

Version and date: final version – 20 September 2017

Study code: WHITE Study

Study Title: WHITE Study: WHICH decision after a first venous ThromboEmbolicism?

[Multicenter, multinational, investigators-initiated, observational, prospective study to evaluate the decisions taken by clinicians at the end of the maintenance treatment of subjects with a first-ever event of deep vein thrombosis of the lower limbs and/or pulmonary embolism, the relevant reasons, and the attending long-term outcomes]



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International study coordinator: Jiří Matuška

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2. List of abbreviations

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|-------|----------------------------------|
| DMSB | Data Monitoring and Safety Board |
| DVT | Deep Venous Thrombosis |
| EC | Ethics Committee |
| e-CRF | Electronic Case Report Form |
| IRB | Institutional Review Board |
| LMWH | low-molecular-weight heparin |
| NOAC | New Oral Anti-Coagulant |
| PE | Pulmonary Embolism |
| VKA | Vitamin K Antagonist |
| VTE | Venous Thrombo-Embolism |

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4. Synopsis

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| Title of the study | WHITE Study: WHICH decision after a first venous ThromboEmbolism? [Multicenter, multinational, investigators-initiated, observational, prospective study to evaluate the decisions taken by clinicians at the end of the maintenance treatment of subjects with a first-ever event of deep vein thrombosis of the lower limbs and/or pulmonary embolism, the relevant reasons, and the attending long-term outcomes] |
| Code of the study | WHITE Study |
| Version | Final Version |
| Date | 20 September 2017 |
| Design of the study | international, non-profit, multicenter, observational, prospective |
| Promoter of the study | Fondazione Arianna Anticoagulazione, Bologna (Italy) |
| International Coordinator of the study | Jiří Matuška |
| Rationale | <p>Patients having experienced a first-ever episode of DVT of the lower limbs and/or PE, receive anticoagulation therapy for a period as recommended by international and/or local practice guidelines. When this recommended period expires, the attending physician has to decide whether to continue with anticoagulation, switch to anti-thrombotic of another class, or stop any prophylactic pharmacological treatment. Little is known as to which proportion of subjects is assigned to each alternative, whether this proportion is equivalent across different countries, different healthcare systems, and very little is known about the reasons guiding the physician's decision.</p> <p>After the decision is taken, a number of validated data is available in the literature regarding the outcomes in subjects assigned to extended anticoagulation for up to one year, whereas little if any information is available for subjects receiving extended anticoagulation for more than one year, or assigned to alternative long-term treatment, or who stopped the treatment.</p> <p>The Fondazione Arianna promotes this international, investigators-initiated, multicenter observational study, to collect data that may possibly answer the first question, and give substantial indications concerning the second question.</p> |
| Main objective of the study | <p>This study includes two sections:</p> <ul style="list-style-type: none"> a) a transversal section, in which the primary objective will be evaluated; b) a longitudinal section, in which the secondary objectives will be evaluated. <p>It is assumed that the distribution of the decision taken during the transversal section (primary objective) may influence the outcomes of the longitudinal section.</p> <p>The primary objective of the study is the evaluation of the distribution of decisions and of the reasons guiding the physician's decision on the modality to manage the secondary prevention of venous thromboembolism (VTE) in patients treated for a first-ever episode of VTE, after the initial 3-12 months of anticoagulation therapy.</p> <p>The secondary objective is the collection of data on the course of VTE recurrence, bleeding and death risk.</p> |
| Endpoints of the study | <p>Primary endpoint:</p> <p>The primary endpoint is the decision taken by the attending physician at the end of the period of maintenance anticoagulation (from the end of the 3rd month to the end 12th month) initiated after the index event (maintenance anticoagulation). The maintenance anticoagulant used may or may not be the same used in the acute phase of DVT (initial 7 days); for the objectives of this study, the acute treatment is not of interest. The primary endpoint will be evaluated at the visit performed at the end of the maintenance anticoagulation.</p> <p>Secondary endpoints</p> <p>The distribution of reasons guiding the physician's decision on the modality to manage the secondary prevention of VTE represents a secondary endpoint.</p> <p>The other secondary endpoints encompass the frequency of thromboembolic complications, of bleeding complications, or death from any cause monitored during the follow-up.</p> |

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| Number of Countries | Nine: Portugal, Poland, Czech Republic, Slovakia, Rumania, Russia, Tunisia, China, Mexico |
| Number of Centers | Approximately from 5 to 20 Centers in each Country. Each center shall recruit not more than 40 subjects. |
| Number of patients | A minimum number of 3,200 subjects will be enrolled across all the countries participating to the study, split into: approximately 200 subjects in China approximately 350 subjects in Czechia; approximately 300 subjects in Mexico; approximately 900 subjects in Poland; approximately 350 subjects in Portugal; approximately 250 subjects in Romania; approximately 800 subjects in Russia; approximately 150 subjects in Slovakia; not less than 100 subjects in Tunisia. |
| Period of enrolment | Not more than eighteen months |
| Period of follow-up | Two years |
| Inclusion criteria | <ul style="list-style-type: none"> a) subjects who provided a written informed consent and authorization for disclosure of protected health information; b) male and female adult or elderly patients (≥ 18 years at the time of signing the informed consent; no upper limit) of any ethnicity having had a first-ever event of provoked or unprovoked DVT of the lower limbs and/or PE given maintenance anticoagulants (NOACs, VKAs, or LMWHs) according to the local procedures (usually for 3 to 12 months) and to be re-evaluated to decide the treatment to be prescribed after such period; c) for whom the center is in possession of all the data relevant to the index event; d) having a permanent reference contact. |
| Exclusion criteria | <ul style="list-style-type: none"> a) subjects < 18 years old; b) subjects unable or unwilling to issue the written informed consent; c) subjects for whom the information relevant to the index event are incomplete or inaccessible to the Investigator; d) subject in whom the index event was a DVT not of the lower limbs; e) subjects with life expectancy of less than 2 years; f) subjects participating in any other clinical study, regardless of its nature; g) subjects considered, by the attending physician, unable to comply with the study procedures. |
| Study Procedures | <p>Enrollment and baseline visit:</p> <ol style="list-style-type: none"> 1. the physician will assess the inclusion/exclusion criteria for entering the study and obtain the informed consent to confer the study data; 2. after obtaining the consent, the attending physician will record the diagnostic and prognostic information required in the CRF and inform the promoter of the recruitment of the patient; 3. the attending physician, based exclusively on the personal judgment and in accordance with the local procedures, will decide whether to continue with anticoagulation (NOACs or VKAs or LMWHs); or to switch to a long-term antithrombotic prophylaxis; or permanently discontinue the pharmacological prophylaxis. This decision generates three sub-populations with regards to the secondary prophylaxis of VTE: <ul style="list-style-type: none"> a] subjects receiving extended anticoagulation, with the same or another substance of the same class, at the same or lower dose as used in the maintenance treatment; b] subjects receiving long-term antithrombotic non-anticoagulant prophylaxis; c] subjects not receiving any long-term pharmacological prophylaxis. 4. the attending physician will record in the CRF the reasons guiding the decision taken; 5. the physician will instruct the subject on the procedures of the follow-up that should be the normal procedures in use at the Center, will provide a contact |

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| | <p>reference and will obtain a contact reference.</p> <p>Follow-up visits The follow-up will be articulated as normally performed at the Center. The common follow-up procedures include a telephone contact every 3/6 months (4/8 in two years) and a direct interview at the center at least once a year (two in two years). At each follow-up contact, by telephone or personal, information will be collected on:</p> <ol style="list-style-type: none"> survival at the time of contact; hospitalizations occurred after the previous contact; events of thromboembolic complication; events of bleeding complication; changes in the antithrombotic/anticoagulant therapy, if any was prescribed, including the institution of an antithrombotic/anticoagulant therapy if none had been prescribed; other events that prevent the continuation of the planned follow-up. |
| | <p>Unplanned follow-up visits It is possible, as usual during long-term monitoring of subjects, that visits are needed at the center upon request by the subject or based on the physician's decision. These unplanned visits, which will typically correspond to an event of recurrence or of bleeding, will record the same information as a standard follow-up visit. Performing an unplanned visit is not by itself considered a reason for terminating the study, unless the visit corresponds to one of the study endpoints (thromboembolic complications, bleeding complications, or other events preventing continuation of the follow-up).</p> <p>End-of-study visit The end-of-study information, collected at the last planned or unplanned contact with the subject, will only include the reason for terminating the observation on the individual subject. The end-of-study visit will have to be completed for all subjects entered into the follow-up, and may occur:</p> <ol style="list-style-type: none"> at the end of the planned follow-up period; when the investigator detects, or is informed of, the occurrence of a secondary endpoint (new thromboembolic event, major bleeding, clinically relevant non-major bleeding requiring a change of treatment; subject's death); change (with the exception of dosage) or interruption of the prophylactic treatment assigned at recruitment (including not pharmacological treatment) by the attending physician or other physician; subject's decision to stop the prescribed prophylaxis; events occurred, which prevented the continuation of the follow-up (subjects lost to follow-up for any reason, including reporting to another center). |
| Sample size justification | <p>The primary endpoint is the decision taken by the attending physician at the end of the maintenance anticoagulation initiated after the index event. Three options are possible and in absence of other determinants, the null hypothesis is that the distribution of subjects by option is uniform. The analysis can therefore be performed with a goodness-of-fit test with 2 degrees of freedom. The alternative hypothesis is that at least one of the three choices is selected in a greater proportion than the other two. This analysis is performed once only at the end of recruitment.</p> <p>With approximately 3,200 subjects, the study has 90% power to detect with 95% confidence a deviation from the uniform distribution, in case one of the options is selected in a proportion exceeding by 10% relative or more the proportion expected from the uniform distribution (i.e., in 36.3% or more of the subjects).</p> <p>The study also has 80% power to detect with a two-tailed 97% confidence (accounting for interim analyses) a deviation of at least one of the sub-populations, by at least:</p> <ol style="list-style-type: none"> ± 1.23 recurrence events from the expected rate of 5 events per 100 subjects per year, and ± 0.55 bleeding events/deaths from the expected rate of 1 event per 100 subjects per year. |
| Statistical-analytical plan | <p>Statistical considerations The statistical analyses will be descriptive and exploratory. Given the nature of the</p> |

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| | <p>study, which is observational, it is not designed to confirm or reject predetermined hypotheses.</p> <p>Populations The analyses will be performed on the total sample monitored. Missing data will not be replaced.</p> <p>Demographic, prognostic and descriptive variables All variables will be summarized with the usual descriptive techniques: categorical variables as contingency table (absolute and relative frequency); continuous variables with sampling statistics: mean, standard deviation, median, minimum, maximum. Whenever appropriate the relevant 95% confidence interval will also be reported.</p> <p>Primary endpoint The primary endpoint will be analyzed at the completion of the recruitment. The proportion of choices made by the attending physician will be reported as proportion with confidence interval by level. The primary analysis will test by goodness-of-fit whether the choices were random or not. The impact of demographic and prognostic factors – including country – on the choice can be tested by chi square and/or logistic regression analysis.</p> <p>Secondary endpoints Frequency of thromboembolic complications and frequency of bleeding complications or death for any reason will be analyzed at the completion of each year of observation. The interim results will be used by the DMSB to decide on whether the observation has to continue or must be stopped. The final analysis will be adjusted for multiplicity using the nominal critical P value of 0.03. Event rates will be reported at the available observations, stratified by sub-population, as proportion with the relevant confidence interval. Proportions will be compared if appropriate by chi square and/or as time to event by survival analysis. Since clinically-relevant non-major bleeding may not be a reason for interrupting the follow-up, and minor bleeding are not a reason for interruption, it is possible that the number of bleeding events per subject can be submitted to analysis by Poisson regression. The other secondary endpoint is the reason(s) justifying the choice analyzed as primary endpoint. These will be tabulated by choice and compared, if appropriate, by chi square test or by ordinal logistic regression. Unplanned post-hoc subgroup analyses may be performed if requested by the Steering Committee.</p> <p>Other endpoints Occurrence of hospitalization and changes of prophylactic therapy, including institution of a therapy in subjects who stopped any prophylactic treatment at recruitment; change of the prophylactic treatment assigned at recruitment, and interruption of the prophylactic treatment assigned at recruitment. Hospitalizations will be analyzed as proportion of subjects with event, compared between sub-populations, if appropriate, by chi square or in case of an appreciable number of events, by Poisson regression. Changes in therapy will be tabulated as absolute number and proportion stratified by sub-population and, if appropriate, analyzed by chi square and/or logistic regression. In addition, the reasons for study termination may be considered an endpoint. These will be tabulated by sub-population and compared, if appropriate, by chi square or ordinal logistic regression.</p> <p>Safety observations Adverse events will be handled by the attending physician according to the local procedures and, as in any observational study, will not be subject to statistical analysis. Only those events that resulted in the interruption of follow-up will be tabulated by sub-population and/or individual medication, without further statistical considerations.</p> |
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5. Amendments

This is the final protocol version subject to the approval by the relevant Ethics Committees (EC)/Institutional Review Boards (IRB). Subsequently, possible amendments will be submitted to the relevant EC/IRB before being implemented and will constitute a separate document. In case of major amendments, a new comprehensive version of the protocol may be prepared, incorporating all the minor and major amendments approved until that date.

6. Rationale and justification

6.1 Background

The reference international guidelines [1] recommend initial treatment of DVT of the lower limbs and/or PE with a direct anticoagulant (oral or parenteral) followed by a period of anticoagulation therapy with the same direct oral anticoagulant or partially overlapping it with a Vitamin K antagonist (VKA), with a preference for the former alternative.

An exception is represented by a VTE associated with an active cancer. In this case, a treatment with parenteral anticoagulant (in particular LMWH) for the whole period of 3 months is recommended.

Anticoagulation therapy is essential for at least three months in all cases. The incidence of VTE recurrence is considered to be very low when an event is triggered by surgery or another specific risk factor. In these cases, a three-month treatment is considered sufficient. In case of idiopathic (unprovoked) events, however, such period may not be sufficient due to the marked tendency of VTE to recur. In these cases, it is advisable to assess each subject's specific benefit (expected decrease in recurrences) in comparison with the risk of bleeding associated with prolonged anticoagulation, and determine the duration of anticoagulation based on this evaluation. However, pre-determined time-limited courses of therapy longer than 12 months are unusual [1]. In addition, based on the local healthcare system, not all regimens can be protracted indefinitely in all cases.

At the end of the three months – or longer, usually not more than one year – of anticoagulation, the attending physician has to decide whether and how to manage the long-term secondary prevention of recurrences, based on an assessment of the individual ratio of risks of recurrence and of bleeding. These individual estimates are often difficult to evaluate. A number of additional factors also influence the decision, including subject's predicaments and preferences, concurrent diseases and treatments, healthcare system support, and availability of potentially effective alternative treatments, such as aspirin [2] and sulodexide [3].

The choice of whether to continue at all the secondary prophylaxis and, if continued, the selection of the appropriate treatment and the relevant duration after maintenance anticoagulation, is therefore far from standardized. The practical clinical behavior may consequently be very dissimilar case to case, and practice guidelines, literature and local healthcare provisions do not help much in facing this problem.

6.2 Justification of the study

At the end of the recommended or practicable period of anticoagulation after a first-ever episode of VTE, the attending physician has therefore three different options:

1. continue with extended anticoagulation using a treatment of the same or other anticoagulant class (NOACs or VKAs or LMWHs) at the same dosage as in the previous period or with a lower dosage;
2. replace the anticoagulant with an alternative antithrombotic (including antithrombotic proper, antiplatelet or vasoprotective drug) with or without compression therapy;
3. interrupt any specific pharmacological treatment (with or without compression therapy).

Little is known as to which proportion of subjects is assigned to each alternative and whether this proportion is equivalent across different healthcare systems, and very little is known about the reasons guiding the physician's decision.

After the decision is taken, a number of validated data is available in the literature regarding the outcomes in subjects assigned to extended anticoagulation for up to one year, [4-6] whereas little if any information is available for subjects receiving extended anticoagulation for more than one year, or assigned to alternative long-term treatment, or who stopped the treatment.

The Fondazione Arianna promotes this international, investigators-initiated, multicenter observational study, to collect data that may possibly answer the first question, and give substantial indications concerning the second question.

7. Research question and objectives

7.1 Research question

The research question prompting this study is the decisional process that assigns subjects with previous VTE who concluded the maintenance anticoagulation, to one of the alternative options: extended anticoagulation, alternative pharmacological prophylaxis, or interruption of the pharmacological prophylaxis. The secondary research question is the estimation of the true rate of events during prolonged observation under true-to-life conditions, among subjects allocated to extended anticoagulation or to alternative prophylaxis or to no pharmacological prophylaxis.

7.2 Objectives

7.2.1 Primary objective

The primary objective of the study is the assessment of the distribution of decisions on the modality to manage the secondary prevention of venous thromboembolism (VTE), at the end of the period of anticoagulation considered standard. This period, initiated after the index event and defined in the present protocol as maintenance anticoagulation, ranges from the end of the 3rd month to the end 12th month. The anticoagulant used for the maintenance anticoagulation may or may not be the same used in the initial acute phase of VTE management (the initial 7 days). To the effect of this study, the treatment applied during the acute phase is of no interest.

7.2.2 Secondary objectives

The distribution of the reasons guiding the physician's decision indicated in § 7.2.1 is to be considered a secondary objective since, to date, there is no indication as to whether and which factor may represent an explanatory variable guiding the decision taken.

The secondary objective is the collection of data on the course of thromboembolic complications, bleeding complications and death risk, during a relatively prolonged follow-up. This information is already available in the literature for subjects who continued with anticoagulation for up to one year [4-6], whereas no solid information is available for subjects under longer treatment or who switched to an alternative antithrombotic prophylaxis or interrupted the treatment.

The period of follow-up after terminating the standard anticoagulation treatment is limited in this study to 2 years, since there is no evidence that after such period the risk of events is different from that of a matched population without a previous VTE episode. Since data on late recurrence rates are contrasting and somewhat obsolete, a DMSB is established to guide the conduct of the study (§ 11.3).

8. Methods

8.1 Study design

This is an international, no-profit, multicenter, observational, prospective study. The study encompasses two sections:

- a] a transversal section, in which the primary objective (and the related secondary objective on the reasons suggesting the primary objective) will be evaluated;
- b] a longitudinal section, in which the other secondary objectives will be evaluated.

The transversal section includes one population; the decision representing the primary endpoint, taken during the initial visit, will instead generate three sub-populations with regards to the secondary prophylaxis of VTE:

- a] subjects receiving extended anticoagulation, with the same or another substance of the same class, at the same or lower dose as used in the maintenance treatment;
- b] subjects receiving long-term antithrombotic non-anticoagulant prophylaxis;
- c] subjects not receiving any long-term pharmacological prophylaxis.

The secondary endpoints collected during the follow-up will be stratified by sub-population.

8.1.1 Primary endpoint

The primary endpoint is the proportion of subjects allocated by the attending physicians at the end of the maintenance anticoagulation initiated after the index event, by free and spontaneous decision, to one of the three possible options:

- a) continue with anticoagulation, using the same substance or a substance of the same class, with the same or lower dosage ("extended anticoagulation"), with or without compression therapy;
- b) replace the anticoagulation with an alternative treatment (with or without compression therapy),
- c) interrupt any pharmacological prophylactic treatment (with or without compression therapy).

The primary endpoint will be evaluated at the first visit, that is, at the end of the maintenance anticoagulation.

8.1.2 Secondary endpoints

The secondary endpoints include:

- the distribution of the reasons that were considered relevant by the attending physician to take the decision indicated as primary endpoint;
- the rate of thromboembolic complications and the combined rate of bleeding requiring at least an interview with the attending physician (major or clinically relevant non-major bleeding), or death from any cause during the 2-year follow-up.

8.1.3 Considerations on the study design

This is an observational study. As such, it allows collecting information based on the usual clinical practice as performed in the day-to-day clinical care of the target subjects.

However, as any investigator-initiated observational study, it may have a bias associated with the propensity of the individual investigator to participate in non-sponsored studies, with the local availability of personnel and time to collect and enter data, and with the investigator's willingness and capability to ensure an appropriate quality assurance on the collected data.

As in any clinical trial, furthermore, the need to obtain the written informed consent to data collection may also introduce a bias, which will probably select the more educated segment of the potential participants and, in any case, is likely to affect the consecutiveness of recruited cases.

8.2 Study set-up

8.2.1 Eligibility

Approximately 3,200 subjects will be enrolled. Each center will recruit not more than 40 among the consecutive subjects coming to the observation after approval of the protocol by the relevant EC/IRB until the total planned number of cases is overall collected. Consecutiveness may be replaced by other mean of bias containment if necessary given the center operational structure (e.g., all consecutive subjects reporting each first week of the month, a definite day in the week, or similar provisions). The selected predefined modality of screening and including patients should be declared by the participant centers. The subjects shall be able and willing to issue the informed consent to confer their data. Male and female adult and elderly subjects of any ethnicity, having had a first-ever event of DVT of the lower limbs and/or PE, treated with anticoagulants according to the local procedures but for not less than 3 and not more than 12 months, and having reached the final decision point on the therapy, are eligible to enter the study.

8.2.2 Inclusion criteria

Subjects meeting all of the following criteria qualify for entry into the study:

- a) subjects who provided a written informed consent and authorization for disclosure of protected health information;
- b) male and female adult or elderly subjects (≥ 18 years at the time of signing the informed consent; no upper limit);
- c) of any ethnicity;
- d) with a first-ever event of provoked or unprovoked DVT of the lower limbs and/or PE treated with anticoagulants (NOACs, VKAs, or LMWHs) according to the local procedures (usually for 3 to 12 months) and to be re-evaluated to decide the treatment to be prescribed after this period;
- e) for whom the center possesses all the data relevant to the index event;
- f) having a permanent reference contact.

8.2.3 Exclusion criteria

Subjects meeting any of the following criteria will not qualify for entry into the study:

- a) subjects < 18 years old at the time of consent request;
- b) subjects unable or unwilling to issue the written informed consent;
- c) subjects for whom the information relevant to the index event are incomplete or inaccessible to the Investigator;
- d) subject in whom the index event was a DVT not of the lower limbs;
- e) subjects with life expectancy of less than 2 years;
- f) subjects participating in any other clinical study, regardless of its nature;
- g) subjects considered, by the attending physician, unable to comply with the study procedures.

8.2.4 Withdrawal from study

Each subject has the right to refuse to continue on study at any moment and without justifications. However, since the study data are the usual data that the investigator collects for the standard subject's care, "withdrawal" should be intended as retiring the consent to the collection of subject's data into the study database. Consequently, from the moment a subject withdraws from the study, subsequent

information should not be collected among the study data. On the contrary, unless specifically indicated by the subject, all data collected up to that point will be retained among the study data.

8.2.5 Replacement

As usual in observational studies, no replacement is planned for subjects who retire the consent to confer the study data.

8.3 Study procedures

Being this an observational study, all the procedures, therapeutic decisions and clinical assessments will be performed according to the standard, country specific clinical practice for the management of this kind of subjects.

8.3.1 Visits

The study does not anticipate other visits than those normally planned in the diagnostic-therapeutic course of the considered subjects. The visits are those of the normal routine. The period of observation for each subject is that normally anticipated by the clinical practice. The informed consent to the collection of data will equally be obtained during the course of a routine visit.

1. Enrollment and baseline visit

The enrollment and baseline visit is the normally planned visit in which the physician has to decide on the continuation of the secondary prophylaxis after a first-ever thromboembolic episode treated for an appropriate period with anticoagulants. Due to organizational reasons, the enrollment and baseline visit may occur after the conclusion of anticoagulation. The time interval between conclusion of anticoagulation and enrollment visit should not exceed one month.

At the enrollment visit, all candidate subjects will receive an information sheet explaining design and aims of the study. The clinician shall explain and ask the subject to sign the informed consent form to confer the study data. The consent will also include the subject's agreement to receive regular phone calls from the investigator during the follow-up and to report annually to the center. The consent form will be part of the center documents and the only information conferred to the database will be whether the consent was signed or not, and in which date. The investigator will be responsible to archive the signed form for possible verification.

Subsequently, the investigator will:

- verify the inclusion/exclusion criteria for entering the study;
- inform by fax/mail the study Promoter that a new subject has been enrolled according to the protocol (form in Appendix III);
- obtain the information on the index event;
- monitor the clinical condition of veins and record the Villalta score;
- record the vascular risk factor, the concurrent diseases and the medications on long-term use;
- record the minimum clinical information required (weight, height, blood creatinine) as available; for creatinine, the last known serum creatinine level not older than three months before entering the study is appropriate;
- record the maintenance anticoagulation treatment received;
- decide on the subsequent subject's management and record the decision; the decision should be taken in the exclusive subject's interest and based exclusively on the personal judgment and in accordance with the local procedures;
- record the new form of management, if any;
- record the reasons influencing the decision taken;

- instruct the subject on the procedures of the follow-up, which should be the normal procedures in use at the center;
- provide a contact reference and obtain a contact reference.

2. Follow-up visit

The normal procedures for the long-term follow-up of these subjects include a number of calls – in general every 3 to 6 months – and a yearly recall at the center for a personal interview. The anticipated number of follow-up contacts is of approximately 4 to 8 calls and 2 interviews at the center, over the 2-year observation.

The information collected at calls and interviews are the usual ones used to monitor the status of the subject, and include:

- a. survival status;
- b. hospitalizations;
- c. thromboembolic complications;
- d. bleeding complications;
- e. review of the prophylactic treatment, if any was prescribed, and relevant changes if deemed necessary;
- f. other events that prevent the continuation of the planned follow-up.

3. Unplanned follow-up visit

Upon request of the subject, or by decision of the investigator based on the communications with the subject, there may be the need for unplanned follow-up interviews. This will usually occur when a thromboembolic complication or a bleeding complication or other events occurred, that make clinically relevant for the well-being of the subject a direct contact with the investigator.

The information to be collected at these visits is the same as that of the follow-up visit. Usually, these visits imply the conclusion of the follow-up on the individual subject.

The follow-up is to be concluded, filling the end-of-study form discussed below, when:

- a. a thromboembolic complication occurred;
- b. a major bleeding complication occurred. Clinically relevant non-major bleedings as well as minor bleedings do not automatically imply the interruption of the follow-up and the relevant decision will be taken by the investigator case by case on the best subject's interest;
- c. there was a substantial change in anti-thrombotic therapy, such as:
 - institution, by the investigator or another physician, of a prophylactic therapy in a subject for whom the decision was taken not to continue the pharmacological prophylaxis;
 - replacement, by the investigator or another physician, of the current therapy with a new therapy of another therapeutic class. Changes of dosage of the same therapy do not imply interruption of the follow-up;
 - interruption, by the investigator or another physician or by subject's spontaneous decision, of the prescribed prophylactic treatment;
- d. an event occurred, that implied the impossibility to continue a correct monitoring, e.g., a planned/unplanned intervention requiring prolonged anticoagulation (e.g., surgery or immobilization).

4. End-of-study visit

Each subject will have an end-of-study visit. This does not represent an independent visit, but a simple recording of the end of monitoring for the individual subject, and will coincide with:

- a. the last contact, usually at the center, at the end of the 2-year observation;
- b. the planned or unplanned follow-up visit at which any of the events terminating the follow-up have occurred, as indicated in the unplanned follow-up visit (thrombotic complication, major bleeding complication, substantial change in therapy, other event preventing continuation of the follow-up);
- c. the investigator is informed that the subject died;
- d. the subject ceased reporting to the center and started reporting to another hospital;
- e. the subject moved the residence to a place preventing continuation of the follow-up;
- f. the subject was lost to follow-up without additional information.

8.3.2 Variables

The variables to be collected in this study are the usual descriptive, diagnostic and prognostic variables normally recorded in the subject's cards, as well as the description of the antithrombotic treatments applied and the reason for change. In the follow-up, the usual outcome variables relevant to the subject's status will also be collected.

a. descriptive variables

These include age, sex, ethnicity.

b. diagnostic variables

These include complete description of the index event, including the putative cause of a secondary event and risk factors for the event.

c. prognostic variables

These include body weight, height and creatinine (to estimate BMI and creatinine clearance); clinical conditions of veins with calculation of the Villalta score; active concurrent diseases, vascular risk factors, medications in long-term use.

d. treatment information

This includes type, dosage and duration of the maintenance anticoagulation performed; type, dosage and planned duration of the new treatment proposed, if any, and the classification of the reasons considered by the investigator for the decision taken.

e. outcome variables during the follow-up

These include type and time of contact, classification of the events (thrombotic complications, bleeding complications, survival, hospitalization) occurred in the period since the last contact, and information on the current therapy, if any, and relevant changes regardless of whether decided by the investigator, another physician, or spontaneously by the subject.

8.3.3 Source of data

The source of data is the information collected into, or to be recorded into, the subject's hospital card or equivalent documents. No additional data are requested.

8.4 Data management

The investigators will directly manage the primary data, as usual. The responsibility to properly collect and record the data into the hospital, center or other subject's documents remains with the individual attending physicians. The responsibility to collect, verify and record possible adverse drug reactions remains with the local responsible for pharmacovigilance.

The investigator and/or specifically appointed co-investigator(s) will transfer the study data to the study database. The study data will be entered into an e-CRF, accessible from a standard personal computer with the use of standard browsers. The database will be unique and centralized, to facilitate maintaining proper database security with the usual maintenance procedures (data encryption, backups, checks of consistency and integrity, etc.). All data to be transferred will be anonymized; only the investigator and co-investigators will locally retain a log in which the correspondence between the study unique code and the subject's identification will be possible. This log will not exit the hospital, but shall be kept available for possible verifications within the frame of the quality assurance procedures (§ 8.5).

Each investigator and duly delegated co-investigator will have a personal username and password allowing access to the centralized database. All investigators at one Center can have access to the data of their center. In this context, "center" means an operating unit in which one or more investigators monitor a number of subjects, who are not seen for the same reason by other units.

8.5 Quality assurance

This is an investigators-initiated study; therefore, each investigator assumes the responsibility to guarantee the quality of the data recorded in the subject's documents. The National coordinator, in accordance with the local investigator, may require to inspect and verify the core data, in particular the subjects' log and the informed consent forms. The local database operators assume the responsibility to guarantee the quality of the data conferred to the central database in accordance with the procedures setup in the database manual. The statistical responsible of the study will verify completeness, accuracy and plausibility of the data recorded onto the database, producing if needed requests for additional verification against the raw data recorded in the subjects' documents. Only after the final verification after the study closure, the database will be frozen and submitted to statistical analysis.

9. Protection of the subject's rights

The study will be performed in compliance with the Declaration of Helsinki (<http://www.wma.net/en/30publications/10policies/b3/>) and the applicable sections of the Good Clinical Practice, as well as in compliance with the international and national regulations.

9.1 Study conduct

This is an observational study in which the medications prescribed, if any, are prescribed by the attending physician according to the relevant Authorization to Commercialization, in the best subject's interest, based on the training and expertise of each physician. No diagnostic or therapeutic action is anticipated by this protocol, which are not normally planned for the appropriate monitoring and follow-up of the subjects.

9.2 Ethics Committee/Institutional Review Board

Each center participating in this study should obtain the authorization to participate by the relevant EC/IRB. Copy of this authorization shall be sent to the promoter of the study and also kept by the investigator until the end of the study, and may be subject to verification by the National Coordinator. In case of protocol amendments, it is the Investigator's responsibility to submit such amendments to the relevant EC/IRB, according to the Center's procedures.

9.3 Informed consent

Before conferring any data to the study database, the investigator shall obtain the consent from each subject, after having supplied adequate information. To be recruited, the subjects must have given the individual consent in writing to the management of personal data in anonymous and aggregate form. Each subject shall be informed that can withdraw the consent at any time of the study, without penalties and without justification (§ 8.2.4). The information sheet and the consent form to the use of personal data are appended to this protocol. The documentation of consent shall be archived by the local investigator until the end of the study, and may be subject to verification by the National coordinator. It is responsibility of the Investigator's or a delegate to record onto the database that the consent was obtained, with the relevant date, and to inform the study promoter of the recruitment of a new subject according to the protocol. This information, however, is associated in the database to the subject's unique study code, without personal identification data.

9.4 Subjects insurance

This study collects data on the routine management of subjects with drugs used in the indications authorized, at doses and in dosage forms duly authorized. The diagnostic, therapeutic and monitoring procedures of the study follow the routine planned for these subjects. The participants do not incur into any additional risk or discomfort because of their participation in the study. Consequently, no specific insurance is needed.

9.5 Confidentiality

All subjects managing the study data guarantee to maintain the confidentiality of the subjects' personal data. In particular, the investigator and co-investigators, who have access to sensible data, guarantee to keep confidential any information they might become aware of, as in the normal clinical practice. The entire documentation available outside the center is instead anonymized and does not contain information that might allow identifying the participating subjects.

10. Statistics

10.1 Statistical considerations

The statistical analyses will be descriptive and exploratory. Given the nature of the study, which is observational, it is not designed to confirm or reject predetermined hypotheses. The hypothesis indicated in the sample size calculation is to be considered supportive of the physicians' attitude towards methods of long-term prophylaxis, to be eventually confirmed by specifically designed motivational investigations.

10.2 Sample size

The study anticipates recruiting approximately 3,200 subjects, based on considerations relevant to the primary endpoint.

The primary endpoint is the decision taken by the attending physician at the end of the maintenance anticoagulation initiated after the index event. Three options are possible: continue with extended anticoagulation (regardless of individual drug and dose), replace the anticoagulation with an antithrombotic, non-anticoagulant treatment, or stop any pharmacological prophylactic treatment.

In absence of other determinants, the null hypothesis is that the distribution of subjects by option is uniform. The analysis can therefore be performed with a goodness-of-fit test with 2 degrees of freedom. The alternative hypothesis is that at least one of the three choices is selected in a greater proportion than the other two. This analysis is performed once only at the end of recruitment.

With approximately 3,200 subjects, the study has 90% power to detect with 95% confidence a deviation from the uniform distribution, in case one of the options is selected in a proportion exceeding by 10% relative or more the proportion expected from the uniform distribution (i.e., in 36.3% or more of the subjects) [7].

Given that the factor “country” (synonymous of “healthcare system”) will be a likely cofactor in the analyses, the sample should be split across the participating countries in such a way the allow a reliable representativeness also for the smaller countries. The limit was considered not less than 100 subjects per country. The anticipated contribution by country was therefore estimated as:

| Country | cases |
|----------|-------------------|
| China | approximately 200 |
| Czechia | approximately 350 |
| Mexico | approximately 300 |
| Poland | approximately 900 |
| Portugal | approximately 350 |
| Romania | approximately 250 |
| Russia | approximately 800 |
| Slovakia | approximately 150 |
| Tunisia | not less than 100 |

Since in this study the secondary endpoints are of clinical relevance as well, it is appropriate to estimate whether the indicated sample can yield reliable information also in relation to such endpoints.

The secondary endpoints are the rate of thromboembolic complications and the combined rate of bleeding complications/death. To allow the DMSB (§ 11.3) to take appropriate decisions on the conduct of the study, these analyses will be performed at yearly intervals, i.e., when the last recruited subject has reached the end-of-year observation. There will therefore be 2 analyses (1 interim and one final), so that the final analysis will have to report as statistically relevant and deserving further investigations, P-values ≤ 0.048 . [8]

The interest of the study is to find whether any of the three constituted sub-populations – extended anticoagulation; long-term antithrombotic prophylaxis; no pharmacological prophylaxis (§ 8.1) – deviates from the expected risk, to an extent deserving investigation of the potential predictors of outcome.

From the literature [2, 3], the estimated annual risk of recurrence in the control group was approximately 5 events per 100 subject-years. The combined risk of bleeding or death was approximately 1 event per 100 subject-years.

Assuming that almost all recruited subjects will be monitored for at least one year, this survey has 80% power to detect with a two-tailed 95% confidence (after accounting for the interim analyses) a Cohen’s effect of the baseline decision taken on the follow-up outcomes, of 0.055 [9]. It can therefore identify as potentially relevant, deviations of at least one of the constituted sub-population from the anticipated recurrence rate of at least ± 0.0123 (3.77 or less, or 6.23 or more, events per 100 patients per year). Similarly, it has 80% power to detect with a two-tailed 95% confidence a deviation of at least one of the three constituted sub-populations from the anticipated bleeding/death rate of ± 0.0055 (0.45 or less, or 1.55 or more, events per 100 patients per year). [10]

10.3 Populations

As usual in the observational studies, the analyses will be performed on the total sample monitored. Only subjects specifically indicated by the Steering Committee as major, irreconcilable deviation will be excluded from analysis (§ 11.1). Missing data will not be replaced. Subgroup analyses are not anticipated, however – given the exploratory nature of the study – unplanned subgroups analyses may be performed *post-hoc*, upon indications by the Steering Committee.

10.4 Data analysis

10.4.1 Demographic, prognostic and descriptive variables

All variables will be summarized with the usual descriptive techniques: categorical variables as contingency table (absolute and relative frequency); continuous variables with sampling statistics: mean, standard deviation, median, minimum, maximum. Whenever appropriate the relevant 95% confidence interval will be reported.

10.4.2 Primary endpoint

The primary endpoint will be analyzed at the completion of recruitment. The proportion of choices made by the attending physician will be reported as proportion with confidence interval by level. The primary analysis will test by goodness-of-fit whether the choices were random or not. The impact of demographic and prognostic factors – including the country – on the choice may be tested, if appropriate, by chi square and/or logistic regression analysis.

Unplanned *post-hoc* subgroup analyses may be performed if requested by the Steering Committee.

10.4.3 Secondary endpoints

The secondary endpoint analyzable at the completion of recruitment is the reason(s) justifying the choice analyzed in 10.4.2. These will be tabulated by choice and compared, if appropriate, by chi square test or by ordinal logistic regression. Unplanned *post-hoc* subgroup analyses may be performed if requested by the Steering Committee.

The other secondary endpoints include the frequency of thromboembolic complications and the frequency of bleeding complications or death for any reason. These will be analyzed at the completion of each year of observation (full year of observation of the last subject entered into the long-term follow-up). The interim results will be used by the DMSB to decide on whether the observation has to continue or must be stopped. The final analysis will be adjusted for multiplicity using the nominal critical P value of 0.048.

Event rates will be reported at the available observations as proportion, stratified by sub-population, with the relevant confidence interval. Deviations from the expected rate of events will be analyzed by chi square and/or time to event by survival analysis. If appropriate, subgroups will be analyzed with the Cox survival model. Impact of putative predictors as indicated by the Steering Committee will be analyzed by logistic regression and/or Cox proportional-risk model.

Since clinically-relevant non-major bleeding may not be a reason for interrupting the follow-up, and minor bleedings are not a reason for interruption, it is possible that the number of bleeding events per subject can be submitted to analysis by Poisson regression.

10.4.4 Other endpoints

Other monitored endpoints include the occurrence of hospitalization and the change of prophylactic therapy, including:

- institution – by the attending physician or other physician - of a therapy in subjects who stopped any prophylactic treatment at recruitment;
- change – by the attending physician or other physician - of the prophylactic treatment assigned at recruitment, and
- interruption – by the attending physician, other physician or by spontaneous subject's decision - of the prophylactic treatment assigned at recruitment.

Hospitalizations do not necessarily imply interruption of the follow-up, unless associated to a primary endpoint (thromboembolic event, bleeding, death) or result in the impossibility to continue an appropriate monitoring (e.g. need for anticoagulation). Consequently, hospitalizations can be analyzed by chi square across sub-populations as proportion of subjects with event or, in case of an appreciable number of events, by Poisson regression.

Any change in therapy, instead, implies interruption of the follow-up. Changes in therapy will be tabulated, stratified by sub-population, as absolute number and proportion and, if appropriate, analyzed by chi square and/or by logistic regression.

In addition, the reasons for study termination may be considered an endpoint. These will be tabulated by sub-population and compared, if appropriate, by chi square or ordinal logistic regression. If required by the Steering Committee, unplanned *post-hoc* subgroup analyses may also be performed.

10.4.5 Safety observations

Being this an observational study in which any prescription is by free physician's choice in accordance with the drug's technical data sheet, all safety information will be handled by the attending physician according to the local procedures. Since, however, events may occur, which are not endpoints but may imply the termination of the follow-up, these events will be tabulated by sub-population and/or individual medication, without additional statistical considerations.

11. Committees

The Promoter will setup the Committees listed at continuation, to ensure the correct execution of the study and the respect of the subjects' rights.

11.1 Steering Committee

The study will be guided and monitored by a Steering Committee. The members of the Steering Committee are listed in § 3.1 above.

The Steering Committee has the responsibility of:

- a. supervising the progress of the study and ensuring that the protocol is carefully followed by every participant. To exert this responsibility the Steering Committee may appoint Monitors and, in such a case, is informed of all monitoring activities and, in particular, of the reports of the Data Monitoring and Safety Board (§ 3.2.3).
- b. proposing Protocol Amendments to solve, clarify and implement possible doubts, questions, or practical difficulties that may arise during the study, or that may become necessary owing to the scientific progress in the specific therapeutic field, to ensure that the scientific validity of the study is maintained.

- c. resolve doubts as to the classification of outcomes, if the need arises. To this aim, the individual subject's data supplied to the Committee will be anonymous as to the subject and to the Center, and blinded as to the applied treatment, if any.
- d. resolve doubts as to the protocol violation, if any, deciding whether the possible violation is to be considered a minor deviation, a major deviation, or a true violation, and whether the case has to be included into the ITT dataset (no other dataset is planned in this study). To this aim, the individual subject's data supplied to the Committee will be anonymous as to the subject and to the Center, and blinded as to the applied treatment.
- e. participate in the Writing Committee.

The Steering Committee appointed a Core Team of five persons, including a statistician. The Core Team has the responsibility of:

- a. managing the study according to the needs that may arise, and reports to the whole Steering Committee as needed;
- b. presenting to the Steering Committee a yearly report on the status of the trial, including the clinical results that may arise, until the closure of the study, which will incorporate the conclusions of the DMSB evaluation. The term "yearly" should be intended as the time at which the data relevant to the end-of-observation-year visit on the last subject recruited have been recorded and validated. Consequently, there will be one interim report; the second report coincides with the final study report.

The components of the Core Team are listed in § 3.1 above.

11.2 Writing Committee

The Writing Committee is composed of the Steering Committee and additional investigators if needed, based primarily on number of subjects enrolled and secondarily by speed of recruitment. The Writing Committee is led by the Core Team.

The Writing Committee has the responsibility of:

- a. preparing the main publication of the study results;
- b. deciding on additional and subsequent publications of planned and unplanned study results;
- c. requesting additional statistical analyses of the study data, in relation to the publications indicated above;
- d. defining the list of authors to each publication;
- e. managing the contacts with the Journals and the requests for clarification and modifications to the submitted papers.

11.3 Data Monitoring and Safety Board

The study shall be supervised by a specifically set-up DMSB.

The main purpose of the DMSB is to protect subjects, primarily those included in the trial but also other subjects with the disease in question. The second responsibility of the DMSB is to ensure the integrity of the study, in particular in the form of compliance with the procedures indicated in the protocol to ensure the data credibility.

The DMSB will be composed of three members including a statistician. The members of the DMSB should not be enrolling subjects into the study.

The DMSB has also the responsibility to recommend to the Steering Committee changes in the conduct of the study, whenever changes of clinical practice or information gathered in the study or in other ongoing studies suggest that the current conduct might have negative effects on the subjects' wellbeing.

The decision of the DMSB will be taken on data collected at the end of every year of long-term follow-up (i.e., when the last subject to be observed has completed the observation at the end of a full year).

Since there will be a total of 2 analyses of the endpoints monitored during the follow-up (one interim and one final), to maintain the overall alpha error at 0.05, the final analysis of these endpoints will report as statistically significant at the 95% level of confidence, P-values ≤ 0.048 .

12. Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov". Results will be disclosed in a publicly available database within the standard timelines.

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the Promoter. Current guidelines and recommendation on good publication practice will be followed (e.g. STROBE [8]). To retain the integrity of the multicenter study, no individual investigator may publish on the results of this study, or their own subjects, or their country's subjects, without prior coordination with the Promoter.

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Appendices

Appendix I – Information sheet

Protocol Code: *WHITE Study*

Final Version of 20 September 2017

PATIENT'S INFORMATION SHEET

Study: **WHITE Study: WHICH decision after a first venous ThromboEmbolism?**
[Multicenter, multinational, investigators-initiated, observational, prospective study to evaluate the decisions taken by clinicians at the end of the maintenance treatment of subjects with a first-ever event of deep vein thrombosis of the lower limbs and/or pulmonary embolism, the relevant reasons, and the attending long-term outcomes]

Center: _____

Investigator: _____

Dear Madam, dear Sir.

You are being requested to participate in this study, promoted by a Foundation for Anticoagulation (Fondazione Arianna Anticoagulazione, Bologna, Italy) because you had a thrombosis that is being treated until now with anticoagulants.

You have now reached the time in which we should decide your treatment for the future. The decision can be to continue with the same treatment, to use another treatment, or simply to stop the treatment. We will take this decision in this visit.

To have a better understanding on how often and why one of these alternatives are taken, it is important that this decision is documented in a great number of persons and, possibly, that the results of the decision taken will have over the next years will also be recorded.

We ask your authorization to make available, within the limits and in compliance with the current regulations, some of your clinical data, which are useful to complete a research that aims at making more clear which decision is taken, why, and what are the effects over the following years, up to two years from now.

Your participation does not imply any additional action from your side: you will be treated and monitored, as you would be in any case. This is the meaning of an “observational” research. The only difference from the normal care and follow-up is that you allow the Promoter – the Fondazione Arianna – to use for research some of your data. These data will remain completely anonymous.

The information you may provide, together with the information collected anonymously in more than 3,000 other patients all over the world, can help designing a more effective and efficient management for future patients with your same problem. The results obtained from these data can also be the object of scientific communications, but in no instance it will be possible that you are identified through these data.

1. OBJECTIVES OF THE STUDY

The objectives of the study are the comprehension of how many patients are allocated to the different alternatives for the long-term management of a previous thrombosis, and why. In addition, there is also the

objective to monitor over a relatively extended period of time the true risks of thrombosis and of bleeding, in specific subgroups of persons.

2. WHAT PARTICIPATING TO THE STUDY IMPLIES

The collaboration that is requested from you consists in the authorization to collect and manage some of your clinical and personal data, in a completely anonymous way, to perform the study.

You will also be requested to permit us to call every three to six months to ask some information, and to plan an interview with us at this center every year, for the next two years. These calls and the yearly visit are in any case part of our normal plans for the long-term follow-up of persons like you. The only difference is that the data we ask or monitor will be recorded into the study data, always in a completely anonymous way.

This “observational” study does not plan for any exam or treatment in addition to those that are normally planned by your doctor to monitor the course of your recovery.

The participation to this study does not imply any additional cost, nor any saving, compared with your normal medical care.

3. POTENTIAL BENEFITS FROM PARTICIPATING TO THE STUDY

Participating to this study will not result in any direct and immediate clinical benefit for you or the other participants. The results of the study, however, can give important indication on how to manage on the long term the recovery of persons who had a thrombosis, that can improve or make more efficient the management of other persons in the future.

4. POTENTIAL RISKS FROM PARTICIPATING TO THE STUDY

There will be no risks due to the administration of drugs or treatments different from those normally prescribed to you by your Doctor.

5. YOUR RIGHTS

You are free to refuse participating in the study, or to retire your consent to the collection of your data, without forewarning or justification. In any case, you will continue receiving the best care appropriate for your medical condition.

The investigator is responsible for correctly carrying out the clinical protocol within the norms and regulation of the good clinical practice and within the frame of this information sheet. The investigator is available for any reasonable request of explanation or clarification from your side for what concerns the collection of the study data.

The results of this study will be retained as strictly confidential and anonymous. The results may be made known to others or published, but excluding any possible reference to you or to other participants. The local norms for the protection of personal data will strictly be adhered to.

For the entire duration of your participation to the study, you may ask information and questions to the Investigator concerning the data collected in the study and the course of the study. Similarly, at the end of the study you may request that your data be communicated to you and/or to your family physician.

6. PATIENT'S RESPONSIBILITIES

This study is “observational”. Consequently, you will have no direct responsibility on the conduct and execution of the study, except the responsibility to decide whether you want to take part or not in the proposed study, by signing the Informed Consent form.

Should you refuse to participate, you will in any case receive the care for your clinical condition you are entitled to.

7. FURTHER USEFUL INFORMATION

This study is no profit; it is promoted by the non-profit Foundation Arianna Anticoagulazione of Bologna (Italy).

The protocol of the study proposed to you was redacted in accordance with the current Good Clinical Practice, with the current Declaration of Helsinki, and was approved by the Ethics Committee/Institutional Review Board of this structure.

8. USE AND PROTECTION OF DATA

The collected information will be read, processed, analyzed and presented by the parties involved in the study and perhaps by the competent Authorities. Your data will be coded and your identity will not be revealed, nor will it be publicly available. This information will be handled as strictly confidential and in accordance with the applicable laws and regulations. This information will be used only for your most appropriate care and for the aims of the study.

As already indicated, the results of this study may be made known to the Authorities, to others or published in scientific papers. The presentation of results will be coded, excluding any possible reference to you or to other participants. You will not be identified in any report or publication. The local norms for the protection of personal data will strictly be adhered to.

The Doctor(s) involved in the collection of your data is/are:

| | |
|------------------|------------------|
| Dr. | Dr. |
| telephone: | telephone: |
| e-mail: | e-mail: |

and are at your disposal for any further information relevant to the study you may want to have. We thank you very much for your attention and collaboration.

Appendix II – Documentation of informed consent

Protocol Code: WHITE Study

Final Version of 20 September 2017

INFORMED CONSENT FORM

Study: **WHITE Study: WHICH decision after a first venous ThromboEmbolicism?**
[Multicenter, multinational, investigators-initiated, observational, prospective study to evaluate the decisions taken by clinicians at the end of the maintenance treatment of subjects with a first-ever event of deep vein thrombosis of the lower limbs and/or pulmonary embolism, the relevant reasons, and the attending long-term outcomes]

Center: _____

Investigator: _____

| | | |
|---|-----|----|
| Did you have sufficient time to read, understand and, if needed, receive additional explanations concerning what is written in the information sheet? | YES | NO |
| Did you receive from the Doctor indicated above sufficient explanations concerning your participation to the observational study indicated above? | YES | NO |
| Could you pose all the questions you deemed necessary, receiving satisfactory answers? | YES | NO |
| Did you consult your family physician or other persons concerning this study? | YES | NO |
| If you did not consult other persons, was it because you considered such request not necessary? | YES | NO |
| Have you been informed of your right to withdraw from the study at any time, without explanations and without affecting your medical care? | YES | NO |
| Are you aware that you may ask at any time information on the course of the study for what you are concerned? | YES | NO |
| Did you receive the name and telephone number of the Doctor you may contact at any time to receive further information relevant to the study? | YES | NO |
| Do you authorize the persons responsible for the conduct of this observational study to handle your data and to have periodical contacts with you to obtain additional data? | YES | NO |
| Do you authorize the persons responsible for the study and other competent authorities to have access to your study data, which will in any case be treated as strictly confidential? | YES | NO |
| Did you receive a copy of the Information Sheet and of this Informed Consent form for your reference | YES | NO |
| Do you freely accept to participate to this observational study, having understood the meaning of the request and the risks and benefits that it implies | YES | NO |

Signing this consent form, I freely consent to participate to the observational study indicated on top of this form, and to confer my data for the study, having understood the meaning of the request and the attending risks and benefits.

| | |
|--|---------------------------|
| Date: | Patient's signature |
| Patient's name and surname in block letters | |
| Signature of the Doctor who informed the patient | |
| Date: | |
| Doctor's name and surname in block letters | |

To the Promoter of the WHITE Study (Arianna Anticoagulation Foundation)

Country:

Centre

Please be informed that I have recruited the patient with WHITE code:

I declare under my responsibility that, based on the document archived at the centre:

1. The subject presents all the required inclusion criteria;
2. The subject is exempt of any exclusion criterion;
3. The subject has signed the informed consent, which is archived in this centre.

Signed: Dr. (full name in capital letters)

signature:

site and date:

**Please send this form by fax to: + 39 051 343604 or by email to <monitor.white@ariannafoundation.org>
as soon as you have completed the recruitment of a new subject.**

BASELINE FORM 1/8**Identification**

| | | |
|---|---|--|
| Centre: _ _ _ (from system based on user/password) | Consecutive number in the centre: _ _ _ | ID (from system) _ _ _ _ _ _ _ _ (proposed by system) NOTE: if >40 issue warning |
| Date of this visit (dd/mm/yyyy): _ _ / _ _ / _ _ _ | | |
| Informed consent signed: <input type="checkbox"/> 0-no [STOP] 1-yes | Consent date (dd/mm/yyyy): _ _ / _ _ / _ _ _ [consent date must be <= date of visit] | |
| Date of birth: _ _ / _ _ / _ _ _ (dd/mm/yyyy) | Age: _ _ _ [computed by system; consent minus birth; must be >=18 years] | |
| Ethnicity: <input type="checkbox"/> 1-White 2-Black 3-Asian 4-Latino 5-Native American (both North and South) 6-Arabic 7-Other (specify) 9-N/A | Specification: [if Ethnicity=7] | Sex: <input type="checkbox"/> 0-Female 1-Male 9-N/A |

Index episode of venous thromboembolism

| | |
|--|--|
| Date of diagnosis: _ _ / _ _ / _ _ _ (dd/mm/yyyy) [must be 90-360 days before consent] | Type of event: <input type="checkbox"/> (only one option among:) 1=proximal or proximal plus distal DVT of lower limbs 2=isolated distal DVT of lower limbs 3=DVT of lower limbs plus pulmonary embolism 4=pulmonary embolism without deep vein thrombosis |
|--|--|

IN CASE OF DEEP VEIN THROMBOSIS:

location of the index episode:
(select all what applicable)

[only if type=1, 2 or 3;

at least one must be checked;

if both right and left are checked, request
confirmation]

[0=no; 1=yes]

| VEIN | left..... | right |
|--------------------------------------|--------------------------|--------------------------|
| external iliac | <input type="checkbox"/> | <input type="checkbox"/> |
| common femoral | <input type="checkbox"/> | <input type="checkbox"/> |
| superficial femoral | <input type="checkbox"/> | <input type="checkbox"/> |
| deep femoral | <input type="checkbox"/> | <input type="checkbox"/> |
| popliteal | <input type="checkbox"/> | <input type="checkbox"/> |
| posterior tibial | <input type="checkbox"/> | <input type="checkbox"/> |
| peroneal | <input type="checkbox"/> | <input type="checkbox"/> |
| anterior tibial | <input type="checkbox"/> | <input type="checkbox"/> |
| medial gastrocnemius | <input type="checkbox"/> | <input type="checkbox"/> |
| lateral gastrocnemius | <input type="checkbox"/> | <input type="checkbox"/> |
| soleal | <input type="checkbox"/> | <input type="checkbox"/> |
| saphenous (great and/or small) | <input type="checkbox"/> | <input type="checkbox"/> |

BASELINE FORM 2/8

Index episode of venous thromboembolism additional information

Superficial vein thrombosis:

☐ 0-no
1-yes

In case of pulmonary embolism:

Recent (≤ 1 month) echocardiography:

☐

If yes: date |_|_|/|_|_|/|_|_|

0=no/1=yes – is NA with date blank if Type of event = 1 or 2

Signs of pulmonary hypertension:

☐

0=no/1=yes – is NA with date blank if Type of event = 1 or 2

HELP BOX: "PULMONARY HYPERTENSION"

THE INDEX EVENT WAS ASSOCIATED WITH:

| | | |
|--|--------------------------|--------------------|
| surgery | <input type="checkbox"/> | 0-no; 1-yes |
| severe trauma | <input type="checkbox"/> | 0-no; 1-yes |
| cancer | <input type="checkbox"/> | 0-no; 1-yes |
| motor function impairment (paraplegia) | <input type="checkbox"/> | 0-no; 1-yes |
| limb immobilization in the 3 months before the event | <input type="checkbox"/> | 0-no; 1-yes |
| central venous catheter | <input type="checkbox"/> | 0-no; 1-yes |
| chronic inflammatory disease | <input type="checkbox"/> | 0-no; 1-yes |
| bed rest >4 days | <input type="checkbox"/> | 0-no; 1-yes |
| pregnancy | <input type="checkbox"/> | 0-no; 1-yes; 9-N/A |
| puerperium | <input type="checkbox"/> | 0-no; 1-yes; 9-N/A |
| obesity | <input type="checkbox"/> | 0-no; 1-yes |
| heart failure | <input type="checkbox"/> | 0-no; 1-yes |
| nephrotic syndrome | <input type="checkbox"/> | 0-no; 1-yes |
| thrombophilia | <input type="checkbox"/> | 0-no; 1-yes; |
| polycythemia/thrombocythemia | <input type="checkbox"/> | 0-no; 1-yes |
| antiphospholipid antibody | <input type="checkbox"/> | 0-no; 1-yes |
| estrogens and/or progestins | <input type="checkbox"/> | 0-no; 1-yes |
| atrial fibrillation | <input type="checkbox"/> | 0-no; 1-yes |
| inferior vena cava filter | <input type="checkbox"/> | 0-no; 1-yes |
| long travel (> 4 h) | <input type="checkbox"/> | 0-no; 1-yes |
| other (specify) | <input type="checkbox"/> | 0-no; 1-yes |
| other; specification | | |

The index thromboembolic event was: idiopathic ☐
secondary ☐

(only one choice; radio-button type)

HELP BOX PULMONARY HYPERTENSION – FOR DATABASE USE ONLY

Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension

| Peak tricuspid regurgitation velocity (m/s) | Presence of other echo 'PH signs' [a] | Echocardiographic probability of pulmonary hypertension |
|---|---------------------------------------|---|
| ≤2.8 or not measurable | No | Low |
| ≤2.8 or not measurable | Yes | Intermediate |
| 2.9–3.4 | No | |
| 2.9–3.4 | Yes | High |
| >3.4 | Not required | |

PH = pulmonary hypertension

[a] see table below

Echocardiographic signs suggesting pulmonary hypertension used to assess the probability of pulmonary hypertension in addition to tricuspid regurgitation velocity measurement

| A: The ventricles [a] | B: Pulmonary artery [a] | C: Inferior vena cava and right atrium [a] |
|---|---|--|
| Right ventricle/ left ventricle basal diameter ratio >1.0 | Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching | Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration) |
| Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole) | Early diastolic pulmonary regurgitation velocity >2.2 m/sec | Right atrial area (end-systole) >18 cm ² |
| | PA diameter >25 mm. | |

PA = pulmonary artery

[a] Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.

Ref: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal* 2016; **37**, 67-119. doi:10.1093/eurheartj/ehv317

Clinical condition of veins

Recent (≤ 1 month) compression ultrasound: ☐ 0-no
1-yes

If yes: date |_|_|/|_|_|/|_|_|

Extent of residual thrombosis:
(mark all locations with extent $\geq 40\%$ of diameter or 4 mm):

0-no; 1-yes; default=no; if all=no and ultrasound=yes, ask confirmation

| LOCATION | left | right |
|-------------------|--------------------------|--------------------------|
| external iliac | <input type="checkbox"/> | <input type="checkbox"/> |
| groin | <input type="checkbox"/> | <input type="checkbox"/> |
| middle of thigh | <input type="checkbox"/> | <input type="checkbox"/> |
| popliteal area | <input type="checkbox"/> | <input type="checkbox"/> |
| distal deep veins | <input type="checkbox"/> | <input type="checkbox"/> |

Presence of:

varicose veins:

☐ 0-absent; 1-present; default: absent

post-thrombotic syndrome:

☐ 0-absent; 1-present; default: absent

oedema:

☐ 0-absent; 1-present; default: absent

lipodermatosclerosis:

☐ 0-absent; 1-present; default: absent

ulcer:

☐ 0-absent; 1-present; default: absent

[check: if ulcer present, PTS must be present]

Villalta score:

| Symptom/clinical signs | none | mild | moderate | severe |
|--------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| default: 0 | =0 | =1 | =2 | =3 |
| Symptoms | | | | |
| pain | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| cramps | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| heaviness | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| paresthesia | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| pruritus | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Clinical signs | | | | |
| pretibial edema | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| skin induration | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| hyperpigmentation | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| redness | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| venous ectasia | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| pain on calf compression | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

Total score: |_|_| [computed from system: sum of all the above marks; ranges 0 to 33]

[system computes and stores classification of PTS; absent if 0-4; mild if 5-9; moderate if 10-14;

severe if 15 or more or if ulcer from previous box is marked present]

[check: if Villalta ≥ 5 and post-thrombotic syndrome is marked absent, issue a warning]

BASELINE FORM 4/8**Concurrent diseases at this visit**

| | | | |
|--------------------------------------|--------------------------|-------------------------|--|
| History of cancer | <input type="checkbox"/> | 0-no; 1-yes; default=no | |
| Active cancer | <input type="checkbox"/> | if yes: | with metastases: <input type="checkbox"/> 0-no; 1-yes |
| | | | under chemotherapy: <input type="checkbox"/> 0-no; 1-yes |
| Diabetes | <input type="checkbox"/> | | |
| Hypertension..... | <input type="checkbox"/> | | |
| TIA/stroke/peripheral embolism | <input type="checkbox"/> | | |
| Ischemic heart disease | <input type="checkbox"/> | | |
| Left ventricular hypertrophy | <input type="checkbox"/> | | |
| Heart failure | <input type="checkbox"/> | | |
| Peripheral vascular disease..... | <input type="checkbox"/> | | |
| History of angioplasty/surgery..... | <input type="checkbox"/> | | |
| Chronic inflammatory diseases..... | <input type="checkbox"/> | | |
| Chronic respiratory diseases..... | <input type="checkbox"/> | | |
| Cirrhosis + esophageal varices | <input type="checkbox"/> | | |
| Kidney failure | <input type="checkbox"/> | | |
| Hypothyroidism..... | <input type="checkbox"/> | | |
| Hyperthyroidism | <input type="checkbox"/> | | |
| Other diseases | <input type="checkbox"/> | | |

Current medications (used for at least 3 months) at this visit

| | | |
|-------------------------------------|--------------------------|--------------------------|
| ASA <250 mg/day..... | <input type="checkbox"/> | 0-no; 1-yes [default=no] |
| Other antiplatelets..... | <input type="checkbox"/> | |
| Antiarrhythmic agents | <input type="checkbox"/> | |
| Antidiabetics | <input type="checkbox"/> | |
| Antidyslipidemic agents..... | <input type="checkbox"/> | |
| ACE inhibitors..... | <input type="checkbox"/> | |
| Sartans | <input type="checkbox"/> | |
| Beta-blockers | <input type="checkbox"/> | |
| Diuretics | <input type="checkbox"/> | |
| Calcium antagonists..... | <input type="checkbox"/> | |
| Other antihypertensive agents | <input type="checkbox"/> | |
| Nitrates | <input type="checkbox"/> | |
| Digitalis..... | <input type="checkbox"/> | |
| Proton pump inhibitors..... | <input type="checkbox"/> | |
| Antiviral agents | <input type="checkbox"/> | |
| Immunosuppressives | <input type="checkbox"/> | |
| Steroids | <input type="checkbox"/> | |
| Drugs for thyroid disorders..... | <input type="checkbox"/> | |
| Analgesic agents | <input type="checkbox"/> | |
| Anti-inflammatory drugs..... | <input type="checkbox"/> | |

Vascular risk factors at this visit

| | | | |
|---|---|--|--------------------------|
| Smoking..... | <input type="checkbox"/> 0-no; 1-yes; 9-N/A | if yes: less than 10 cigarettes per day | <input type="radio"/> |
| | | 10-20 cigarettes per day | <input type="radio"/> |
| | | more than 20 cigarettes per day | <input type="radio"/> |
| Thrombophilia test..... | <input type="checkbox"/> 0-negative; 1-positive; 9-not done | | |
| if positive: specify which..... | | Factor V Leiden | <input type="checkbox"/> |
| | | Factor II G20210A | <input type="checkbox"/> |
| | | Protein C deficiency | <input type="checkbox"/> |
| | | Protein S deficiency | <input type="checkbox"/> |
| | | AT deficiency | <input type="checkbox"/> |
| | | LAC+aCL Anti-Beta2GP1 | <input type="checkbox"/> |
| | | Hyperhomocysteinemia | <input type="checkbox"/> |
| | | JAK2 | <input type="checkbox"/> |
| | | other | <input type="checkbox"/> |
| | | (specify other) | |
| | | [0-negative; 1-positive; 9-not done; default: N/A] | |
| Dementia (assumed absent unless there is evidence it is present)... | <input type="checkbox"/> 0-no; 1-yes | | |
| Chronic bed rest..... | <input type="checkbox"/> | | |
| Wheelchair..... | <input type="checkbox"/> | | |
| Tendency to falls..... | <input type="checkbox"/> | | |
| History of major bleeding | <input type="checkbox"/> if yes: | | |
| | | cerebral hemorrhage | <input type="checkbox"/> |
| | | gastrointestinal bleeding | <input type="checkbox"/> |
| | | retroperitoneal hemorrhage | <input type="checkbox"/> |
| | | ocular haemorrhage | <input type="checkbox"/> |
| | | intra-articular haemorrhage | <input type="checkbox"/> |
| | | hemoglobin drop by 2 or more g/dL | <input type="checkbox"/> |
| | | transfusion | <input type="checkbox"/> |
| Living alone | <input type="checkbox"/> | | |
| Absence of family or social support..... | <input type="checkbox"/> | | |
| Family history of thromboembolism | <input type="checkbox"/> | | |
| Family history of coronary disease | <input type="checkbox"/> | | |
| Family history of TIA/stroke..... | <input type="checkbox"/> | | |
| Alcohol consumption | <input type="checkbox"/> if yes: | 1 unit per day | <input type="radio"/> |
| | | 2 units per day | <input type="radio"/> |
| | | more than 2 units per day | <input type="radio"/> |
| 1 unit = 1 glass (125 ml) of wine or 1 can (330 ml) of beer or 1 tumbler (30 ml) of spirit | | | |

BASELINE FORM 6/8

Other clinical information

Body weight (kg): |_|_|_|_|. |_|

check limits: 40-200

height (cm): |_|_|_|_|

check limits: 90-230

BMI: |_|_|_|. |_|

computed: kg/m²

If available: last creatinine value recorded during the 3 months before the visit:

Creatinine: units ☐ mg/dL (default)

value: |_|_|_|. |_|_|_|

clearance: |_|_|_|_|. |_|

☐ μmol/L

computed; Cockcroft-Gault formula

if creatinine is in μmol/L multiply by 0.01131222; round to 3 digits

clearance (in mL/min): $\frac{(140 - \text{age}[\text{in years}] \times \text{bodyweight}[\text{in kg}])}{72 \times \text{creatinine}[\text{in } \frac{\text{mg}}{\text{dL}}]} \times 0.85 \text{ if female (no change if male; missing if sex is NA)}$

Maintenance anticoagulation treatment prescribed after the index event (the treatment to continue-resume/stop/change at this visit)

Treatment start date (dd/mm/yyyy): |_|_|/|_|_|/|_|_|_|_| [check: must be >= Date of diagnosis]

[if (visit minus start) <90 days or >360 days, warning]

Treatment actual stop date (dd/mm/yyyy): |_|_|/|_|_|/|_|_|_|_| [check: must be <=Date of this visit]

[and >= Date of this visit minus 30 days]

Treatment prescribed: vitamin-K antagonist

[one MUST be selected]

low molecular weight heparin

direct anticoagulants (NOACs)

other

☐

0-no; 1-yes; if yes open window VKA

☐

0-no; 1-yes; if yes open window LMWH

☐

0-no; 1-yes; if yes open window NOACS

☐

0-no; 1-yes; if yes open window below

[if "other"=yes] specify other (common name): [text]

daily dose: dose units: ATC if known: |_|_|_|_|_|_|_|_|

[number, floating point]

[text]

[text]

WINDOWS FOR CLASS VKA, LMWH, NOACS – FOR DATABASE USE ONLY

The following tables are called-in upon selection of the drug class.

The operator can select one only from each of these, and is requested to input the daily dose as number
CHECK supplies the acceptable range for the number. Doses out of range require a warning-
TO BE RECORDED: ATC CODE and DAILY DOSE. There should be not more than one per class (VKA, LMWH,
NOAC); two of them may be empty if OTHER is empty; all three can be empty if OTHER is marked.

VKA

| Name | unit | DAILY DOSE | ATC code | CHECK |
|----------------------|------|------------|----------|----------|
| dicoumarol | mg | | B01AA01 | 25-400 |
| phenindione | mg | | B01AA02 | 25-400 |
| warfarin | mg | | B01AA03 | 1.25-30 |
| phenprocoumon | mg | | B01AA04 | 0.5-12 |
| acenocoumarol | mg | | B01AA07 | 1.25-20 |
| ethyl biscoumacetate | mg | | B01AA08 | 125-2400 |

LMWH

| Name | unit | DAILY DOSE | ATC code | CHECK |
|------------|---------|------------|----------|---------|
| bemiparin | Ux1,000 | | B01AB12 | 5-10 |
| certoparin | Ux1,000 | | B01ABXX | 8-16 |
| dalteparin | Ux1,000 | | B01AB04 | 0.15-18 |
| enoxaparin | Ux1,000 | | B01AB05 | 6-15 |
| nadroparin | Ux1,000 | | B01AB06 | 3-8.5 |
| parnaparin | Ux1,000 | | B01AB07 | 4-12.8 |
| reviparin | Ux1,000 | | B01AB08 | 5-10.5 |
| tinzaparin | U/kg | | B01AB10 | >=175 |

NOACS

| Name | unit | DAILY DOSE | ATC code | CHECK |
|-------------|------|------------|----------|---------|
| rivaroxaban | mg | | B01AF01 | 5-30 |
| apixaban | mg | | B01AF02 | 5-20 |
| edoxaban | mg | | B01AF03 | 30-60 |
| dabigatran | mg | | B01AE07 | 220-300 |

Decision on next therapy

From this visit onward, the therapy will be:

- ☐ continued with same anticoagulant *if yes specify:* at the same dose: ☐ 0
 at reduced dose: ☐ 1
 dose units: total daily dose: |_|_|_|_|. |_|_|
 [text] [number, floating point]
- ☐ continued with an anticoagulant of the same class open the box "replaced_1".
☐ replaced by an anticoagulant of a different class open the box "replaced_1".
☐ replaced by another class of antithrombotic open the box "replaced_2".
☐ discontinued without replacement

one and only one of these choices MUST be selected

Please specify:

Treatment prescribed in this visit:

- vitamin-K antagonist ☐ 0-no; 1-yes; if yes open window VKA
 low molecular weight heparin ☐ 0-no; 1-yes; if yes open window LMWH
 direct anticoagulants (NOACS) ☐ 0-no; 1-yes; if yes open window NOACS
 other ☐ 0-no; 1-yes; if yes open window "other"

Box "replaced_1"

Treatment prescribed in this visit:

- aspirin ☐ 0-no; 1-yes
 if aspirin=yes:
 ATC: B01AC06
 daily dose: ☐ 75-175 mg
☐ 176-250 mg
☐ 251-500 mg
☐ >500 mg
- sulodexide ☐ 0-no; 1-yes
 if sulodexide = yes:
 ATC: B01AB11
 daily dose: ☐ 500 LSU
☐ 1000 LSU
 other ☐ 0-no; 1-yes; if yes open window "other"

Box "replaced_2"

[if "other"=yes] specify other (common name):

daily dose: dose units: ATC if known: |_|_|_|_|_|_|_|_|
 [number, floating point] [text] [text]

Box "other"

Please specify whether compression therapy is prescribed:

- no: ☐ 0
 yes: ☐ 1 specify mmHg recommended: | ____ | [text]

Reasons for taking this decision
(please tick all what applicable)

| | | | |
|---|--|---|---|
| No need of further treatment | <input type="checkbox"/> | 0-no; 1-yes; default=no | |
| Risk of thromboembolic recurrence | <input type="checkbox"/> | specify: | <input type="radio"/> high-medium <input type="radio"/> low [HELP BOX FOR CRITERIA] |
| Risk of bleeding | <input type="checkbox"/> | specify: | <input type="radio"/> high <input type="radio"/> medium <input type="radio"/> low [HELP BOX FOR CRITERIA] |
| Major bleeding event during treatment | <input type="checkbox"/> | | |
| Difficulty to maintain the proper INR | <input type="checkbox"/> | | |
| Consideration of patient's age | <input type="checkbox"/> | | |
| Presence of Post Thrombotic Syndrome | <input type="checkbox"/> | | |
| Presence of thrombophilia | <input type="checkbox"/> | specify: _____ | [text] |
| Familiarity for venous thromboembolism | <input type="checkbox"/> | | |
| Implantation of vena cava filter | <input type="checkbox"/> | | |
| Presence of pulmonary hypertension | <input type="checkbox"/> | | |
| Worsening of general conditions (not cancer) | <input type="checkbox"/> | | |
| Worsening/onset of renal insufficiency | <input type="checkbox"/> | | |
| Tendency to falls | <input type="checkbox"/> | | |
| Presence of cancer | <input type="checkbox"/> | | |
| Onset of contraindications | <input type="checkbox"/> | specify: _____ | [text] |
| Decision by the patient's family doctor | <input type="checkbox"/> | | |
| Choice of the patient | <input type="checkbox"/> | | |
| Cost for the patient | <input type="checkbox"/> | | |
| Positive D-dimer value | <input type="checkbox"/> | specify value: _ _ _ D-DU <input type="radio"/> FEU <input type="radio"/> | |
| Negative D-dimer value | <input type="checkbox"/> | specify value: _ _ _ D-DU <input type="radio"/> FEU <input type="radio"/> | |
| [if D-dimer value specified, one of the units MUST be specified] | | | |
| Patient involved in choosing the prescribed therapy | <input type="checkbox"/> | 0-no; 1-yes; default=no | |
| Patient's GP involved in choosing the prescribed therapy | <input type="checkbox"/> | 0-no; 1-yes; default=no | |
| Planned duration of this therapy: | <input type="radio"/> not applicable [if decision=2, only possible choice] <input type="radio"/> not defined <input type="radio"/> to be evaluated <input type="radio"/> defined; specify: _ _ _ <input type="radio"/> months <input type="radio"/> years | | |

FOLLOW-UP FORM 1/3

SECTION 2 – FOLLOW-UP

The follow-up is intended for up to 2 years, with total maximum 8 contacts plus unpredictable number of unplanned contacts (few).

Interview ID

| | | |
|-------------------------------|---|--|
| ID (from system) | _ _ _ _ _ _ _ | [obtained from database based on username/password and number within center] |
| Nominal contact time (month): | _ _ | [options: 3-6-9-12-15-18-21-24 plus 9# (starting from 90 and increased by 1 at each new unplanned visit: unplanned proposed by system, can be replaced. CHECK: baseline must be present; conclusion must not be present. Investigator informed forty days in advance by mail. If not completed within 2 weeks from due date, new mail to the investigator. For visits 12-and 24 the mail should indicate that a visit at the center should be planned.)] |
| Date of contact (dd/mm/yyyy): | _ _ / _ _ / _ _ _ _ | |
| Type of contact: | <input type="checkbox"/> 1=telephone call; 2=visit at center | if type=2: Type of visit: <input type="checkbox"/> 1=planned by investigator 2=planned, requested by patient 3=unplanned |

| | | | | |
|--|--|-----------------------|---|---|
| Thrombotic complications: | <input type="checkbox"/> 0-no 1-yes | if yes, specify: | deep vein thrombosis <input type="checkbox"/> pulmonary embolism <input type="checkbox"/> superficial vein thrombosis <input type="checkbox"/> transient ischemic attack (TIA) <input type="checkbox"/> ischemic stroke <input type="checkbox"/> acute myocardial infarction <input type="checkbox"/> sudden/cardiac death <input type="checkbox"/> other; specify <input type="text"/> | <input type="checkbox"/> 0-no; 1-yes; default=no [CHECK death below] |
| | | | | |
| Bleeding complications: if yes, specify how many: if yes, specify: | <input type="checkbox"/> 0-no; 1-yes; default=no | type of complication: | _ _ 0; if bleeding complication=yes, should be ≥1 <input type="checkbox"/> major bleeding <input type="checkbox"/> clinically relevant non-major bleeding <input type="checkbox"/> other bleeding | |
| | | | N/A; if bleeding complication = yes, at least one should be indicated | |
| | | | HELP BOX BLEEDING CLASSIFICATION | |
| if yes, specify the nature of the complication: | | | cerebral hemorrhage/hemorrhagic stroke <input type="checkbox"/> gastrointestinal hemorrhage <input type="checkbox"/> retroperitoneal hemorrhage <input type="checkbox"/> intra-ocular hemorrhage <input type="checkbox"/> retinal bleeding <input type="checkbox"/> intra-articular hemorrhage (hemarthrosis) <input type="checkbox"/> hemoglobin drop by 2 or more g/dL <input type="checkbox"/> transfusion of 2 or more units of red cell concentrate <input type="checkbox"/> uterine bleeding <input type="checkbox"/> skin/muscle hematoma <input type="checkbox"/> nose bleed <input type="checkbox"/> bleeding gums <input type="checkbox"/> anal bleeding <input type="checkbox"/> other; specify <input type="text"/> | |
| | | | | |
| Hospitalization: | <input type="checkbox"/> 0-no 1-yes | if yes, specify: | date (dd/mm/yyyy) _ _ / _ _ / _ _ _ _ reason: _____ | [text] |
| | | | | |
| Patient's death: | <input type="checkbox"/> 0-no 1-yes | if yes, specify: | date (dd/mm/yyyy) _ _ / _ _ / _ _ _ _ reason: _____ | [text] |
| | | | | |
| Any other event preventing continuation of the follow-up | <input type="checkbox"/> 0-no 1-yes | if yes, specify: | date (dd/mm/yyyy) _ _ / _ _ / _ _ _ _ reason: _____ | [text] |

HELP BOX BLEEDING

1. A major bleeding is defined as having a symptomatic presentation and:
 - is fatal, and/or
 - occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
 - causes a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leads to transfusion of two or more units of whole blood or red cells.
2. A clinically relevant non-major bleeding is defined as any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the definition of major bleeding above, but does meet at least one of the following criteria:
 - requiring medical intervention by a healthcare professional;
 - leading to hospitalization or increased level of care;
 - prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.
3. All bleedings that do not meet definition 1 or definition 2 are classified as “other”.

Reference: Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, for the Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost* 2015; **13**: 2119–26.

Antithromboembolic therapy

There was any change in the prescribed anti-thromboembolic therapy after the last contact (in the last 3/6 months)?

☐ 0-no; 1-yes

If yes, the therapy was:

- ☐ dose reduced (not discontinued): 1
 dose increased: 2
 newly instituted: 3
 discontinued without replacement: 4
 replaced with another therapy: 5
 [if change=0, blank; if change=1 MUST be filled;
 if replaced, continue with boxes below]

Specify if change was decided by:

- ☐ investigator or co-investigator
☐ other physician
☐ spontaneously by patient

If replaced with another therapy, please specify:

Treatment switched to:

- vitamin-K antagonist ☐ 0-no; 1-yes; if yes open window VKA
 low molecular weight heparin ☐ 0-no; 1-yes; if yes open window LMWH
 direct anticoagulants (NOACS) ☐ 0-no; 1-yes; if yes open window NOACS
 aspirin ☐ 0-no; 1-yes
 if aspirin=yes:
 ATC: B01AC06
 daily dose: ☐ 75-175 mg
☐ 176-250 mg
☐ 251-500 mg
☐ >500 mg
 sulodexide ☐ 0-no; 1-yes
 if sulodexide = yes:
 ATC: B01AB11
 daily dose: ☐ 500 LSU
☐ 1000 LSU
 other ☐ 0-no; 1-yes; if yes open window below

[if "other"=yes] specify other (common name): [text]

daily dose: dose units: ATC if known: |_|_|_|_|_|_|_|_|
 [number, floating point] [text] [text]

DECISION: in case of

- a) thrombotic complication;
 b) death
 c) event preventing continuation
 d) newly instituted therapy
 e) discontinued therapy
 f) change to new therapy
 go to END-OF-TRIAL.

IN CASE OF:

- a) bleeding complication
 b) hospitalization, ASK if patient remains on trial or goes to END-OF-TRIAL.

END-OF-STUDY FORM

SECTION 3 – CONCLUSION – END-OF-TRIAL form

Patient's end-of-study information

ID (from system) |_|_|_|_|_|_|_|_|_| [obtained from database based on username/password and number within center]
Date of form completion (dd/mm/yyyy): |_|_|/|_|_|/|_|_|_|_|_| [obtained from system]

Reason for concluding the follow-up of this patient

| | | |
|---|--------------------------|--|
| The patient reached the end of the planned observation period | <input type="checkbox"/> | date: _ _ / _ _ / _ _ _ _ _ |
| | 0=no; 1=yes; default=no | exact date: dd/mm/yyyy |
| Shown a thromboembolic event | <input type="checkbox"/> | date: _ _ / _ _ / _ _ _ _ _ |
| Shown a major bleeding event | <input type="checkbox"/> | date: _ _ / _ _ / _ _ _ _ _ |
| Had a major change in therapy | <input type="checkbox"/> | date: _ _ _ _ / _ _ _ _ _ |
| Reported another event preventing continuation of the follow-up | <input type="checkbox"/> | date: _ _ _ _ / _ _ _ _ _ |
| | | these dates may be incomplete (no day) |
| The patient died | <input type="checkbox"/> | date: _ _ / _ _ / _ _ _ _ _ |
| The patient reported to another hospital | <input type="checkbox"/> | date: _ _ _ _ / _ _ _ _ _ |
| The patient moved to another place | <input type="checkbox"/> | date: _ _ _ _ / _ _ _ _ _ |
| The patient was lost to follow-up | <input type="checkbox"/> | date: _ _ _ _ / _ _ _ _ _ |

CHECK: at least one must be marked yes; if thromboembolic event is marked, there must be a thromboembolic event in the last follow-up form; if bleeding event is marked, there must be a bleeding event in the last follow-up form, items 1-9; if died is marked, there should be death=yes in last follow-up form, if other event is marked, there must be a "other event" marked in the last follow-up form.

After this form is concluded, the case is closed and cannot be modified by the users. It can be re-opened upon request (ticket), endorsed by the study supervisors.