tibia shaft fracture	**3**
Tibial plateau fracture	
Achilles tendon rupture	
Intermediate-risk trauma	
Bi or tri-malleolar ankle fracture	
Patellar fracture	**2**
Ankle dislocation, Lisfranc injury	
Severe knee sprain (with oedema / haemarthrosis)	
Severe ankle sprain (grade 3)	
Low-risk trauma	
Single malleolar ankle fracture	
Patellar dislocation	**1**
(Meta)Tarsal bone(s) or forefoot fracture	
Non-severe knee sprain or ankle sprain (grade 1 or 2)	
Significant muscle injury	
Immobilisation ‡	
Upper-leg cast	**3**
Lower-leg cast	**2**
Foot cast (ankle free) or any semi-rigid cast without plantar support	**1**
Other cast or bracing with plantar support	**0**
Patient characteristics §	
Age <35 years	**0**
Age ≥ 35 and <55 years	**1**
Age ≥ 55 and <75 years	**2**
Age ≥ 75 years	**3**
Male sex	**1**
Body Mass Index BMI ≥25 and <35 kg/m^2	**1**
Body Mass Index BMI ≥35kg/m^2	**2**
Family history of VTE (first-degree relative)	**2**
Personal history of VTE or known major thrombophilia	**4**
Current use of oral contraceptives or Estrogenic hormone therapy	**4**
Cancer diagnosis within the past 5 years	**3**
Pregnancy or puerperium	**3**
Immobilisation (other) within the past 3 months ||	**2**
Hospital admission, bedridden or flight > 6 hours, Lower limb paralysis	
Surgery within the past 3 months	**2**
Comorbidity	**1**
Heart failure, rheumatoid arthritis, chronic kidney disease, COPD, IBD	
Chronic venous insufficiency *(varicose veins)*	**1**

* Thrombosis Risk Prediction in patients with cast immobilisation score
TRiP(cast) score is the sum of the Trauma, Immobilisation and Patient component scores
† Trauma: Choose one, (the most severe trauma)
‡ Immobilisation: Choose one
§ Patient: multiple points can be scored
|| Other immobility next to cast immobilisation

Table 2. List of the principal investigators of participating centres

Surname	First Name	Country	Hospital
Baudin	Laure	France	CH Cholet
Brice	Christian	France	CH St Brieuc
Casalino	Enrique	France	APHP Paris, Bichat
Douillet	Delphine	France	CHU Angers
Dumas	Florence	France	APHP Paris, Cochin
Lecoules	Nathalie	France	CHU Toulouse
Maignan	Maxime	France	CHU Grenoble
Malet	Anne	France	CHRU Orléans
Marjanovic	Nicolas	France	CHU Poitiers
Montassier	Emmanuel	France	CHU Nantes
Penaloza	Andrea	Belgium	Bruxelles, Universités cliniques Saint-Luc
Polisset	Nathalie	France	CHU Tours
Schotté	Thibault	France	CH Le Mans
Soulat	Louis	France	CHU Rennes
Vives	Philippe	France	CH Agen

Table 3. Experimental design of the stepped-wedge methodology

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Step 9	Step 10	Step 11	Step 12	Step 13	Step 14	Step 15	Step 16
Centre 1	C	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Centre 2	C	C	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Centre 3	C	C	C	I	I	I	I	I	I	I	I	I	I	I	I	I
Centre 4	C	C	C	C	I	I	I	I	I	I	I	I	I	I	I	I
Centre 5	C	C	C	C	C	I	I	I	I	I	I	I	I	I	I	I
Centre 6	C	C	C	C	C	C	I	I	I	I	I	I	I	I	I	I
Centre 7	C	C	C	C	C	C	C	I	I	I	I	I	I	I	I	I
Centre 8	C	C	C	C	C	C	C	C	I	I	I	I	I	I	I	I
Centre 9	C	C	C	C	C	C	C	C	C	I	I	I	I	I	I	I
Centre 10	C	C	C	C	C	C	C	C	C	C	I	I	I	I	I	I
Centre 11	C	C	C	C	C	C	C	C	C	C	C	I	I	I	I	I
Centre 12	C	C	C	C	C	C	C	C	C	C	C	C	I	I	I	I
Centre 13	C	C	C	C	C	C	C	C	C	C	C	C	C	I	I	I
Centre 14	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I	I
Centre 15	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I

Each step lasts for 2 weeks, except for step 1 which last for 4 weeks and step 16 which last 7 months. I Intervention, C Control.

PARTICIPANT INFORMATION LETTER

Stratification of the thromboembolic risk using the TRriP(cast) score to guide preventive care decisions in patients having suffered isolated leg trauma requiring rigid or semi-rigid orthopedic immobilization: prospective multicenter interventional trial.

Sponsor
CHU d'Angers
4, rue Larrey
49933 Angers cedex 9

Coordinating Investigator
Dr. Douillet Delphine
Department of Emergency Medicine, CHU Angers
Tel.: 02 41 35 66 50
Fax: 02 41 35 66 51

Principal Investigator
Name: .....
Department: .....
Telephone: .....
Fax: .....

To Whom It May Concern:

You are invited to participate in a clinical trial entitled **CASTING**. The CHU d'Angers is the sponsor of this trial: it assumes responsibility for the trial, its organization, and data management.
Data processing within the scope of the trial is necessary to fulfill a mission of public interest that the CHU d'Angers has invested in.

Before deciding to participate in this trial, it is important that you understand its objective and the implications of your involvement. Please take the time to carefully read through the following information. If you have questions or require further information, please do not hesitate to speak with your physician. You may take as much time as necessary to decide whether or not to participate in the trial.

If you agree to participate, we will ask you to sign a consent form.

1. OBJECTIVE OF THE TRIAL

This trial seeks to assess the interest of screening risk factors for thrombosis (phlebitis or pulmonary embolism) in patients whose leg must be immobilized following trauma.
In fact, having suffered leg trauma exposes you to a risk of phlebitis, i.e. the formation of blood clots in the leg veins, and to the risk of pulmonary embolism (formation of blood clots in a lung artery). In usual practice, a preventative (low) dose of anticoagulant treatment (which reduces the risk of forming a blood clot) is prescribed. However, if you exhibit few or no factors increasing the risk of phlebitis, this treatment would not be useful. This trial aims to confirm this.

This trial will consist of two phases at each participating center: an initial "neutral" phase during which the decision to prescribe a preventative treatment for phlebitis shall be made according to the prescribing physician's usual practices, and a second "interventional" stage during which this decision depends on a score known as TRiP(cast). The TriP(cast) score takes into consideration the characteristics of the trauma, the prescribed immobilization, and the patient. All of these criteria are collected on a daily basis in the usual manner.

The objective of this trial is to demonstrate that this score allows patients to be identified for whom preventative treatment is necessary (significant risk factors) and those for whom it is not useful.

This trial shall take place in France at 15 hospitals and anticipates the participation of approximately 2100 patients.

2. TRIAL PROCESS

If you chose to participate in this trial, the study doctor will fill out an information form to calculate your TRiP(cast) score. Preventative treatment for phlebitis will then be prescribed if applicable according to the conditions corresponding to the respective phase at the center where you are receiving care.

After your visit to the ER, all information regarding you will be sent in a completely secure manner to an assistant to the study doctors, all of whom are bound to patient confidentiality. This assistant will consult your medical records to complete the data gathered for the trial, if necessary. Either the assistant or one of the center's study doctors will contact you twice by telephone approximately 30 and 90 days after your ER visit. You will be asked about the potential onset of a clinical event (phlebitis or pulmonary embolism, bleeding, etc.) as well as the use of healthcare resources related to your care (medications, tests, medical visits, possible hospitalizations). In case you cannot be reached, your primary care physician and/or a healthcare proxy will be asked instead. You may also be contacted by mail. After this phone conversation, access to personal information allowing you to be identified will be deleted, giving you complete anonymity.

Your participation is voluntary and you will not be compensated.

During your participation in this trial, you are forbidden from participating in another interventional trial taking place at the same time. Furthermore, you may not participate in another interventional trial for 3 months after your participation in this trial.

3. ALTERNATIVES TO THE TRIAL PRODUCTS OR THE PROPOSED TRIAL

With the exception of the decision to prescribe (or not) preventative care based on your TRiP(cast) score calculated in the interventional phase, your participation in this trial will not affect the conditions of your care.

4. POTENTIAL RISKS OF THE TRIAL

Adverse events expected in patients included in the trial are the occurrence of thromboembolic events (phlebitis, pulmonary embolism) or bleeding. In the short term, phlebitis causes pain, edema of the leg, involves treatment that thins your blood for several weeks, and may in rare cases lead to long-term complications: postphlebitic syndrome involving feelings of heaviness, cramping, pain, or even a pins and needles sensation in your leg. In the short term, a pulmonary embolism can lead to difficulty breathing, chest pain, or malaise. In very rare cases, pulmonary embolisms can be fatal. In the long term, a pulmonary embolism can in rare cases lead to persistent difficulty breathing related to effort or everyday actions. A low occurrence rate is expected, less than 2%, in the target population of this trial, and participation in the interventional phase of the trial does not seem to pose an increased risk compared to usual practices. In fact, data from previous studies on the TRiP(cast) score show that prescribing a preventative anticoagulant to the sub-group of low-risk patients (score<7) does not yield benefits.

5. POTENTIAL BENEFITS OF THE TRIAL

If the trial hypotheses are confirmed, this study will have a direct impact on future patients receiving care for leg trauma requiring immobilization (reducing prescription rates with no increased risk of thromboembolism) and for insurance agencies (avoiding unnecessary treatment).

6. VOLUNTARY PARTICIPATION

Your participation in this trial is completely volunteer.

You are free to refuse to participate as well as to withdraw your consent at any time without need for justification and without any consequences regarding the quality of care that you will receive. In this case, you must inform the study doctor of your decision.

During the trial, the study doctor will inform you of anything that may influence your willingness to continue participating in the trial.

The Healthcare Authorities, the study doctor, or the sponsor may decide to end your participation in the trial at any time without your prior consent. If this should happen, you would be informed and the justification would be explained to you.

7. RECEIVING ADDITIONAL INFORMATION

A study doctor can respond to your questions concerning this trial and your medical care.

At the end of the trial, you may request to be informed of the overall results of the trial by a study doctor.

8. CONFIDENTIALITY AND MEDICAL DATA USAGE

The objective of processing your data is to carry out this trial, which is compliant with the public interest criteria defined by law. They will be processed pursuant to European

regulations (no. 2016/679 of April 27, 2016) on personal data protection and the French Data Protection Act.

The people who will have access to your medical records for this trial are the team providing care, the clinical research technicians responsible for collecting data under the supervision of the center investigator, and the clinical research associates selected by the CHU d'Angers to ensure the quality of the trial data. All of these individuals are bound to total confidentiality.

The data collected will be sent to the CHU d'Angers. The investigator agrees to never disclose your name and to encode your data before sending it to the database manager. Your data will be associated with a code consisting of the center number and a rank number. Your initials as well as the month and year you were born will also be collected.

The encoded trial data may also be sent to the French Healthcare Authorities.

In compliance with the current legislation for this type of trial, your encoded data will be saved for 15 years after the end of the trial (starting at the end of the final participant's participation). After this time, you will no longer be able to exercise your rights regarding the data processed.

You have the right to access, amend, delete, and limit the processing of your data. These rights may be exercised with the physician performing follow-up as part of the trial and who knows your identity.

If you withdraw your consent during the trial, the data already collected will be processed unless you object thereto. However, this right may not be exercised if the deletion of your data would compromise the analysis of the trial data or make it impossible.

Barring your opposition, research projects on the same subject could be conducted using the data collected for this study. The data that will be used are the anonymized data, preventing you from being identified. If necessary, these data will be sent to other teams of the sponsor and/or other public or private partners, nationally or internationally. The CHU d'Angers will send these data under conditions compliant with the demands of European regulations and will ensure that the destination countries offer a level of data protection considered to be adequate by the European Community.

Before transmission to a third party, including for data analysis, the data will be anonymized by the database manager in the following manner:

- month and year of birth will be replaced by age,
- initials will be deleted,
- all dated related to your care will be replaced by durations.

Data processing in this trial meets the criteria for "Reference Methodology" (MR-001) in accordance with the regulations of the French Act on Data Processing, Data Files and Individual Liberties. The CHU d'Angers, sponsor of the trial, has signed a compliance undertaking regarding this "Reference Methodology."

If you have questions, comments, or complaints regarding the management of your personal data, please contact the physician providing follow-up as part of the trial or the principal investigator of the center. If you have questions regarding data protection in the scope of the trial, you may contact the Data Protection Delegate of the CHU d'Angers (dpo@chu-angers.fr).

The French National Commission on Informatics and Liberty (https://www.cnil.fr) is the French authority authorized to receive all official complaints regarding the processing of your data.

9. PROTECTION OF PEOPLE

This trial is being conducted in compliance with Law No. 2012-300 of March 5, 2012 as well as the regulatory texts concerning research involving human subjects.

Participation in this trial requires that you be affiliated with or a beneficiary of the Social Security system.

10. INSURANCE

The Sponsor has taken insurance guaranteeing its own civil responsibility as well as that of any physician or collaborator involved in conducting the trial for the duration thereof from SHAM (Société Hospitalière d'Assurances Mutuelles, 18 rue Edouard Rochet, 69372 Lyon Cédex 08), SHAM insurance agreement number 147412. It will also ensure complete compensation for any damages resulting from the trial for the person affected and their successors-in-interest unless there is evidence that the damage cannot be attributed to its fault or to that of any contributor and barring any opposition to third-party acts or the voluntary withdrawal of the person who had initially consented to participate in the trial.

11. IRB APPROVAL

The Institutional Review Board CPP Sud-Méditerrannée I has reviewed this research project and granted its approval on October 16, 2019.

If you agree to participate in this trial, please complete and sign the data collection form drawn up in duplicate. You will keep this information letter and a copy of the consent form.

CONSENT FORM

Stratification of the thromboembolic risk using the TRriP(cast) score to guide preventive care decisions in patients having suffered isolated leg trauma requiring rigid or semi-rigid orthopedic immobilization : prospective multicenter interventional trial.

To be filled out by the investigation team

Sponsor
CHU d'Angers
4, rue Larrey
49933 Angers cedex 9

Coordinating Investigator
Delphine DOUILLET

Department of Emergency Medicine
Telephone: 02 41 35 66 50
Fax: 02 41 35 66 51

***Center No.:**|__|__| **Participant No.:**|__|__|__| **Participant Initials:**|__|__|

LAST NAME First Name

**This number will be recorded at least on the investigator copy*

Participant

Last Name:.....

First Name:.....

Date of birth: |__|__|/|__|__|/|__|__|__|__|

My physician has suggested that I participate in the CASTING trial.

I have read and understood the information letter that I received. I have understood the information provided to me orally and in writing. The physician has responded to my questions concerning the trial. I am aware that I may ask questions or request additional information from the physician who informed me of the trial.

I am aware that my participation is completely voluntary. I understand that I will not be responsible for the costs associated with the trial.

I can decide at any time to withdraw from the trial without need for justification and without any consequences regarding the quality of my care.

I understand that the data processed during the trial will be managed in accordance with confidentiality. They will only be consulted by people bound to complete confidentiality belonging to the study doctor's team, the team selected by the sponsor, or by representatives of the French Healthcare Authorities.

I agree to the computer processing of my personal data in accordance with the conditions set forth by the General Data Protection Regulation and by the French Data Protection Data. I was informed of my right to access, amend, and erase my data upon request to the study doctor.
I agree to the computer processing of my encoded data for other subsequent research projects that may be conducted by the sponsor's researchers and/or other public or private partners, nationally or internationally. I was informed of my right to object to this data processing at any time.

I certify that I am affiliated with the Social Security system.

I freely and voluntarily agree to participate in the **CASTING** trial under the conditions set forth by law, as indicated in the information letter I was given.

I was informed that, pursuant to the regulation on trials involving human subjects, the CPP Sud-Méditerranée I granted its authorization to conduct this trial on October 16, 2019.

My consent does not release the trial organizers from their responsibilities. I reserve all my rights guaranteed by law.

Investigator *(To be filled out by the investigator himself)*		**Participant** *(To be filled out by the participant himself/herself)*	
Last name, first name		Last name, first name	
Date		Date	
Signature		Signature	

Made in two original copies, one for the investigator and one for the participant.

Participant letter for the "CASTING" clinical trial

Last Name: _____ **First Name:** _____

Date of Birth: __ __/__ __/__ __ __ __ Date of End of Treatment: __ __/__ __/__ __ __ __

Study Doctor: _____

Telephone: ____ ____ ____ ____ ____

Clinical Research Technician: _____

Telephone: ____ ____ ____ ____ ____

CHU ANGERS CENTRE HOSPITALIER UNIVERSITAIRE

This trial is being carried out by the CHU d'Angers *version 1*
from 09/27/2019

Contact us as well as your primary care physician / center 15 in case of the following symptoms:

- Symptoms and signs of phlebitis
  - Swollen leg and/or leg pain and/or appearance of localized redness and heat
- Symptoms and signs of pulmonary embolism
  - Difficulty breathing, shortness of breath
  - Chest pain
  - Malaise, loss of consciousness
  - Coughing up blood

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract Page 4
	2b	All items from the World Health Organization Trial Registration Data Set	Page 4
Protocol version	3	Date and version identifier	Title
Funding	4	Sources and types of financial, material, and other support	Page 10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page Page 10 Page 11
	5b	Name and contact information for the trial sponsor	Title page
	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	Page 10

	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)	Page 5 Acknowlegment Page 10
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	Page 3
	6b	Explanation for choice of comparators	Page 5
Objectives	7	Specific objectives or hypotheses	Page 4
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, noninferiority, exploratory)	Page 5
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	Page 5
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)	Page 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 6
	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)	NA

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 6
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	Page 4
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)	Page 5 Table 3
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	Page 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 6
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 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	Page 5
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	Page 5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 5

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	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 known. Reference to where data collection forms can be found, if not in the protocol	Page 6
	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	Page 7
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	Page 5
Statistical methods	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	Page 7-8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 7-8
	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)	Page 7-8
Methods: Monitoring			

Data monitoring	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 its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 5
	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	NA
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	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 5
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 9
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)	Abstract Page 4
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	Page 6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
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	NA
Dissemination policy	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	Page 11
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 1
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	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.