PROTOCOL

TITLE: Global Anticoagulant Registry in the FIELD observing treatment and outcomes in patients with treated acute Venous Thromboembolic Events in the real world

SHORT TITLE: Global Anticoagulant Registry In the FIELD – Venous Thromboembolic Events (GARFIELD-VTE)

REGISTRY NUMBER: TRI08889

PROTOCOL VERSION NUMBER/DATE: Protocol Version 2.0 22\textsuperscript{nd} May 2014

SPONSOR: Thrombosis Research Institute
Manresa Road
Chelsea
London SW3 6LR
United Kingdom

EudraCT number: 2013-004758-55

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## CONTACT DETAILS OF KEY PERSONNEL

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<thead>
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<th>Name: Prof. Ajay K. KAKKAR</th>
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<td>Tel.: + 44 (20) 7351 8309</td>
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<table>
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<tr>
<th>REGISTRY MANAGEMENT</th>
<th>Name: Gloria Kayani</th>
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<td>E-mail: <a href="mailto:okayani@tri-london.ac.uk">okayani@tri-london.ac.uk</a></td>
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<table>
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<tr>
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<th>Company: Thrombosis Research Institute</th>
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<tr>
<td>Website:</td>
<td><a href="http://www.tri-london.ac.uk">www.tri-london.ac.uk</a></td>
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PROTOCOL APPROVAL

CO-ORDINATING AND CHIEF INVESTIGATOR:

I have read all pages of this clinical Registry protocol. I agree that it contains all the information required to conduct this Registry.

Name: Prof. Ajay K. KAKKAR
Signature: .......................... Date: 22/MAY/2014
dd/mmm/yyyy

STATISTICIAN:

The statistical analyses described in this protocol TRI 08889 are appropriate for this Registry.

Name: Gabriele Accetta
Statistician – Thrombosis Research Institute, London
Signature: .......................... Date: 22/MAY/2014
dd/mmm/yyyy

SPONSOR STATEMENT

Thrombosis Research Institute, London (TRI, the sponsor) authored and approves the contents of this protocol TRI 08889 for Registry.

Name: Gloria Kayani
Chief Operating Officer - Thrombosis Research Institute, London
Signature: .......................... Date: 22/MAY/2014
dd/mmm/yyyy
INVESTIGATOR STATEMENT

Title of Registry: Global Anticoagulant Registry in the FIELD observing treatment and outcomes in patients with treated acute Venous Thromboembolic Events in the real world.

I have read the protocol, and case report form. I agree:

a) To conduct this clinical Registry to ICH Good Clinical Practice (GCP), where applicable, Good Pharmacoepidemiological Practice (GPP), and all applicable national laws and regulations including those of the Ethics Committee.

b) To comply with procedures for data recording/reporting.

c) To permit monitoring, auditing and inspection.

d) To retain the Registry related essential documents until the sponsor informs the investigator/institution these documents are no longer needed.

I will not change any Registry requirements without this first being agreed with the other Investigators and TRI and formally acknowledged by a signed protocol amendment.

As the Investigator, I agree to ensure the confidentiality of my patients; however, I agree to make available to TRI, the sponsor of this Registry or its mandated representatives and competent authorities my subject’s medical charts which concern this Registry. I am aware of the details of my responsibilities as an Investigator as provided to me by TRI.

PRINCIPAL SITE INVESTIGATOR

Signature: .................................................. Date: ............................
                                     dd/mmm/yyyy

PRINT NAME:________________________

SITE: _______________________________
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### Abbreviations

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<th>Description</th>
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<tbody>
<tr>
<td>ACS</td>
<td>Acute Coronary Syndrome</td>
</tr>
<tr>
<td>ACTS</td>
<td>Anti Clot Treatment Scale</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetylsalicylic Acid</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>CTEPH</td>
<td>Chronic thromboembolic Pulmonary Hypertension</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep Venous Thrombosis</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>EC, IEC</td>
<td>Ethics Committee, Independent Ethics Committee</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GCS</td>
<td>Graduated Compression Stockings</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro-Intestinal</td>
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<tr>
<td>GU</td>
<td>Genitourinary</td>
</tr>
<tr>
<td>GPV</td>
<td>Global Pharmacovigilance</td>
</tr>
<tr>
<td>Hb</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>HEOR</td>
<td>Health Economics and Outcomes Research</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior Vena Cava</td>
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<tr>
<td>LMWH</td>
<td>Low Molecular Weight Heparin</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
</tr>
<tr>
<td>PISCF</td>
<td>Patient information sheet and consent form</td>
</tr>
<tr>
<td>PTS</td>
<td>Post-Thrombotic Syndrome</td>
</tr>
<tr>
<td>QA/QC Plan</td>
<td>Quality Assurance/Quality Control Plan</td>
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<td>SADR</td>
<td>Serious Adverse Drug Reaction</td>
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<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<tr>
<td>SmPC/SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischaemic Attack</td>
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<tr>
<td>VKA</td>
<td>Vitamin K Antagonist</td>
</tr>
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<td>VTE</td>
<td>Venous Thromboembolism</td>
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# 1 Protocol Summary

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<th>Title of Registry</th>
<th>Global Anticoagulant Registry in the FIELD observing treatment and outcomes in patients with treated acute Venous Thromboembolic Events in the real world</th>
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<tr>
<td>Registry Number</td>
<td>TRI08889</td>
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</table>
| Protocol Version Number | Protocol version 2.0  
22nd May 2014                                                                                                                                    |
| Sponsor           | The Thrombosis Research Institute, London                                                                                                                                                       |
| Phase             | Phase IV Registry Study                                                                                                                                                                           |
| Investigational Medicinal Product | None                                                                                                                                                                                  |
| Chief Coordinating Investigator | Professor the Lord Kakkar                                                                                                                                         |
| Registry Objectives | The study objectives are to describe acute, sub-acute and extended duration of anticoagulation management, clinical and economic outcomes in patients with treated acute VTE (DVT and PE) in the real-world setting.  
Main objectives are to clarify the:  
- Treatment related details for acute VTE (either conventional anticoagulation therapy, treatment with a direct oral anti-coagulant or other modalities of treatment)  
- Rate of early and late VTE recurrence  
- Rate and nature of complications of VTE, including:  
  - post thrombotic syndrome and  
  - chronic thromboembolic pulmonary hypertension  
- Rate of bleeding complications  
- Rate of all-cause mortality at six months  
Other objectives are to clarify the additional outcomes of:  
  - Stroke  
  - TIA  
  - STEMI  
  - NSTEMI |
<table>
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<tr>
<th>Registry Outcome Measures</th>
<th>• Rate of recurrent VTE (DVT and fatal or non-fatal PE)</th>
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<tr>
<td></td>
<td>• Bleeding events:</td>
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<tr>
<td></td>
<td>• Frequency</td>
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<td></td>
<td>• Location</td>
</tr>
<tr>
<td></td>
<td>• Severity (classified as major or non-major)</td>
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<tr>
<td></td>
<td>• Stroke</td>
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<tr>
<td></td>
<td>• Ischaemic stroke</td>
</tr>
<tr>
<td></td>
<td>• Haemorrhagic stroke</td>
</tr>
<tr>
<td></td>
<td>• Hospitalisation</td>
</tr>
<tr>
<td></td>
<td>• Post Thrombotic Syndrome (PTS)</td>
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<td></td>
<td>• Chronic Thromboembolic Pulmonary Hypertension (CTEPH)</td>
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<tr>
<td></td>
<td>• TIA</td>
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<td></td>
<td>• STEMI</td>
</tr>
<tr>
<td></td>
<td>• NSTEMI</td>
</tr>
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<td></td>
<td>• Unstable angina</td>
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<td></td>
<td>• IVC filter placement</td>
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<tr>
<td></td>
<td>• Other urgent interventions for VTE</td>
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<tr>
<td></td>
<td>• Anticoagulation therapy Persistence</td>
</tr>
<tr>
<td></td>
<td>• All-cause Mortality, and these subsets as causes of death:</td>
</tr>
<tr>
<td></td>
<td>• PE</td>
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<tr>
<td></td>
<td>• Stroke</td>
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<td></td>
<td>• Cardiac</td>
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<td>• Cancer-related</td>
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<td>• Bleed</td>
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<td></td>
<td>• Other</td>
</tr>
<tr>
<td></td>
<td>• Direct and indirect cost associated with therapy and secondary prevention</td>
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<td>• Quality of life and patient treatment satisfaction over a three year period</td>
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</table>
For patients treated with VKAs:

- Frequency of INR monitoring
- INR readings
- Outcomes in relation to INR fluctuation

**Registry Design**

Global, prospective, observational, multi-centre VTE registry to be conducted in sequential cohorts.

In order to observe temporal trends in management of VTE a minimum of 2 cohorts will be recruited. Recruitment into the second (or subsequent cohorts) will commence when recruitment is completed into the first or previous cohort. It is estimated that each cohort will take approximately 9 months to recruit. Potential patients must be assessed for eligibility within 30 days of their acute VTE diagnosis.

**Cohort One**

5000 consecutive unselected patients treated for acute VTE and followed prospectively for a minimum of 36 months

**Cohort Two**

A further 5000 consecutive unselected patients treated for acute VTE and followed prospectively for a minimum of 36 months

**Study Population**

Sites will be selected at random from a representative list reflecting treatment patterns in each country. Consecutive male and female VTE patients at the randomly selected sites will be included in the registry if they meet the eligibility criteria below.

**Inclusion Criteria**

1. Written informed consent
2. Age 18 years and over
3. Treated first time or recurrent DVT (lower or upper extremity), PE alone or overlapping DVT and PE confirmed by appropriate diagnostic methods (patients must be assessed for eligibility within 30 days of diagnosis)
4. Patients included with recurrent VTE must have completed treatment for the previous VTE episode

**Exclusion Criteria**

1. Patients for whom long-term follow up is not envisaged within the enrolling hospital or the associated primary care physician
2. Patients participating in an interventional study that dictates treatments, visit frequency, or diagnostic procedures
3. Patients with only superficial vein thrombosis (SVT)

### Statistical considerations

**General statistical approach**

The statistical analysis will include a descriptive analysis of the population characteristics and outcome variables. It will be explorative and descriptive and will be summarised into frequency tables (ordinal or nominal data) or summary statistics with mean, standard deviation, minimum, maximum, median, lower and upper quartile.

All analyses will be performed for the total study sample and separately for each country and region if the patient numbers are sufficient.

All details regarding derived variables, format and content of tables will be described in the Statistical Analysis Plan.

**Determination of sample size**

Since there are no specific hypotheses to be tested, a power calculation cannot be performed. However it is desirable to assess the viability of the registry to produce useful estimates of the main outcomes. Confidence intervals with half-widths of up to 5% may arbitrarily be regarded as useful. Accordingly, the VTE recurrence in PE patients estimate is expected to have acceptable precision in high recruiting countries, whereas low recruiting countries may have to merge results to achieve useful precision.

### Registry Conduct

Suitable patients will be identified in hospitals and other care settings treating VTE.

Investigator sites will be selected randomly in participating countries and will be representative of national geography and the distribution of care settings treating patients with VTE in the acute
phase and during long-term follow up.

National Coordinators will be appointed in each participating country and will advise on national distribution of VTE care settings to ensure that Investigator sites are representative of care in each country.

Patient’s medical history will be assessed and consecutive patients satisfying the inclusion/exclusion criteria within 30 days of the acute VTE episode will be invited to take part in the registry.

All patients will be provided with the patient information sheet, and written informed consent will be obtained according to local requirements before any transfer of data from the medical records to the eCRFs is carried out.

Data will be collected at Baseline (and up to 30 days post event), 3, 6, 12, 24 and 36 months. These time points will be used as markers for collection of all data from the preceding period. The aim of data collection will be to accurately capture all data relevant to registry endpoints from medical records. An additional annual check of the patient status may occur following this period for up to 2 years.

A log of all patients invited to participate in the registry, including those who declined the invitation to join, will be kept at each site.

| Registry Duration | It is anticipated that the duration of data collection in the registry will be approximately 4.5 years for the first two cohorts, allowing 9 months for recruitment of each of the sequential cohorts and a minimum of 36 month follow up for each patient. Additional optional data collection may occur annually (month 48 and month 60) for up to 2 years following the 36 month follow up period for all cohorts. There may also be additional cohorts added to the registry. Additional cohorts will also have approximately 9 months of recruitment and a minimum of 36 months follow up period. |

---
## Schedule for Data Entry at Site – Cohort 1 and 2

<table>
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<th>Tests and Assessments</th>
<th>Baseline and up to 30 days&lt;sup&gt;1&lt;/sup&gt;</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
<th>48 and 60 Months (optional annual check-up for 2 years)&lt;sup&gt;3&lt;/sup&gt;</th>
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<td>Diagnosis of current VTE</td>
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<td>Bleeding Events</td>
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<td>Diagnosis of CTEPH</td>
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<tr>
<td>Patients assessment of PTS symptoms according to Villalta Scale&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>Patient Questionnaire -SF-12 (Burden of disease)</td>
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<td>Physician’s Evaluation of PTS using Clinical signs from Villalta Scale</td>
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</table>

<sup>1</sup>Patients must be assessed for eligibility within 30 days of confirmed diagnosis of the acute VTE event.

<sup>2</sup>ACTS questionnaires will be completed by patients in a subset of countries where local language versions are available.

<sup>3</sup>Optional additional annual check on patient status for 2 years following the 36 month follow up period.

<sup>4</sup>Patient assessment of PTS will be completed by Villalta where available.
2 Background

2.1 Epidemiology of VTE

Venous thromboembolism (VTE) is a common, potentially lethal disease that may recur frequently and can cause long term complications. VTE encompasses deep venous thrombosis (DVT) and/or pulmonary embolism (PE), both complementary manifestations of the same pathophysiology and the long-term complications arising therefrom (including post thrombotic syndrome and chronic thromboembolic pulmonary hypertension). The clinical presentation of about two thirds of VTE patients is with DVT and the remaining one third present with PE.

Even though a common disorder, uncertainties remain about VTE prevalence and incidence as well as early and long-term clinical and economic consequences: published VTE annual incidence data range from 1 to 2 cases per 1000 persons in the general population. Furthermore, VTE is the third most common cause of vascular death (after stroke and myocardial infarction).[1]

Incidence-based epidemiological models estimate total annual incidence of VTE across EU member states (population of 454 million) to be 640,000 symptomatic DVTs and 383,000 symptomatic PEs.[2] Epidemiological modelling also estimates that the total annual incidence of VTE in the USA is 376,642 cases of symptomatic DVTs and 236,781 cases of symptomatic PEs. VTE-related deaths in the USA is estimated to be between 100,000 to 180,000 annually.

VTE-related deaths in the EU are estimated to be 480,000 annually.[2] Of these only 7% of patients had been diagnosed with VTE and treated accordingly. To put these figures into context, the annual number of deaths associated with VTE in Europe is more than double the combined number due to AIDS (5,860), breast cancer (86,831), prostate cancer (63,636), and road traffic accidents (53,599).[3]

2.2 VTE complications

Early and long-term VTE management aim is to prevent acute and long-term complications and sequelae such as PE in patients presenting with DVT, recurrent VTE, PTS and CTEPH.

2.2.1 Recurrent VTE

The risk of recurrence after VTE is highest during the first 6-12 months, but continues for at least 10 years. Cumulative risk of VTE recurrence reaches about 25% at 5 years and 30% at 10 years.[4] Up to 25% of all VTEs occur in those that have had a previous VTE and the risk for recurrence is greater if the initial VTE was unprovoked.
Retrospective, 3 year data in patients with PE have shown that patients with PE had a 5.7% incidence of recurrent PE, 13.7% had a recurrence of either DVT or PE and 14.9% experienced a major bleeding episode (i.e. requiring transfusion). In patients who presented with isolated DVT over the same period, PE occurred in 5.6%; DVT in 19% and 12.8% had a major bleeding episode. Morbidity and mortality increases with each recurrence [6].

### 2.2.2 Post-thrombotic syndrome (PTS)

PTS causes substantial morbidity because of its chronic nature. Clinical studies have shown PTS incidences of 20-60% within 1-2 years [6]. Recent evidence suggests that despite progress in diagnosis and treatment of DVT of the lower extremities, one of every 2-3 patients (30-50%) will develop PTS within 2 years, which is severe in approximately 10% of cases causing considerable clinical and socio-economic consequences.[7]

Clinical studies have shown severe PTS involving leg ulcers to increase from 2.7% at 1 year after symptomatic DVT to 8.1% after 5 years.[8, 9]
PTS has a substantial impact on Quality of Life (QoL); in epidemiological and economic studies self-reported quality of life in patients with PTS was similar to CHF, COPD, diabetes. PTS has a substantial economic impact in the US and Europe\[10\] with estimated annual costs of PTS in the US at 20,569 US$ compared to 15,843 US$ in matched control with DVT and/or PE but no PTS.\[11\]

### 2.2.3 Chronic thromboembolic pulmonary hypertension (CTEPH)

The incidence of chronic thromboembolic pulmonary hypertension (CTEPH) is not well documented. Prospective study data in patients followed-up over 2 years have shown cumulative incidence of symptomatic CTEPH to be 1% at 6 months, 3.1% at one year and 3.8% at two years.\[12\]

### 2.3 Treatment of VTE

The primary aim of VTE treatment is to limit thrombus growth and to prevent the patient from dying. Further aims are to prevent VTE recurrence and the development of late sequelae such as PTS or CTEPH.

The mainstay of treatment is anticoagulant therapy, usually involving parenteral administration of heparins or fondaparinux and oral anticoagulants.

Thrombolytics are the first-line drugs in an emergency situation. In cases of massive embolism, thrombolytic therapy with agents such as tissue-plasminogen-activator (tPA) may be used to dissolve the thrombus and so relieve the obstruction.

Embolectomy can be used in emergency situations for patients with acute, massive PE, for patients with contraindications to thrombolytic therapy, and for patients who have not responded to intensive medical treatment and thrombolysis.\[13\] Thrombectomy is also used in patients with extensive limb threatening DVT, particularly in those with contraindications to fibrinolytic therapy.\[14\] In patients with venous thrombosis or PE in which anticoagulant therapy is contraindicated or has failed, patients may be treated with an inferior vena cava filter.

The duration of anticoagulation is mainly determined by the question if VTE was provoked or unprovoked. Guidelines recommend treatment with anticoagulation for three months over treatment of a shorter period in patients with VTE provoked by surgery. In patients with an unprovoked VTE, treatment with anticoagulation is recommended for at least three months and after three months of treatment, patients should be evaluated for the risk-benefit ratio of extended therapy.\[15\]

### 2.4 Economic Implications of VTE

Annual hospital costs for VTE management in the UK are estimated to be around £280 million and the community costs are estimated at £360 million. The total cost burden (direct and indirect costs) to the UK of management of VTE is estimated at approximately £640 million.
Inpatient treatment costs account for almost 50% of the total cost burden. Approximately 20% of costs are attributable to the chronic care costs of PTS.[16]

In the United States annual per patient cost in VTE with PTS is US$ 20,569 versus US$ 15,843 without PTS.

In Canada per patient costs range from $7,594 to $16,644, depending on the type of event and if it was a primary or secondary diagnosis.

Recurrent DVT events were associated with 21% greater cost compared with the initial DVT event; there was no difference in cost for the recurrent PE event compared with the initial PE event.[17]

2.5 Rationale for the study

VTE is an important global patient safety issue. It is a common and increasing cause of morbidity and mortality with early and long-term management required to prevent acute and long-term chronic complications, such as onset of PE in patients presenting with DVT, recurrent VTE, Post Thrombotic Syndrome (PTS) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

In consideration of the changing clinical landscape with the introduction of new oral anticoagulants, there is a definite need to observe the developments related to managing VTE around the world and gather data in order to understand the quality of treatment for patients and its impact on clinical outcomes.

2.6 Type of study

This is a non-interventional prospective registry not interfering with patient treatment at any time.
3 Objectives

The study objectives are to describe acute, sub-acute and extended duration of anticoagulation management, clinical and economic outcomes in patients with treated acute VTE (DVT and PE) in the real-world setting.

3.1 Main Objectives – to clarify:

- Treatment related details for acute VTE (either conventional anticoagulation therapy or treatment with a direct oral anti-coagulant or other modalities of treatment)
- Early and late VTE recurrence
- Nature of complications of VTE, including:
  - post thrombotic syndrome and
  - chronic thromboembolic pulmonary hypertension
- Bleeding complications
- All-cause mortality

3.2 Additional Objectives

Other objectives are to clarify additional outcomes:

- Stroke
- TIA
- STEMI
- NSTEMI
- Unstable angina
- Quality of life and patient reported outcomes
- Costs associated with the management of VTE
4 Study Design

4.1 Overview of study design

This is an observational, prospective, multi-centre VTE registry of male and female patients with acute VTE and is to be conducted in sequential cohorts.

The main focus of this Registry is to capture the real-life management of VTE from the time of diagnosis and to follow up on outcomes in national care settings that are treating VTE patients in the long term. National Coordinators will be appointed in each participating country and will advise on national distribution of VTE care settings on a geographical basis to ensure that Investigator sites are representative of care in each country. In order to observe temporal trends in management of VTE patients will be recruited into consecutive cohorts. Recruitment into the second (and subsequent cohorts) will commence when recruitment is completed into the first or previous cohort. It is estimated that each cohort will take approximately 9 months to recruit.

Data will be collected from the patients’ medical records according to specifications outlined in the electronic case report form. This Registry will not undertake any experimental intervention. Patients will be treated according to standard local practices and no additional visits, tests or procedures are required by the protocol. Patients must be assessed for recruitment into the registry within 30 days of VTE diagnosis. Patient progress and events will be monitored for a minimum of 36 months from the date of VTE diagnosis onwards. Patients may be asked to have additional optional data collection annually for up to 2 years following the 36 month follow up period.

Cohort One
5000 consecutive unselected patients treated for acute VTE (either conventional anticoagulation therapy, treatment with direct oral anti-coagulant or other modalities of treatment) and followed prospectively for a minimum of 36 months.

Cohort Two
5000 consecutive unselected patients treated for acute VTE (either conventional anticoagulation therapy, treatment with direct oral anti-coagulant or other modalities of treatment) and followed prospectively for a minimum of 36 months.

Further cohorts may be added when Cohort 2 is completed.
4.2 Screening and initial visit

Patients must be assessed for inclusion into the registry within 30 days of VTE diagnosis. The physician will inform the patient about the study after the treatment decision has been made. This ensures that participation in the study is not considered a requirement for treatment. All patients potentially satisfying the inclusion/exclusion criteria will be considered for enrolment and their medical history checked to exclude any patients not suitable. Patients who meet the inclusion criteria and do not meet any of the exclusion criteria will be invited to take part in the registry. Patients will be provided with the patient information sheet and consent form (PISCF) once the study physician has explained to them what treatment he or she has chosen for them. All patients must provide written informed consent by reviewing and discussing the PISCF and by completing the consent form in the presence of a study Investigator. This can be done during a hospital admission or by the patient returning to the participating study centre following review as appropriate. Written informed consent will be obtained according to local requirements before any transfer of data from the medical records to the eCRFs is carried out.

Patients could be diagnosed and treated in one of many clinical settings, including the hospital (vascular medicine, angiology, internal medicine, and emergency room) or general / family practice setting. The identifying participating clinician will register the patient using the on-line electronic CRF.

Physicians involved in initial diagnosis of VTE in patients may transfer or refer the cases to other physicians who will treat and follow up the patients in the long-term. Thereafter, data on outcomes relevant to the Registry will be collected by the sites from several clinical sources associated with the patient – including hospitals, emergency rooms and general / family practitioner.

Patients will be enrolled consecutively. A log of all patients invited to participate in the registry will be kept at each site. No personal patient identifiers will be collected on the patient log form.

All data related to Baseline and up to the first 30 days (month 1) of observation will be collected from a review of the patients’ medical records and entered into the electronic data capture system.
4.3 Follow up observation points

The study protocol does not dictate follow-up frequency or timing; these will be determined by routine practice. For the 36 month minimum follow up period data will be collected approximately at Baseline, 3, 6, 12, 24 and 36 months after diagnosis through review of patient notes and medical records. These time points will be used as markers for collection of all data from the preceding period. The aim of data collection will be to accurately capture all data relevant to registry endpoints. Additional optional data collection may occur annually for up to 2 years following the 36 month minimum follow up period.

In case no patient data or patient visits have been recorded in the patient's medical records at the site (i.e. a patient has not been seen by his treating physician) during the months following the last data entry, a follow-up phone contact will be made by the site and documented to verify that all events are being captured and patients are not lost to follow up.

4.4 End of Observation

Completion of the initial data collection (last observation) will occur no earlier than 36 months after the diagnosis of the index acute VTE episode. The exceptions to this are instances of premature discontinuation.

4.5 Allocation of Treatments

This is a non-interventional, multi-centre, prospective registry and patients will be treated according to normal clinic practice.

The assignment of the patient to a particular therapeutic strategy is not required or encouraged in the Registry but falls within local practice and the prescription of the medicine must be clearly separated from the decision to include the patient in the study.

Medicinal products prescribed and observed in this registry are to be prescribed according to the indications approved in their marketing authorisations, as described in the Summary of Products Characteristics.

4.6 Duration of Patient Participation

It is anticipated that the total registry duration will be approximately 4.5 years, allowing 18 months for recruitment of the sequential cohorts and a minimum of 36 months follow up for each patient. Total registry duration for patients with extended follow up will be approximately 60 months.
4.7 Number of Patients

Approximately 10,000 male and female VTE patients from randomly selected sites will be included consecutively in the registry based on eligibility according to the inclusion and exclusion criteria. Cohort 1 will be recruited before recruitment commences into Cohort 2. Patients will not be replaced if they withdraw from the study.

4.8 Sites

Approximately 500 centres from approximately 25 countries will participate in this registry.
5 Study Populations

5.1 Inclusion and Exclusion Criteria

The study population will consist of male and female VTE patients from randomly selected sites included in the registry based on the following inclusion and exclusion criteria.

5.1.1 Inclusion Criteria

1. Written informed consent
2. Age 18 years and over
3. Treated first time or recurrent DVT (lower or upper extremity), PE alone or overlapping DVT and PE confirmed by appropriate diagnostic methods (patient must be assessed for eligibility within 30 days of diagnosis)
4. Patients included with recurrent VTE must have completed treatment for the previous VTE episode

5.1.2 Exclusion Criteria

1. Patients for whom long-term follow up is not envisaged within the enrolling hospital or the associated primary care physician
2. Patients participating in any study that dictates treatments, visit frequency, or diagnostic procedures
3. Patients with only superficial vein thrombosis (SVT)

5.2 Site Selection and Representativeness

The maximum number of patients that can be recruited at an individual site will be agreed between the sponsor and the site as part of the site set up process and should be a fair proportion of the total number of patients in the country.

Although site selection is by random allocation (from a list of representative sites reflecting treatment patterns in each country), the site qualification process will check the ability of each site to fulfil the documentation requirements and to follow patients for a minimum of 36 months.

5.3 Discontinuation Criteria

As this is a data Registry there are no specific withdrawal criteria. However, the patient is free to withdraw consent at any time and the Investigator should try to obtain the reason for withdrawal and record this in the eCRF.
6 Registry Observations and Data Collection

The following clinical assessments and outcomes will be captured for all patients in the Registry.

6.1 Outcome measures

- Recurrent VTE (DVT and fatal or non-fatal PE)
- Bleeding events:
  - Frequency
  - Location
  - Severity (classified as major or non-major)
- Stroke
  - Ischaemic stroke
  - Haemorrhagic stroke
- Hospitalisation
- Post Thrombotic Syndrome (PTS)
- Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
- TIA
- STEMI
- NSTEMI
- Unstable angina
- IVC filter placement
- Other urgent interventions for VTE
- Anticoagulation therapy persistence
- All-cause Mortality, and these subsets as causes of death:
  - PE
  - Stroke
  - Cardiac
  - Cancer-related
  - Bleed
  - Other
- Direct and indirect cost associated with therapy and secondary prevention
- Quality of life and patient treatment satisfaction over a three year period
- For patients treated with VKAs:
6.2 Definition of clinical assessments and outcome measures

6.2.1 Demography

For demographic assessment, the following demographic, anthropometric and lifestyle data will be recorded in the eCRF:

- Sex
- Year of birth
- Race/Ethnicity in countries where recording is permitted (Asian, Caucasian, Black, other)
- Tobacco use

6.2.2 Vital Signs

As part of the vital signs, patient notes will be reviewed for the following:

- Weight (kg or lb)
- Height (cm or inches)

For follow-up assessments only weight is required to be recorded where available.

6.2.3 Medical History

The patient’s medical records will be reviewed and the following will be recorded in the eCRF where available:

- Relevant medical or surgical history
- Previous relevant treatments

6.2.4 Laboratory Assessments

The documentation of laboratory tests will strictly follow clinical practice. Only routinely performed laboratory tests can be documented in this non-interventional study and normal ranges for the local study laboratory parameters will not be provided to the sponsor. The following lab tests will be recorded in the eCRF if available:

- INR (date and value of INR )
- Haemoglobin (Hb)
- Platelets
- Creatinine
6.2.5 Diagnosis of the acute VTE event

Data regarding the diagnosis of current VTE will include a collection of underlying risk factors associated with VTE:

- Diagnosis of VTE: Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE)
- Date of diagnosis

- For DVT the method of diagnosis will be selected from the following list:
  - Impedance plethysmography
  - Compression ultrasonography
  - Contrast Venography
  - Vein Computed Tomography (CT) Scan
  - Pre-test probability scores (e.g. Wells and Hamilton)
  - D-Dimer Assay
  - Magnetic Resonance Venography

- For classification of DVT:
  - Site
  - Extent

- For PE, the method of diagnosis will be selected from the following list:
  - Lung Scan (Ventilation Perfusion Scan)
  - Spiral Computed Tomography (CT) Scan
  - Chest CT Pulmonary Angiography
  - CT Pulmonary Angiography
  - Echocardiography (Transthoracic and/or Transesophageal)
  - Biomarkers (Troponin and/or BNP)
  - Magnetic Resonance Angiography

- The result of the above tests will be captured in the eCRF
- For PE, classification of section of Pulmonary Arterial Branch involved: Main, Lobar, Segmental, and Sub-segmental

- Underlying risk factors associated with VTE:
  - The presence of an inherited hypercoagulable states (e.g. Factor V Leiden mutation, prothrombin gene mutation, protein S deficiency)
  - Acquired hypercoagulable state:
    - Family History of VTE (first degree relatives)
    - Hospitalisation
    - Surgery
    - Trauma of the lower limb
    - Chronic heart failure
    - History of cancer
    - Active cancer
6.2.6 Treatment for VTE

Both initial therapy and extended therapy for the management of the VTE episode will be collected, including start and stop dates, dosing, changes in therapy, overall expected duration of therapy and the reason why therapy was suspended or terminated sooner than intended (reasons will include bleeding, patient decision, physician decision). Therapy for VTE will be selected from the following list:

- Anticoagulants (Low Molecular Weight Heparin, Unfractionated Heparin, Fondaparinux, Vitamin K Antagonist, Dabigatran, Rivaroxaban, Apixaban, Edoxaban, Other Anticoagulant drugs)
- Thrombolytic/Fibrinolytic Therapy (systemic, catheter directed)
- Surgical/Mechanical Interventions (Insertion of IVC filter, Pulmonary Embolectomy, Thrombectomy)
- Compression Therapy (bandages, graduated compression stockings)

6.2.7 Changes in VTE Treatment

If a patient changes VTE treatment, the follow up or changed treatment (drug and dose) should be documented in the CRF. Observation of the patient on the subsequent therapies will continue until the end of planned observation period (a minimum period of 36 months after diagnosis).

6.2.8 Other Relevant Therapies

All medication taken by the patients in addition to the VTE therapy are termed concomitant medication. Treatment of a previous event of VTE will be recorded as part of the medical history. For other relevant concomitant therapies (e.g. invasive procedures, procedures that require the administration of other drugs, radiotherapy, surgery) all relevant treatments will be recorded in the eCRF.

- Analgesics (NSAIDs, steroids, Aspirin, Clopidogrel, other)
- Hormonal therapy
6.2.9 Diagnosis of Recurrent VTE

Details for a recurrent VTE event will be captured in the same manner as the initial VTE.

6.2.10 Diagnosis of PTS

Patients will record their PTS symptoms using the Villalta Scale [18]

- Symptoms:
  - Pain
  - Cramps
  - Heaviness
  - Paresthesia
  - Pruritis

And the Physician/Nurse will record independently the clinical signs of PTS

- Clinical Signs:
  - Pretibial Oedema
  - Skin Induration
  - Hyperpigmentation
  - Redness
  - Venous Ectasia
  - Pain on calf compression
  - Venous ulcers

6.2.11 Diagnosis of CTEPH

Symptoms of CTEPH will be recorded:

- Shortness of breath
- Discomfort
- Fatigue

The method of diagnosis will also be captured as one of the following:

- Transthoracic Echocardiogram (TTE)
- Ventilation-Perfusion Scan (V/Q Scan)
- Invasive Pulmonary Angiography
- Heart Catheterisation
- Chest CT Pulmonary Angiography

6.2.12 Bleeding Events

All bleeding events will be recorded according to severity (major and non-major). The bleeding location (e.g. CNS, ENT, GI, GU, retroperitoneal, vascular access site) and type of the intervention
required and outcome of the bleeding event (recovered, permanently disabled, fatal etc.) will also be captured.

The following detailed definitions will be used to classify bleeding events:

**Major bleeding**

Major bleeding is defined as clinically overt bleeding that is associated with:

- A fall in haemoglobin of 2 g/dl or more, or
- A transfusion of 2 or more units of packed red blood cells or whole blood, or
- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal
- A fatal outcome

**Non-major bleeding**

Non-major bleeding is defined as any overt bleeding not meeting the criteria for major bleeding.

6.2.13 Strokes / TIAs

These will be captured in the eCRF including:

- Ischaemic stroke
- Haemorrhagic stroke
- TIA

6.2.14 Cardiac Ischemia

Cardiac ischemic outcomes will be captured in the CRF including:

- Myocardial Infarction (MI)
- Acute Coronary Syndrome (ACS)

6.2.15 Hospitalisation/Interventions

All hospitalisations will be captured on the eCRF, the data will include duration of hospital stay, reason for hospitalisation, any VTE-related thrombosis or bleeding, whether the hospitalisation was expected or unexpected and the intervention for VTE required if any.

6.2.16 All-Cause Mortality

Data for mortality will include date of death as well as the cause of death chosen from the list below:
6.2.17 Physician and Patient Reported Outcomes

Both physician and patient reported outcomes will be captured in order to gauge health-status, patient treatment satisfaction, cost-effectiveness of treatment and burden of disease.

- The Villalta score will be used to evaluate PTS. Physicians will assess the seven clinician-rated physical signs of the Villalta scale by the final minimum follow up interval (Month 36) during a patient’s follow up clinical visit per the standard of care in that particular country. Patients will be asked to record their ratings for each of the five symptoms required for the Villalta scale on a PTS Symptoms Form. Symptoms will be collected at Baseline / Month 1, Month 3, Month 6, Month 24, and at Month 48 and 60 during the optional additional follow up, where available.

- Patients will answer a modified SF-12 quality of life questionnaire (to evaluate overall burden of illness) at Baseline / Month 1, Month 3, Month 6, and Month 24.

- Patients will answer the ACTS questionnaire (to evaluate treatment satisfaction) at Baseline/Month 1, Month 3 and Month 6 in selected countries where local language versions are available.

6.3 Schedule of observations

Data will be collected at Baseline and up to one month after diagnosis then at 3, 6, 12, 24 and 36 months. Additional optional data collection may occur annually for up to 2 years following the 36 month follow up period for patients who consent to further follow up. These time points will be used as markers for collection of all data from the interim period. The aim of data collection will be to accurately capture all data relevant to registry endpoints.

6.3.1 Baseline visit and up to 1 month after diagnosis

Available data will be collected from the medical notes on the following:

- Informed consent
- Demographics
- Vital signs
• Laboratory results (INR, Haemoglobin, Platelets, Creatinine)
• Medical History
• Diagnosis of current VTE (including date, classification and method of diagnosis)

• Previous VTE episodes
• Treatment for VTE
• Other Relevant Therapies
• Bleeding events
• Hospitalisation/Interventions
• Assessments of events (Stroke/TIA, MI/ACS)
• All-cause Mortality
• Assessment of Recurrent VTE
• Patient assessment of PTS symptoms (Villalta scale)
• Patient treatment satisfaction questionnaire (ACTS) in selected countries where local language versions of the questionnaire are available.
• Patient burden of illness evaluation (SF-12)

6.3.2 Follow up visits

• Vital Signs
• Completion of a follow up phone contact if there is no patient data or patient visits recorded in the patient’s medical records since last follow up.
• Laboratory results (INR, Haemoglobin, Platelets, Creatinine)
• Changes to Treatment for VTE
• Other Relevant Therapies
• Bleeding events
• Hospitalisation/ Interventions
• Assessments of events (Stroke/TIA, MI/ACS, Cancer)
• Assessment of Recurrent VTE
• Any VTE complications (PTS or CTEPH)
• Patient assessment of PTS symptoms (Villalta scale)
• Physician PTS evaluation at final follow up (Villalta scale)
• Patient treatment satisfaction questionnaire (ACTS) in selected countries where local language versions of the questionnaire are available.
• Patient burden of illness Evaluation (SF-12)
• All-cause Mortality
7 Handling of Drug Safety Information

At Baseline and throughout the study, patients will be assessed for relevant medical history and current use of medications. All sites should use all medications as per the SmPC/SPC for each medication. Consequently, adverse events may become apparent and some will be attributable to administered drug(s). This section presents relevant definitions and methods for capturing and assessing safety parameters.

7.1 Adverse Event (AE) definition

According to the ICH guideline for GCP, an AE is any untoward medical occurrence in a clinical investigation subject administered a medicinal product, regardless of causal attribution. An AE can be:

- Any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether considered related or not to the product
- Any new disease or exacerbation of existing disease (or worsening in the character, frequency, or severity)
- Any deterioration in laboratory value or other clinical test that is associated with symptoms or leads to change in treatment or discontinuation from treatment

7.2 Adverse Drug Reaction (ADR) definition

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. A causal relationship between the medicinal product and an AE should at least be a reasonable possibility. An ADR in post-marketing situations normally refers to ADRs occurring at therapeutic doses, but for the purposes of reporting any dosage should be considered.

7.3 Serious Adverse Event and Serious Adverse Drug Reaction definition

A serious AE or ADR is one that fulfils at least one of the following criteria:

- Fatal (AE that causes or leads to death)
- Life threatening (places the patient at immediate risk of death)
- Requires or prolongs hospitalisation
- Results in disability/incapacity
- Congenital anomaly/birth defect in infant born to a mother exposed to the drug
• Significant medical event that may require medical or surgical intervention to prevent one of the outcomes listed above

Minimal criteria required to consider an AE reportable:

• An identifiable patient
• An identifiable reporter
• An event (AE or fatal outcome)
• Product exposure

7.4 Events of special interest in GARFIELD-VTE

The following events of special interest are monitored and reported in the eCRF, for GARFIELD-VTE:

• Recurrent VTE
• Chronic thromboembolic pulmonary hypertension
• Post thrombotic syndrome
• Stroke
• Bleeding
• Death
• Acute myocardial infarction

These events are captured, analysed and reported as outcomes in the GARFIELD Registry.

7.5 Methods for capturing and assessing safety parameters

Any AEs, whether reported by the patient or noted by a health care personnel, significant enough to be recorded in the patient’s medical record will be treated in the following way:

1. Those AEs that constitute events of special interest mentioned above will be reported to the sponsor via the electronic CRF. All details regarding events characteristics and recent drug exposure(s) required by the protocol should be checked and captured. Since these events constitute common outcomes of the underlying venous thromboembolism, expedited reporting to other parties is not required. However, should the investigator find particular reason for bringing some serious ADR from this category to the attention of the Marketing Authorisation Holders (MAHs), Authorities or Ethics Committees, he or she can report them in a manner described under point (2).
2. All events that do not fall into the category of Events of special interest will be assessed for seriousness (see above definition of serious AE/ADR) and possible association with use of anti-thrombotic drug(s). Those considered serious ADRs will be reported by the investigator directly to the marketing authorisation holder(s) of the drug(s) suspected to have caused the ADR. In the same manner as serious ADRs, any antithrombotic drug exposure during pregnancy, regardless if the pregnancy is continuing or has been terminated, will be reported. Reporting will be done without delay (usually within 24 hours) on country-specific commonly accepted ADR forms. The investigator will ensure that the patient’s participation in the GARFIELD registry is noted on the ADR form. It is the responsibility of the MAH to assess the reports and decide if they need to be submitted to competent authorities.

The sponsor will provide appropriate training to the study personnel on identification and handling of reportable adverse events including assessment of seriousness and drug association. The sponsor will assist the sites, if specific questions regarding safety reporting should emerge.
8  Statistical Methods

8.1  General statistical approach

The statistical analysis will include a descriptive analysis of the population characteristics and outcome variables. It will be explorative and descriptive and will be summarised into frequency tables (ordinal or nominal data) or summary statistics with mean, standard deviation, minimum, maximum, median, lower and upper quartile. Confidence intervals, rather than p-values, will be the standard method for presenting the statistical results of major findings.

All analyses will be performed for the total study sample and separately for each country and region if the patient numbers are sufficient.

All details regarding derived variables, format and content of tables will be described in the Statistical Analysis Plan. In addition to the Statistical Analysis Plan the Health Economics Analysis Plan will contain all details in regards to the analysis of HEOR data.

8.2  Determination of sample size

Since there are no specific hypotheses to be tested a power calculation cannot be performed. However it is desirable to assess the viability of the registry to produce useful estimates of the main outcomes. Table 2 refers to an example of the outcome of recurrent VTE in PE patients and looks at the precision that might be expected in terms of half the width of a 95% confidence interval (i.e. 2 standard deviations). It is expected that around one third of patients in the registry will have had PE, and amongst those, between approximately 5% and 15% will suffer recurrence of PE or DVT. The table shows the expected half-width of 95% confidence intervals in various scenarios.

Table 2: Estimated half-widths of 95% confidence intervals for PE patients

<table>
<thead>
<tr>
<th>Expected rate</th>
<th>Small country</th>
<th>Large country</th>
<th>All countries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single cohort n=50</td>
<td>Both cohorts n=100</td>
<td>Single cohort n=200</td>
</tr>
<tr>
<td>5%</td>
<td>6.6%</td>
<td>4.8%</td>
<td>3.3%</td>
</tr>
<tr>
<td>10%</td>
<td>9.2%</td>
<td>6.4%</td>
<td>4.4%</td>
</tr>
<tr>
<td>15%</td>
<td>10.5%</td>
<td>7.4%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

A "small" country is considered to be one recruiting 300 patients in all. A "large" country/region is one recruiting 1200 patients.

A half-width of 5% may arbitrarily be regarded as the upper limit of a useful result. Half-widths wider than 5% will still provide information but at a poor level of accuracy. In the example above it may be necessary to merge the results from certain countries with low recruitment levels. Large countries or regions will have acceptable precision.
9 Data Collection, Management and Quality Assurance

9.1 Electronic CRF

An electronic CRF will be used. The database will be hosted by an EDC provider who will ensure that the computer system used complies with all national and international laws concerning security, privacy and data protection and in accordance with the directive 95/46/EC of the European Parliament (or national directives for protection of individuals with regard to processing of personal data and on the free movement of such, whichever may apply). Protection will be ensured by state-of-the-art software.

9.2 Data Quality Assurance

The Registry Monitor will review 5% of all CRFs against source documentation at the Registry sites according to the monitoring plan. All data modifications to the database will be recorded electronically in an audit trail.

Variables defined as critical to the statistical analysis will be subjected to a 100% electronic audit periodically for the duration of the Registry.

The Registry will be conducted in accordance with the spirit of the most recent Declaration of Helsinki.

9.3 Source Data Documentation

Study monitors will perform ongoing source data verification to confirm that source data entered into the eCRFs by authorised site personnel are accurate, complete and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, patient reported outcomes, evaluation checklists, pharmacy dispensing records, data from instruments, x-rays, microfilm or magnetic media.

To facilitate source data verification, the Investigators and institutions must provide the sponsor (or designee) direct access to applicable source documents and reports for study related monitoring and sponsor audits. The site must also allow access for IRB or IEC review as well as inspection by applicable health authorities.
10 Ethics and General Study Administration

10.1 Independent Ethics Committee (IEC) Approval

All protocols (and applicable amendments, if any), patient information and consent forms and required study documents must be approved by the appropriate IEC according to local regulations before implementation. Appropriate reports on the progress of the Registry will be made by the Investigator or Sponsor to the IEC including informing them on completion or termination of the Registry.

10.2 Patient Information and Consent Form

These documents will be generated according to ICH-GCP and GPP guidelines and will be provided as stand-alone documents to the Ethics Committees. Only the approved versions will be used in the Registry.

In obtaining and documenting informed consent, the investigator must comply with the applicable local regulatory requirements and adhere to the ICH-GCP and GPP guidelines and the requirements in the Declaration of Helsinki.

Prior to any Registry-related activity, the investigator must give the subject oral and written information about the Registry in a form that the subject can read and understand.

A voluntarily, signed and dated Informed Consent Form will be obtained from the subject prior to any Registry-related activity. The written informed consent must be signed and dated by the person who conducted the informed consent procedure.

Patients participating in the Registry will be advised that they are free to refuse to participate without affecting their medical care; that information regarding their medical condition will be collected and recorded and all findings treated with the strictest confidentiality. Written informed consent will be collected in all cases prior to enrolment in the Registry.

The patient will be given copies of the patient information and consent form.

10.3 Essential Documentation

The following documents must be inspected by the Sponsor.

- Current curriculum vitae of the Principal Investigator.
- Signed Investigator page from the protocol
- A copy of the dated, documented approval of the IEC to the protocol and the local investigator, including any amendments, patient information and consent forms, advertisements for patient recruitment, patient compensation (if any) and any other documents submitted. The IEC approval should quote versions numbers and/or dates of documents reviewed.
- Signed contract between the sponsor and the investigative site.
- Local Hospital management approval (“R&D”) if required.
All other relevant documents essential prior to Registry initiation should be placed appropriately in the Registry Trial master files.

10.4 Retention of Records
The Investigator will retain all essential documents associated with the Registry according to local regulations.

10.5 Patient Insurance
In this study, data on routine medical practice is observed, and for the patient no additional risks exist as a result of participating in the registry. As no study related risks exist, there is no need to protect the patient additionally by patient insurance. The Investigator's professional indemnity insurance and respectively, the institutions involved provide sufficient protection for both patient and Investigator.

10.6 Indemnity
The Sponsor will indemnify all Investigators participating in this Registry against future claims by Registry participants in accordance with local requirements. The indemnity will only apply where all Registry procedures have been carried out according to this protocol. The Investigator(s) confirm that they/he/she hold their/his/her own professional indemnity insurance, suitable for the activities of the investigator(s) in relation to the Registry and, in addition, that the insurance of the investigator satisfies any local insurance requirements, or is a member of a medical union which provides such cover for its members.

10.7 Registry Finance
The Sponsor will pay participating Institutions/Investigators where the Registry is conducted for the costs of running the Registry. All financial arrangements for the conduct of the Registry are detailed in contracts between the Sponsor and the Institution/Investigator. Details of financial compensation for services rendered will be recorded.

10.8 Registration and Results Posting
This study will be registered at www.clinicaltrials.gov and results will be posted at www.clinicalstudyresults.org.
11 Publication Plan

Publication Policy

The GARFIELD-VTE Registry has been designed and will be managed by the Thrombosis Research Institute in London, and conducted under the supervision of an independent international steering committee comprising scientific representatives from relevant clinical disciplines and two representatives from the sponsoring pharmaceutical company. The steering committee will take responsibility for the data, conduct and publication of GARFIELD-VTE. Day to day operational management will be the responsibility of a commercial contract research organisation where delegated by TRI.

A Registry council comprising a national co-ordinator representative from each country will provide a leadership forum and will participate in publication planning and execution.

At the end of the Registry, one or more manuscripts for joint publications will be prepared in collaboration between the Investigators. The Investigator(s) offered authorship will be asked to comment and approve the publication. Any other participating centres will be mentioned.

The publication of data from this Registry should aim at following the guidelines from The New England Journal of Medicine.
12 Protocol Amendments

The Investigator, Sponsor and the Registry Monitor will not modify or alter this protocol without first obtaining agreement from all parties (notification of administrative changes will be sent to IECs). Approval of any modification by the Investigator's IEC must be obtained before implementation, except when necessary to eliminate apparent immediate hazard to the patient or where the changes do not involve patient safety or affect the patient's rights. The party initiating a modification must confirm it in writing. The Sponsor should submit any protocol amendments to the appropriate national regulatory body, ethics committees and notify all other participating Investigators of the change(s) to the protocol.
13 Bibliography