STATISTICAL ANALYSIS PLAN

Trial Registry No.:	TRI08889
Title:	Global Anticoagulant Registry in the FIELD observing treatment and outcomes in patients with treated acute Venous Thromboembolic Events in the real world
Study Phase:	Registry
Study Protocol Version:	22nd May 2014 / Protocol Version 2.0
SAP author:	TRI Statistics team – TRI, London
SAP date and version:	8 December 2015
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Statistical Analysis Plan: TRI08889

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

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3 Abbreviations

ACTS	Anti Clot Treatment Scale
AE	Adverse Event
ASA	Acetylsalicylic Acid
CNS	Central Nervous System
CRO	Contract Research Organization
CTEPH	Chronic thromboembolic Pulmonary Hypertension
DVT	Deep Venous Thrombosis
EDC	Electronic Data Capture
EC, IEC	Ethics Committee, Independent Ethics Committee
eCRF	Electronic Case Report Form
EU	European Union
GCP	Good Clinical Practice
GCS	Graduated Compression Stockings
GFR	Glomerular Filtration Rate
GI	Gastro-Intestinal
GU	Genitourinary
GPV	Global Pharmacovigilance
Hb	Haemoglobin
HEOR	Health Economics and Outcomes Research
ICH	International Conference on Harmonization
INR	International Normalised Ratio
IRB	Institutional Review Board
IVC	Inferior Vena Cava
LMWH	Low Molecular Weight Heparin
MI	Myocardial Infarction
NSAID	Non-Steroidal Anti-Inflammatory Drug
PE	Pulmonary Embolism
PISCF	Patient information sheet and consent form
PTS	Post-Thrombotic Syndrome

QA/QC	Quality Assurance/Quality Control Plan
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SmPC/SP C	Summary of Product Characteristics
TIA	Transient Ischaemic Attack
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

4 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Date of formal SC approval	Author	Changes from the Previous Version

5 Purpose of the statistical analysis plan

This document is the 'master SAP' of the GARFIELD-VTE registry which might require subsequent supplemental Analysis Specification Forms (ASFs). Supplemental ASFs might be triggered by new research questions emerging aftert the development of this document. The rationale to split the statistical plan into a master SAP and in supplemental documents is well described in Gliklich et al. (2014).

As per ICH E9 guidelines the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the Registry Protocol TRI08889, entitled 'Global Anticoagulant Registry in the FIELD observing treatment and outcomes in patients with treated acute Venous Thromboembolic Events in the real world'.

The SAP is based on the working Registry Protocol dated 22nd May 2014, In particular, the SAP is based on the planned analysis specification as written in Registry Protocol Section 8 "Statistical Methods". Any further amendments to the protocol or eCRF may necessitate an update to the SAP.

Results of the analyses described in this SAP will be included in the Registry Final Report and in Interim Cohort Reports. Any post-hoc or unplanned analyses performed to provide results for inclusion in the Registry Reports but not identified in this SAP will be identified in the Registry Reports.

SAS® version 9.4 or later will be used for all analyses. R version 3.2 or later and STATA version 14 or later can be used for ad-hoc analyses.

6 Analysis 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, pure NOAC treatment (defined as any NOAC treatment started directly, rivaroxaban or apixaban, or after a 1–2 day administration of UFH, LMWH or fondaparinux).

Patients for whom NOAC was planned, but who initially received conventional anticoagulant therapy (i.e. UFH, LMWH or fondaparinux for at least 2–14 days ± vitamin K antagonist for 1–14 days) before switching to NOACs will be designated "early switchers".

- ~~treatment with a direct oral anti-coagulant~~ O~~or o~~ther 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
  - Unstable angina
  - Quality of life, and patient reported outcomes
- Costs associated with the management of VTE ~~Objectives in the protocol~~

"The choice of epidemiological methods to answer a research question is based on principles rather than on rules. These principles may provide opportunities for creativeness and new innovative methods, when appropriate and needed."[ENCePP] Although, it is recommended to plan as much as possible in advance details of the analysis are left open to be decided sequentially, under the provision that rules and definitions for the analysis will be well documented. This SAP is not a list of mandatory rules to be applied in analysis, but it is a guide to perform analysis properly.

Detailed statistical methodology of the analyses to be performed for Health Economics are documented separately in the Health Economics Analysis Plan.

7 Analysis set

Patients who consented to partake in the study and were subsequently found to not be eligible have been hidden in the study database. A summary of all hidden patients together with the reason for hiding them will be included as an appendix to each final cohort report.

7.1 Full Analysis Set

The Full Analysis Set (FAS) includes patients eligible for the analysis with baseline data locked as complete.

Eligible patients have to satisfy all the inclusion criteria: (INCPRE)

1. Written informed consent [INCPRE].[ASSEDAT]
2. Age 18 years and over[INCPRE].[INC1]
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) [INCPRE].[INC2]
4. Patients included with recurrent VTE must have completed treatment for the previous VTE episode [INCPRE].[INC3]

Eligible patients are excluded if they fulfil any of the following exclusion criteria:

1. Patients for whom long-term follow up is not envisaged within the enrolling hospital or the associated primary care physician [INCPRE].[EX1]
2. Patients participating in an interventional study that dictates treatments, visit frequency, or diagnostic procedures [INCPRE].[EX2]

3. Patients with only superficial vein thrombosis (SVT) [INCPRE].[EX3]

A table will describe the number of enrolled patietns and the number of patients who do not meet the inclusion and exclusion criteria.

8 Overview of planned analysis

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.

The inclusion of both continuous and categorical demographic data allows for the application of Principal Component Analysis (PCA) and other multivariate statistical methods. Such techniques can enable the researcher to model the contribution of lifestyle factors on disease.

All analyses will be performed for the total study sample and separately for each country and region if the patient numbers are ≥ 30. Data from individual countries may be added together to achieve adequate numbers. Results may contain caveats if numbers are borderline. ~~sufficient.~~

Analyses will be performed specifically after completion of enrolment to describe the baseline characteristics. Outcome data collected during follow-up every three months and will be analysed and reported for the enrolled patients. Patients will be recruited into two cohorts so that temporal changes in clinical practice and outcomes can be recorded over time. Data can be compared between cohort 1 and 2. A schedule of analysis for ~~Cohorts~~ Cohorts 1 and 2 can be seen in Table 1.

A formal 'Cohort X' report on planned analyses as specified in this SAP will be provided for each cohort after the final 'Cohort X' patient has completed the study.~~follow-up.~~

Table 1 Schedule for Data Entry at Site – Cohorts 1 and 2.

Tests and Assessments	Baseline and up to 30 days[1]	3 Months	6 Months	12 Months	24 Months	36 Months
Informed Consent	X					
Demography	X					
Vital Signs	X	X	X	X	X	X
Medical history	X					
Previous VTE Episodes	X					
Diagnosis of current VTE	X					
Laboratory Results	X	X	X	X	X	X
Treatment for VTE (Assessment & Changes in Therapy)	X	X	X	X	X	X
Other Relevant Therapies	X	X	X	X	X	X
Bleeding Events	X	X	X	X	X	X
Hospitalisation Interventions	X	X	X	X	X	X
Assessment of Events (Stroke/TIA, MI/ACS, Cancer)	X	X	X	X	X	X
Assessment of Recurrent VTE	X	X	X	X	X	X
Diagnosis of CTEPH		X	X	X	X	X
Patients assessment of PTS symptoms according to Villalta Scale[4]	X	X	X		X	
All-cause Mortality	X	X	X	X	X	X

Patient questionnaire – ACTS (Treatment satisfaction)[2]	X	X	X			X
Patient Questionnaire - SF- 12 (Burden of disease)	X	X	X		X	
Physician`s Evaluation of PTS using Clinical signs from Villalta Scale						X

[1]Patients must be assessed for eligibility within 30 days of confirmed diagnosis of the acute VTE event.

[2]ACTS questionnaires will be completed by patients in a subset of countries where local language versions are available.

[3]Optional additional annual check on patient status for 2 years following the 36 month follow up period.

[4]Patient assessment of PTS will be completed by Villalta where available

8.1 Within cohort analyses

Analyses will be performed independently within each of the two cohorts at each of three time-points:

1. After completion of enrolment into a cohort (analysis of baseline data)
2. After patients have completed 1 year of follow-up
3. After all patients have completed the follow-up

At the first cut-off, the baseline characteristics of patients will be analysed.

Major clinical events during the follow-up will be analysed at 1-year and After the completion of the follow-up . If appropriate, updated analyses of certain registry endpoints will be performed on an annual basis up to the end of follow-up.

8.2 Between cohort analyses

To examine temporal changes in clinical practice and clinical outcomes, analyses will be performed, as appropriate, to describe data between cohort 1 and cohort 2.

This will occur at three time-points:

1. After completion of enrolment into ~~a~~ both cohort (analysis of baseline data)
2. After all patients have completed 1 year of follow-up (or were lost to follow-up one year after enrollment)
3. After all patients have completed the follow-up

8.3 Country/region analyses

All analyses performed on baseline registry data will be repeated for each country and region that has enrolled patients into a cohort.

Where appropriate, certain analyses on follow-up data will be repeated on an individual country or regional basis to provide information on clinical care and outcomes for patients on a local rather than global level. Country and region level analyses will not be included in the formal cohort reports and final registry report, but will be sent in a separate document to the NCI from each country. In this document the header will state 'GARFIELD Registry Cohort X baseline data for Country XXX'.

8.4 Adhoc and intermediate anaysis

Any adhoc analyses or intermediate analyses performed for other purposes and not planned in the study protocol or SAP (e.g. for investigator meetings, steering committee meetings, congress submissions and publications) will be described elsewhere in a specific ASF.

8.5 Heath economics

Analyses relating to health economics outcomes will be described in a separate Health Economics SAP together with detailed programming specifications. This will be provided by the Health Economist.

8.6 Final analysis

The final analysis of all registry data will take place when all patients have completed 3~~2~~ years of follow-up and after data locking and freezing. All relevant analyses will be included in a Final Registry Report.Describe the population/subpopulation to be analyzed

9 Baseline characteristics

This section of the SAP continues to develop as so is subject to change, improvement and definition. Where possible the domain names are followed by specific variables to be analysed.

9.1 Statistical procedures to describe baseline characteristcs

The following descriptive statistics will be used to summarise the registry data on the basis of their nature unless otherwise specified:

- Continuous variables: number of missing and non-missing observations, mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum~~, and percentage change from baseline when applicable~~.
- Categorical variables: frequencies and percentages.

Percentages will be rounded to one decimal place. Therefore, there may be occasions where for instance the total of the percentages does not exactly equal 100%. The denominator for percentage will be defined in each table.

For 'multi choice' variables a table footnote will be provided to indicate that 'categories are not mutually exclusive'.

The following sections use descriptive statistics to describe all patients, medical conditions and treatments at baseline. Principal Component Analysis and Logistic Regression could be used to investigate relationships between variables describing medical condition by stratifying the results using demographic and geographical ~~variables~~variables.

9.2 Care setting at diagnosis

The patient care management setting [CARESET] at VTE diagnosis will be defined according to specialty, location, and medical insurance (see CRF Baseline and up to 30 days, Care setting at diagnosis), as follows:

Care Specialty [CARESET].[SPECIAL]

- [1] Vascular medicine
- [2] General Practitoner
- [3] Internal medicine (Haematology and Intensive care)

Care Facility [CARESET].[LOCATION]

- [1] Hospital
- [2] Outpatient setting

How is your patient's medical treatment being funded [CARESET].[PATINSUR]

- [1] All costs covered by medical insurance
- [2] Partial costs covered by medical insurance
- [3] All costs covered by public health
- [4] Other

9.3 Demographics, vital signs, and social habits

The main demographic characteristics [DEMOG] destribed in the statistical report will be:

Sex[DEMOG].[SEX]

- [1] Male
- [2] Female

Age (derived variable see section xxx)

Race/Ethnicity in countries where recording is permitted [DEMOG].[ETHNIC]

- [1] Asian
- [2] Black
- [3] Caucasian
- [4] Multi-racial
- [5] Patient unwilling to declare

- [98] Other
- [99] Unknown

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

Weight (kg or lb) [PHYSEX].[WEIGHT]

Height (cm or inches) [PHYSEX].[[HEIGHT]

BMI (derived variable see section xxx)

Tobacco use [SOCHAB.TOBACCO]

- [1] Tobacco use Never
- [2] Ex Smoker
- [3] Smoker

9.4 Acute VTE Episode

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

Primary suspected diagnosis [CLASS].[PDIAG]

- [1] Deep Vein Thrombosis (DVT)
- [2] Pulmonary Embolism (PE)
- [3] DVT and PE

For patients with 'Primary suspected diagnosis=DVT or DVT and PE' [CLASS].[PDIAG]=[1] or [3] the site of DVT [SITEEXTDVT].[SITEDVT]

- [1] Upper limb
- [2] Lower limb
- [3] Caval vein (Inferior)
- [4] Caval vein (Superior)

For patients with 'Primary suspected diagnosis=DVT or DVT and PE' [CLASS].[PDIAG]=[1] or [3] the site of DVT – Unilateral or bilateral [SITEEXTDVT].[SITELRB]:

- [1] Left
- [2] Right
- [3] Both

~~For~~ For patients with primary suspected diagnosis = DVT or DVT and PE [CLASS].[PDIAG] = [1] or [3] and 'Please confirm a confirmatory test for DVT was conducted? = Yes' [CONFDVT].[CONFYN] = [1] the method of DVT diagnosis will be selected from the following list:

- Compression ultrasonography [COMPULTRA]
- Impedance plethysmography [IMPPLETH]
- ~~Compression ultrasonography [COMPULTRA]~~
- Contrast Venography[CONVENO]
- Vein Computed Tomography (CT) Scan [VEINCT]
- Pre-test probability scores (e.g. Wells and Hamilton) [PTPROB]
- D-Dimer Assay[DDIMER]
- Magnetic Resonance Venography [MAGRESVE]

For patients with primary suspected diagnosis = PE or DVT and PE [CLASS].[PDIAG] = [2] or [3] the Classification of PE [CLASS].[PABRINV]:

- [1] Main
- [2] Lobar
- [3] Sebmental
- [4] Sub Segmental

~~For~~ For patients with 'Primary suspected diagnosis = PE or DVT and PE' [CLASS].[PDIAG] = [2] or [3] ~~and~~ ' and Please confirm a confirmatory test for PE was conducted? = Yes' [CONFEXTPE].[CONFYN]=[1] the method of PE diagnosis will be selected from the following list:

- Lung Scan (Ventilation Perfusion Scan) [LUNGSCAN]
- Spiral Computed Tomography (CT) [SPIRALCT]
- Scan Chest CT Pulmonary Angiography[CHESTCT]
- CT Pulmonary Angiography[CTPULANG]

- Echocardiography (Transthoracic and/or Transesophageal) [ECG]
- Biomarkers (Troponin and/or BNP) [ECG]
- Magnetic Resonance Angiography [MAGRESAN]

9.5 Laboratory assessments

The documentation of laboratory tests [ANYYN] 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 recorded in the eCRF will be described in the statistical report:

- INR[ANYYN].[INRRES]

  Range [1] 0.50-0.99

  [2] 1.00-1.49

  [3] 1.50-1.99

  [4] 2.00-2.49

  [5] 2.50-2.99

  [6] 3.00-3.49

  [7] 3.50-3.99

  [8] >4.00

- Haemoglobin (Hb) [HAEMO]
- Platelets [PLATELET]
- ~~Creatinine~~Creatinine unit)|mg/dL|µmol/L [CREAT]

9.6 Risk factors associated with VTE

The following risk factors associated with VTE will be included in the statistical report:

- Underlying risk factors associated with VTE[RISKFACTOR].[ANYYN]: [1] Yes, [2] No
- If [RISKFACTOR].[ANYYN]=[1] then
    - Prior episode of DVT and/or PE [RISKFACTOR].[PRIORVTE]

    If Prior episode of DVT and/or PE has been selected [RISKFACTOR].[PRIORVTE] then:

    - Family history of VTE [RISKFACTOR].[FMHISVTE]
    - History of cancer [RISKFACTOR].[HISCANC]
    - Oral contraception [RISKFACTOR].[ORACONTR]
    - Hormone replacement therapy [RISKFACTOR].[HORMONET]
    - Known thrombophilia [RISKFACTOR].[THROMFIL]
    - Chronic immobilisation [RISKFACTOR].[IMMOBI]
    - Chronic heart failure [RISKFACTOR].[CHRONHF]
    - Renal insufficiency [RISKFACTOR].[RENALINS]

- If [RISKFACTOR].[ANYYN]=[1] then Provoking risk factors of VTE during the past 3 months
    - Surgery [RISKFACTOR].[SURGERY]
    - Trauma of the lower limb [RISKFACTOR].[TRAUMALL]
    - Acute medical illness [RISKFACTOR].[ACUMEDIL]
    - Hospitalization [RISKFACTOR].[HOSPITAL]
    - Long-haul travelling [RISKFACTOR].[LONGTRAV]

- If [RISKFACTOR].[ANYYN]=[1] then Special risk factors associated with VTE
    - Active cancer [RISKFACTOR].[ACTCANC]
    - Pregnancy [RISKFACTOR].[PREG]
    - Recent bleed or anaemia [RISKFACTOR].[RECBLEED]
    - If Recent bleed or anaemia [RISKFACTOR].[RECBLEED] has been selected then
        Bleeding [RISKFACTOR].[RECBLETP]=[1]
        Anaemia [RISKFACTOR].[RECBLETP]=[2]

Both [RISKFACTOR].[RECBLETP]=[3]

9.7 Previous VTE

For patients with a prior episode of VTE we will describe:

- Previous DVT [PREVVTE].[PREVDVT]
- Time since the Previous DVT [PREVVTE].[DVTDAT]
- Previous PE [PREVVTE].[PREVPE]
- Time since the previous PE [PREVVTE].[PEDAT]
- Previous DVT and PE (combined event) [PREVVTE].[PREVDVTP]
- Time since the previouos DVT and PE [PREVVTE].[DVTPEDAT]

The occurrence of the previous event is described using the modalities Yes [1], No [2]

The time since the previous events has the following options: <6 months [1] , 6 to 12 months [2], 1 to 5 years [3], >5 years [4].

9.8 Medications

Both prior relevant medications taken prior to the date of VTE diagnosis and ongoing concomitant medications taken after VTE diagnosis will be described.

Prior relevant medications [PRIORMED].[ANYYN] will be selected from the following list:

- Low Molecular Weight Heparin [PRIORMED].[LMOLHEPA]
- Unfractionated Heparin [PRIORMED].[HEPARIN]
- Fondaparinux [PRIORMED].[FONDAPA]
- Vitamin K Antagonist [PRIORMED].[VKAS]
- Dabigatran [PRIORMED].[DABIGATI]
- Rivaroxaban [PRIORMED].[RIVAROXY]
- Apixaban [PRIORMED].[APIXABAN]
- Edoxaban [PRIORMED].[EDOXABAN]

- Other Anticoagulant drugs [PRIORMED].[OTHDRUG]
- Analgesics [PRIORMED].[ANALGESI]
- NSAIDS [PRIORMED].[NSAIDS]
- Steroids [PRIORMED].[STEROIDS]
- Aspirin/other AP therapy [PRIORMED].[ASPIRIN]

VTE treatment strategy [TREATSTRATEGY].[ANYYN] will be selected from the following list:

- Anticoagulants [TREATSTRATEGY].[ANTICOAG]
- Thrombolytic/Fibrinolytic Therapy [TREATSTRATEGY].[THROMBOF]
- Surgical/Mechanical Interventions [TREATSTRATEGY].[SURGMECH] ([1] Insertion of IVC filter, [2] Pulmonary Embolectomy, [3] Thrombectomy)
- Compression Therapy [TREATSTRATEGY].[COMPRESS] ([1] bandages, [2] graduated compression stockings)

9.9 Complications

The following complication will be included in the statistical report:

- Symptoms of PTS [COMPPTSCTEPH].[PTS]
- VTE episode since the date of diagnosis [RECVTEDIAG].[RECVTEYN]
- CTEPH
- Recurrent VTE

10 Clinical endpoints

10.1 Statistical procedures to describe the occurrence of events of special interest

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

- Death
- Major Bleeding
- Post thrombotic syndrome
- Chronic thromboembolic pulmonary hypertension
- ~~Stroke~~
- ~~Bleeding~~
- ~~Acute myocardial infarction~~
- Hospitalization and interventions
- Stroke
- Acute myocardial infarction

~~Bleeding~~

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

Events of special interest will be analysed using descriptive statistics, person-time based event rates and time-to event models.

OCCURRENCE OF DISEASE

Analysis of data from a cohort study involves estimation of the rates of diseases of interest that occur among cohort members during the study period. Occurrence is most appropriately measured in terms of incidence rates. Occurrence of mortality, recurrent VTE, ~~new stroke/SE,~~ major bleeding, and other clinical outcomes will be described using:

- Population at risk at the beginning of the follow-up
- Number of first events, cumulative incidence (%)
- Person-time event rates (per 100 person-years) and 95% CI

The total number of events including first events and repeated events will also be presented.

TIME-TO-EVENT ENDPOINTS

The analysis time in time-to-event models will be measured from the date of enrollment to the date of the first occurrence of the relevant event in patients with an event of interest, unless indicated otherwise.

If the event has not occurred prior to the analysis cut-off date then time will be computed from the date of enrolment to the last known date of follow-up unless specified otherwise.

The Cox proportional hazards model or parametric time-to-event models will be used to estimate hazard ratio (HR) and 95% CI in subgroups.

Comparisons among groups will be adjusted appropriately for confounding baseline factors, which may include age, gender, smoking habit, medical history including cancer, CKD, anaemia, pregnancy and body weight < 50 kgs. Adjusted HRs and 95% CIs will also be presented graphically using forest plots on a logarithmic scale, as appropriate.

For each analysis, the proportional hazards assumption in the Cox model will be tested using appropriate graphical procedures. If the proportionality assumption is not valid, it may be necessary to include a time-varying covariate in the model.

10.2 All-cause mortality

Data for mortality [DEATH] will include date of death as well as the cause of death (DEACAUSE) chosen from the list below:

- PE [1]
- Stroke [2]
- Cardiac [3]
- Cancer-related [4]
- Bleeding [5]
- VTE complications [6]
- Other [98]
- Unknown [99]

10.3 PTS

Patients will record their PTS symptoms using the Villalta Scale [NOTDOEIG].[PAT_VILLALTA)

Symptoms of PTS

[1] Pain

[2] Cramps

[3] Heaviness

[4] Paresthesia

[5] Pruritis

Clinical Signs of PTS

[1] Pretibial Oedema

[2] Skin Induration

[3] Hyperpigmentation

[4] Redness

[5] Venous Ectasia

[6] Pain on calf compression

~~[7] Venous ulcers~~

~~CTEPH~~

Symptoms of chronic thromboembolic pulmonary hypertension -CTEPH [SIGNSYMPCTEPH]:

[1] Shortness of breath

[2] Discomfort

[3] Fatigue

The method of diagnosis of CTEPH:

Transthoracic Echocardiogram (TTE) [xxxx]

Ventilation-Perfusion Scan (V/Q Scan) [xxxx]

Invasive Pulmonary Angiography [xxxx]

Heart Catheterisation [xxxx]

Chest CT Pulmonary Angiography [xxxx]

10.4 Stroke and TIA

Stroke and TIA [STRTIA] will be captured in the eCRF including:

[STRTIA].[EVTTYP]

[1] Stroke

[2] Transient Ischaemic Attack

[STRTIA].[STRTYPE]

[1] Ischaemic stroke

[2] Haemorrhagic stroke

[3] Unknown

10.5 Bleeding events

All bleeding events [BLEED] will be recorded according to severity and outcome

[BLEED].[BLESEVER]

[1] Major

[2] Non-major

[BLEED].[OUTCOME]

[1] Resolved

[2] Ongoing

[3] Death

[4] Permanently disabled

[99] Unknown

10.6 Cardiac ischemia

Cardiac ischemic outcomes will be captured in the CRF including:

- ~~Myocardial Infarction [MI]~~
- Acute Coronary Syndrome [ACS]

10.7 Hospitalisation and intervetions

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.

10.8 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~~ 12 symptoms required for the Villalta scale on a PTS Symptoms Form. Symptoms will be collected at Baseline / Month 1, Month 3, Month 6, 12 and at 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.

11 Handling of missing values

Missing dates

When the day of the event date is missing (but month & year is available), then in order to take the most conservative approach (worst case scenario), the day will be imputed to the "1st day of the reported month" (e.g. if the reported date is --/JAN/2015, the imputed date will be 01/JAN/2015).

When the day and month of the event date is missing (but year is available), then in order to take the most conservative approach (worst case scenario), the date will be imputed to the "1st day of the 1st month of the reported year" (e.g. if reported date is --/--/2015, imputed date will be 01/JAN/2015). The exception to this imputation rule would be if the patient has a later follow-up/event date where it is known that the event has not occurred. In this case the date will be imputed as one day after the date of last follow-up/event. For example if a patient

is known to have died in ~~2012~~2015 but was last seen or contacted on 15/JUN/2015, then the date of death would be imputed to 16/JUN/2015.

In all cases every attempt should be taken to obtain the exact date and the imputation rule should only be used as a last resort, and its use documented appropriately. Note that the above rules are used directly by the sites for date imputations and are not for programming purposes. This was a decision made previously when the study was set up.

Where endpoints that are planned to be regularly monitored, for example INR, are missing then the last value will be carried forward for a maximum of two occasions for the calculation of any derived variables. Any missing sequence of results extending beyond two occasions will not be imputed. Further details of imputation methods will be included in the registry reports

Multiple imputation

Multiple imputation appears to be one of the most attractive methods for handling of missing data in multivariate analysis. The basic idea is quite simple:

- Impute missing values using an appropriate model that incorporates random variation
- Produce multiple complete data sets
- Average the values of the parameter estimates across the M samples to produce a single point estimate

Multiple imputation can be used with any kind of data and any kind of analysis. Multivariate imputation using chained equations (MICE) is an approach used for multiple imputation with arbitrary missing-data pattern. Despite the lack of general theoretical justification, MICE is very popular in practice due to its flexibility. Imputed data exceeding 20% should be used with caution.

We will use multiple imputation as implemented by:

- The MI procedure in SAS
- or IVEWare (Imputation and Variance Estimation Software) developed by the researchers at the University of Michigan.
- or the command MI in STATA software

Predictors describing baseline characteristics and follow-up events potentially involved in the definition of the complete data estimators are included in the imputation model, as suggested by Sterne et al. [Sterne 2009].

12 Data conventions

12.1 Age

The variable age at enrollment collected in the eCRF assess whether or not the patient meet the inclusion criteria: patietns aged ≥ 18 years.

Unless specified otherwise, in the statistical age will be calculated as:

(date of diagnosis of AF – date of birth)/365.25

and will be reported in completed years.

Note that when only the year of birth is captured the date of birth will be imputed as 1 July.

12.2 Body mass index

The variable body mass index will be calculated as:

(weight in Kilograms) / (height in meters)^2

If the formula returns implausible values (<5 or >100 kg/m^2) we will remove BMI data from that individual~~replace weight, height, and BMI by missing values~~.

12.3 Calculations and conversions

The following conversion factors will be used to convert days to weeks, to months or years, where applicable:

- 1 week = 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

The following conversion factors will be used to convert pounds (lbs) to kilograms (kg) and feet/inches (in) to centimetres (cm) and cm to metres (m).

- 1 lb = 0.4536 kg
- 1 foot = 12 in

12.4Regions

Countries will be classified into the following geographical regions:

Table 2 Geographic regions involved in study

Regions	List of Countries
Europe	Czech Republic, Norway, Russia ,Belgium, Denmark, Germany, Italy, Netherlands, Spain, Great Britain, Switzerland, France
Asia	China, Japan, South Korea, Thailand, Hong Kong, Taiwan, Malaysia, United Arab Emirates, Turkey
North America	Canada, United States of America
Latin America	Brazil, Mexico, Argentina
Other countries	Australia, South Africa

Other regional or economic comparisons may be considered as appropriate. For example:

- ~~Combinations of the above listed regions~~S
- Subgroups of the above listed regions

- World Bank Classification into countries with lower middle, upper-middle and high incomes

12.5 Rounding

Whenever applicable, i.e. when reporting will require placement of decimals, only one decimal will be reported for percentages and two decimals will be reported for events rates.

Unless stated otherwise the rounding will be performed to the closest integer / first decimal using the common mid-point between the two consecutive values. E.g. 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

13 Deviation from the analysis planned in the protocol

Not applicable.

14 References

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