SECRET: Study of rivaroxaban for CeREbral venous Thrombosis

Long title: Multicentre, prospective randomized open label, blinded-endpoint (PROBE) controlled trial of anticoagulation with rivaroxaban versus standard of care in determining safety at 365 days in symptomatic cerebral venous thrombosis

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Table of Contents

TABLE OF CONTENTS 2

1 PROTOCOL SYNOPSIS 5

2 TRIAL ORGANIZATION 7

3 STUDY OBJECTIVES – INTERNAL PILOT PHASE 7

4 BACKGROUND 8

4.1 BULLET POINT RATIONALE 8
4.2 EXTENDED BACKGROUND AND RATIONALE 8
4.2.1 CHOICE OF ANTICOAGULANT – CURRENT GUIDELINES 9
4.2.2 RIVAROXABAN AND DIRECT ORAL ANTICOAGULANTS (DOACS) FOR CEREBRAL VENOUS THROMBOSIS: POTENTIAL ROLE 9
4.2.3 EARLIER INITIATION OF THERAPEUTIC ORAL ANTICOAGULATION 10
4.2.4 OTHER THERAPEUTIC UNCERTAINTIES IN CVT 11
4.2.5 PROGNOSIS IN CVT 11
4.2.6 ECONOMIC EVALUATION 12

5 STUDY DESIGN 12

5.1 STUDY OVERVIEW 12
5.2 SAFETY OUTCOMES 13
5.2.1 PRIMARY 13
5.2.2 SECONDARY 13
5.3 FEASIBILITY OUTCOMES 14
5.3.1 PRIMARY 14
5.3.2 SECONDARY 14

6 SELECTION AND ENROLMENT OF PARTICIPANTS 14

6.1 INCLUSION CRITERIA 14
6.2 EXCLUSION CRITERIA 14
6.3 SELECTING PATIENTS 15
6.4 ENROLMENT 16

7 STUDY INTERVENTIONS 16

7.1 EXPERIMENTAL 16
7.2 CONTROL 17
7.3 RANDOMIZATION 17
7.4 STUDY DRUG 18
7.4.1 STORAGE AND STABILITY 18
7.4.2 DOSAGE FORMS AND PACKAGING: 18
7.5 SCHEDULE OF ASSESSMENTS 18

8 EVALUATIONS 19

8.1 TIME POINTS 19
8.1.1 BASELINE 19
8.1.2 30 (±5) DAYS 19
8.1.3 90 (±14), 180 (±14), 365 (±14) DAYS 19
8.1.4 CONTINUOUS 20
8.1.5 SAFETY VISIT (POST 30 DAYS) 20
8.2 ASSESSMENTS 20
8.2.1 COGNITIVE ASSESSMENTS 20
8.2.2 QUALITY OF LIFE ASSESSMENT 20
8.2.3 NEUROIMAGING 20
8.2.4 ASSESSMENT OF RECANALIZATION 21
8.2.5 SOCIETAL COSTS AND HEALTHCARE RESOURCE UTILIZATION 21
8.3 MODIFICATIONS FOR TELEMEDICINE ASSESSMENT 21

9 PROHIBITED MEDICATIONS AND PROCEDURES 22

10 GUIDELINES FOR CLINICAL CARE 22

10.1 GUIDELINES FOR ANTITHROMBOTIC THERAPY – CONTROL GROUP 23
10.2 GENERAL CARE CONSIDERATIONS 26
10.3 HYPERCOAGULABILITY 27

11 CRITERIA FOR STUDY DRUG DISRUPTION/DISCONTINUATION 27

12 SEIZURES 28

13 IMAGING 28

14 EVENT DEFINITIONS AND REPORTING 29

14.1 ADVERSE EVENT 29
14.2 SERIOUS ADVERSE EVENT 29
14.2.1 SEVERE ADVERSE EVENT DEFINITIONS 29
14.3 REPORTING AND REVIEW 30

15 EXPECTED DRUG REACTIONS 32

16 TREATMENT GUIDELINES FOR BLEEDING/SUSPECTED BLEEDING 32

17 ANTICIPATED CHALLENGES 33

17.1 BEACON-AND-SATELLITE MODEL 34

18 STEERING COMMITTEE 34

19 STATISTICS AND DATA ANALYSES 34

19.1 MEASURES OF SUCCESS - INTERNAL PILOT PHASE 35
19.2 SAMPLE SIZE - INTERNAL PILOT PHASE 35
19.3 SOCIETAL COST AND HEALTHCARE UTILIZATION VALUATION 35
19.4 HANDLING OF MISSING DATA 38

20 ETHICS AND CONFIDENTIALITY 38

20.1 HUMAN SUBJECTS 38
20.2 ETHICS APPROVAL 38
20.3 CONFIDENTIALITY 38

21 CONDITIONS FOR TERMINATING THE STUDY 39

22 DATA COLLECTION, MANAGEMENT, AND MONITORING 39

22.1 STUDY DOCUMENTATION, CRFS AND RECORD KEEPING 40
22.1.1 INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS 40
22.1.2 SOURCE DOCUMENTS AND BACKGROUND DATA 40
22.1.3 CASE REPORT FORMS 41
22.2 SITE MONITORING AND AUDITS 41
22.2.1 DATA SAFETY AND MONITORING BOARD 41

23 PATIENT ENGAGEMENT STRATEGY 41

23.1 PATIENT FORUMS 42
23.1.1 PRE- AND POST-SURVEY 42
23.1.2 PATIENT FORUM 42
23.2 PATIENT ADVISORY CORE 43
23.3 PATIENT WEBSITE 43

24 ANCILLARY STUDIES POLICY 43

25 DATA-SHARING PLAN 44

26 PUBLICATION AND PRESENTATION POLICY 44

27 REFERENCES 44

1 Protocol synopsis

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Objective	Primary objective: To demonstrate safety of using rivaroxaban to treat symptomatic cerebral venous thrombosis
Experimental Design	A prospective, randomized, controlled, open-label with blinded outcome assessment (PROBE) trial with a modified internal pilot design to assess feasibility, inform sample size estimation, refinement of the primary endpoint, and randomization minimization algorithm.
Population	50 male and female participants in the internal pilot phase. Inclusion Criteria: a) Patients aged 18 and above b) New diagnosis of symptomatic cerebral venous thrombosis as confirmed on CT/CT venogram or MRI/MR venogram c) Ability to randomize within 14 days of neuroimaging-confirmed diagnosis d) The treating clinician is of the opinion that the patient is appropriate for oral anticoagulation as per standard of care e) Patient or legally authorized representative is able to give written informed consent Exclusion Criteria: a) Patient has known antiphospholipid antibody syndrome with a previous history of venous or arterial thrombosis b) Patient is anticipated to require invasive procedure (e.g., lumbar puncture, thrombectomy, hemicraniectomy) prior to initiation of oral anticoagulation c) Patient is unable to swallow due to depressed level of consciousness d) Impaired renal function (i.e., CrCl < 30 mL/min using Cockroft-Gault equation) e) Pregnancy; if a woman is of childbearing potential a urine or serum beta human chorionic gonadotropin (β-hCG) test is positive f) Breastfeeding at the time of randomization g) Bleeding diathesis or other contraindication to anticoagulation h) Any concurrent medical condition requiring mandatory antiplatelet or anticoagulant use i) Concomitant use of strong CYP3A4 inducers (e.g., ongoing use of dilantin, carbamazepine, HIV protease inhibitors) or CYP3A4 inhibitors (e.g., diltiazem, ketoconazole)

	j) Patient has a severe or fatal comorbid illness that will prevent improvement, or cannot complete follow-up due to the same, or cannot complete follow-up due to co-morbid non-fatal illness, non-residence in the city, or for any other known reason for which follow-up would be impossible
Regions	North America
Treatments	Participants will be randomized to **a) rivaroxaban**, or **b) a Vitamin K antagonist** (INR 2.0-3.0) or **therapeutically-dosed low molecular weight heparin**. In the intervention group, rivaroxaban 20 mg daily will be initiated within 24 h of randomization and will continue for a minimum of six months. The dose will be adjusted to 15 mg daily in participants with a creatinine clearance of 30-49 mL/min as per the Cockroft-Gault equation. The control group will receive anticoagulation with regimen (i.e., initial use of unfractionated heparin or low-molecular weight heparin with transition to an oral vitamin K antagonist or continuation with low-molecular weight heparin) with choice of agent at the treating physician's discretion.
Duration of Treatment	Treatment is for a minimum of six months (180 days) with optional extension of study medication to one year (365 days) as per the treating physician's discretion.
Evaluation Criteria	**FEASIBILITY OUTCOMES** **a) PRIMARY –** Rate of recruitment, defined as number of patients providing informed consent per year. **b) SECONDARY – (1)** Rate of refusal, defined as the proportion of eligible patients declining informed consent; **(2)** Rate of retention, defined as the proportion of participants withdrawing informed consent before the end of their 365-day follow-up period. **SAFETY OUTCOMES** **a) PRIMARY –** Composite proportion of patients who die from any cause, experience symptomatic intracranial bleeding, or experience major extracranial bleeding by Day 180. **b) SECONDARY – (1)** The individual components of the composite safety outcome; **(2)** Proportion of subjects with recurrent venous thromboembolism (any thrombosis at a new site including cerebral venous thrombosis in a separate location from index event) at Day 180 or end of anticoagulation, whichever is sooner; **(3)** Proportion with major bleeding or clinically relevant non-major bleeding at Day 180 or end of anticoagulation, whichever is sooner. A clinically relevant minor bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of: (a) a hospital admission for bleeding, or (b) a physician guided medical or

	surgical treatment for bleeding, or (c) a change in antithrombotic therapy (including interruption or discontinuation of study drug); **(4)** Proportion of subjects who have partial or complete venous recanalization by Day 180 and 365; **(5)** Proportion of subjects with functional independence (modified Rankin Score [mRS] 0-1) at Day 365 or the last rating; **(6)** Shift of one or more categories to reduced functional dependence analyzed across the whole distribution of scores on the mRS at Day 365 or the last rating; **(7)** Societal costs and health care resource utilization including number of hospitalizations (e.g., length of stay, critical care unit use), emergency room visits, unscheduled outpatient consultations, post-acute care (e.g., home care, rehabilitation stays, long-term care) at Day 365; **(8)** Improvement on each of EQ-5D-5L, fatigue assessment scale, HIT-6, cognitive function and PHQ-9 at Day 365.
Sample Size	50
Randomization	Randomization will be 1:1 to rivaroxaban or control. Randomization will be central, computer-generated and fully concealed. A minimization algorithm with minimum sufficient balance on key variables will be generated following the internal pilot.
Consent	Written informed consent is required.

2 Trial Organization

The trial will be coordinated and executed by a steering committee (SC) based in Vancouver. An independent Data Safety Monitoring Board (DSMB) will provide safety evaluation during the trial.

The trial will be led by principal investigator, Dr. Thalia Field. Dr. Michael Hill will be the Contract Research Organization for data management of the study.

3 Study Objectives – internal pilot phase

During this internal pilot phase, our primary objective is to successfully reach a recruitment target of 50 patients.
Secondary objectives include:

a) Refining event rates for the primary safety outcome to inform sample size recalculation
b) Refining measurement strategies for certain secondary outcomes, including cognition, venous recanalization and cost-effectiveness
c) Implementation of our patient engagement strategy
d) Determining rates of eligibility for the trial amongst patients with a new diagnosis of symptomatic CVT

4 Background

4.1 Bullet Point Rationale

- Cerebral venous thrombosis (CVT) is a cause of stroke that mainly affects the young and results in death or disability in 15% and impairment of quality of life (QoL) in up to 60% of patients.
- The optimal antithrombotic strategy is unknown.
- Direct oral anticoagulants (DOACs) are widely used for atrial fibrillation and venous thromboembolism (VTE), including limb and pelvic deep venous thrombosis (DVT) and pulmonary thromboembolism (PE) treatment and prevention. DOACs are associated with lower rates of intracerebral hemorrhage than Vitamin K antagonists (VKAs) and are safe and effective for these indications.
- DOACs may provide an improved antithrombotic strategy for CVT due to superior safety, primarily from a lower risk of symptomatic intracranial hemorrhage, and through decreased length of hospital stay.
- Though a minority of clinicians currently use DOACs for CVT and small case series suggest the treatment may be safe and effective, studies regarding the safety of this approach do not exist and most physicians avoid DOACs for this reason.
- Proof of safety for DOACs in CVT is likely to change clinical practice.
- Additionally, several aspects of treatment for CVT are unknown, including duration of anticoagulation, role of venous recanalization in prognosis and its role in determining duration of therapy, and true burden of functional impairment in these mainly young stroke patients. Improved characterization of these potential prognostic markers may lead to appropriate surrogate outcomes for Phase III trials.

4.2 Extended Background and Rationale

CVT refers to thrombosis of the draining cerebral dural sinuses extending to the jugular vein, deep cerebral veins, including the cavernous sinus, or superficial cortical veins. It affects approximately 10 patients per million annually,[1-3] and nearly 80% of cases occur in patients under the age of 50.[4] The clinical spectrum of presentation is related to thrombus burden and location and includes refractory headache, seizures, visual impairment, focal neurological deficits, encephalopathy, decreased level of consciousness and death.[5] Thrombus burden can also precipitate secondary neurological injury through venous infarction, intracerebral hemorrhage and increased intracranial pressure.[6] Long-term complications include dural arteriovenous fistula formation secondary to persistent thrombus, chronic visual impairment and chronic neurological impairment due to seizures, cognitive impairment or focal deficits. Rates of death and disability are approximately 15%,[4,7] and over one-half of patients may experience long-term neurological and neuropsychiatric sequellae, with one-quarter of patients left unable to return to work.

4.2.1 Choice of anticoagulant – current guidelines

Immediate initiation of anticoagulation with unfractionated heparin (UFH) or low-molecular weight heparin (LMWH), even in the presence of intracranial bleeding, with transition to a VKA or ongoing LMWH for 3-12 months, is the current recommendation for CVT treatment.[8,9] The goals of anticoagulation are to prevent thrombus extension, facilitate thrombus dissolution, and treat systemic procoagulability. However, the evidence for anticoagulation in CVT is based on two small, underpowered trials;[10,11] therefore, the optimal therapy for CVT is not well-defined. Significant equipoise regarding the choice of initial and maintenance anticoagulation and length of therapy is demonstrated in physician surveys.[12,13] Further, repeat vascular imaging for CVT is common practice, though the role of venous recanalization in determining prognosis or to guide duration of anticoagulation is also unclear.

Although there is well-established clinical experience with UFH and LMWH for initial therapy in CVT, use of either is resource-intensive. UFH requires in-hospital monitoring IV administration and needs ongoing dose adjustment based on regular bloodwork. LMWH is injected and requires patient education for effective at-home administration. Practical challenges with VKAs as a maintenance anticoagulant are well-documented from both clinical trials and real-world experience. For many, the frequent bloodwork required with VKA monitoring is poorly tolerated, or international normalized ratio (INR, a measure of anticoagulation in VKA patients) is labile. There are multiple interactions with medications using several CYP pathways, including many anti-seizure medications commonly prescribed with CVT, and dietary changes may alter Vitamin K levels, and thus, VKA effectiveness. Even in the context of clinical trials, time in therapeutic range for VKAs averages ~67%. The risks of even small INR deviations are profound. Compared with an INR of 2-2.5, risk of embolism increases fourfold at an INR of 1.4-1.7 in patients with atrial fibrillation. Risk of intracranial hemorrhage (ICH) similarly increases at INRs of 3.6-4.5.[14]

In summary, there is scant underlying evidence from clinical trials to support current anticoagulation regimens for CVT. Practice is variable and current therapies are resource-intensive, requiring close monitoring to ensure safety and effectiveness.

4.2.2 Rivaroxaban and direct oral anticoagulants (DOACs) for cerebral venous thrombosis: potential role

Rivaroxaban is a daily-dosed direct factor Xa inhibitor with a half-life of 7-11 hours. For treatment of acute VTE, rivaroxaban was as effective as conventional therapy (parenteral anticoagulant followed by a VKA for VTE) and was associated with fewer major bleeding events and improved treatment satisfaction and cost-effectiveness.[15-19] The pharmacokinetics, safety and efficacy for various dosing regimens for rivaroxaban in VTE and in special populations are extremely well characterized.[20,21]

Rivaroxaban and other DOACs may be a safe and effective treatment choice for patients with CVT and may reduce risk of later intracranial bleeding. In populations

anticoagulated for VTE or atrial fibrillation, DOACs as a medication class have consistently demonstrated superior safety profiles for risk of ICH, with non-inferior or superior efficacy to VKAs[15,16,22-30] and significantly decreased rates of intracranial hemorrhage, in particular for all DOACs compared to VKAs.

Current clinical experience also supports use of DOACs for CVT. Three small recent clinical series of dabigatran and rivaroxaban for CVT provide additional reassurance that these treatments are effective and well-tolerated in CVT, with the majority of patients achieving partial or complete recanalization and no major bleeding.[31-33] In our recent Canadian survey, a significant minority (i.e., 30%) of neurologist and hematologist respondents have used DOACs for CVT patients, and those who have not, primarily cite a lack of evidence or concerns about liability, as opposed to safety concerns, as the deterrent for use of these agents.[34]

4.2.3 Earlier initiation of therapeutic oral anticoagulation

The average inpatient length of stay for a patient with a diagnosis of CVT is over one week.[3,35,36] Neurologists will often initiate UFH with a transition to oral VKA[13] and the patient will be discharged when the INR is therapeutic at 2.0-3.0. While a minority of patients present with serious neurological deficits and coma, or seizures that may affect their length of stay, for most patients, the rate-limiting step to discharge is monitoring on UFH and awaiting therapeutic anticoagulation while the VKA is titrated.

DOACs provide therapeutic anticoagulation within hours of their ingestion and earlier initiation of therapeutic anticoagulation could significantly shorten length of stay. This is associated with potential reductions in healthcare resource utilization and reduction in hospital-acquired infections or other iatrogenic complications.

A significant minority (i.e., 30-40%) of CVT patients present with some intracranial blood on their preliminary CT scans, primarily petechial hemorrhage. Despite this, anticoagulation is standard of care for CVT, regardless of the presence of intracranial blood. Unlike primary intracerebral hemorrhage, intracranial bleeding in the context of CVT is due to increased pressure in draining veins and resultant increased intradural pressure with associated extravasation into venous infarctions and rupture of draining venules.[37] *Thus, treating the clot will treat the cause of the bleeding*. Though neurologists have a preference for UFH over LMWH,[13] the latter of which has a shorter half-life and can be reversed if necessary with protamine sulfate, this is presumably due to fears regarding potential additional intracranial bleeding. However, existing evidence suggests that risk of further bleeding after initial presentation is low. Of those who present with bleeding on their scans at presentation, *only a very small minority (i.e., <10%) will go on to have further symptomatic of asymptomatioc bleeding on subsequent scans*. Similarly, in those patients who do not present with bleeding at onset, less than 10% develop subsequent hemorrhage[35,38] (refer to Figure 1).

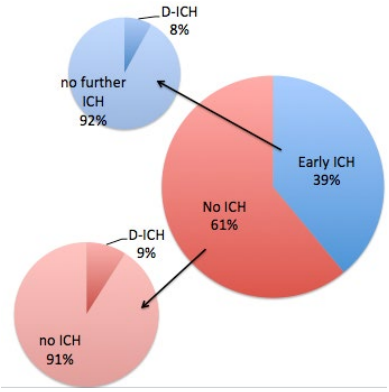

Figure 1: Rates of hemorrhage at presentation ("Early ICH") and risk of further bleeding ("Delayed ICH" (D-ICH)).

Studies examining early use of DOACs after ischemic stroke suggest that early initiation is safe and well-tolerated. This cohort compared to the CVT population is older and with more comorbidities, and therefore, at a higher risk of bleeding than in our target population. Two series with serial neuroimaging found no development of symptomatic or asymptomatic parenchymal hemorrhage in patients with or without baseline petechial hemorrhage when treated with early rivaroxaban (initiated a median (interquartile range) of 3 (5) days after cardioembolic stroke/TIA)[39] or early dabigatran (initiated within 24 hours of TIA/minor stroke).[40]

Earlier initiation of therapeutic oral anticoagulation for cerebral venous thrombosis should be safe, well-tolerated, and should result in decreased length of hospital stay.

4.2.4 Other therapeutic uncertainties in CVT

Optimal duration of anticoagulation for uncomplicated cases of CVT (i.e., those not requiring life-long anticoagulation) is unknown, with guidelines recommending 3-12 months of therapy, and clinical practice varies widely. A minority of clinicians use repeat venous imaging to guide duration of therapy, with continuation of anticoagulation only if recanalization has failed. However, whether this strategy has any impact on prognosis is unclear.[41] High quality data that will inform the minimum duration of anticoagulation in this generally young, active population will likely result in improved safety and QoL.[42,43]

4.2.5 Prognosis in CVT

There are no high quality prospective data in the literature regarding patient-centered functional outcomes after CVT. While several observational studies report a consistently high proportion of "excellent" functional outcomes using a modified Rankin Scale (mRS) of 0-1, data from retrospective series suggests that the mRS inadequately captures the substantial long-term impact of CVT on patients' daily function and QoL. A quarter of CVT patients cannot return to work after more than one year following their

diagnosis.[44,45] In one cohort at 3 years post-CVT, 68% had persisting symptoms including cognitive issues, headache and depression, despite an mRS of 0-1 in 82%.[44] Extended long-term follow-up information is also scant and informed by a few small case studies.[44-47]

Given the absence of high-quality evidence to guide practice and clear clinical equipoise, there is a strong need for a randomized trial to guide antithrombotic strategy for CVT.

4.2.6 Economic evaluation

In economic evaluation, there are multiple perspectives that can be taken to conduct an analysis: Health System, Governmental, and Societal. In some countries, a societal perspective is required as part of their economic evaluation submissions.[48] In Canada, the Canadian Agency for Drugs and Technology in Health (CADTH) guidelines recommend a health system perspective in the reference case analysis, and governmental and societal perspectives in sensitivity analyses.[49] To conduct a societal analysis, crucial components include costs to patients, informal caregivers, and costs to society due to missed work.[49] In economic theory, a patient missing work is considered a productivity loss based on the concept of a production function whereby output is a function of capital input, labour input, and technology.[50] Labour input and thus productivity can be lost due to health status in the form of absenteeism and presenteeism. Absenteeism includes time away from work, and presenteeism includes reduced productivity at work. Despite some work being unpaid (e.g., household work, care for children, volunteer work), if this work is not performed and production is lost due to health status, others would sacrifice time otherwise spent on other activities.[51] Therefore, although these forms of unpaid work are uncompensated, the opportunity costs of these activities warrant a cost to society from reduced levels of production.[51] These same principles also apply to informal caregivers that must sacrifice time to take care of their loved one that could have been otherwise spent on paid or unpaid work.[51] As such, unpaid forms of work and care performed by informal caregivers could be included in societal cost calculations in addition to absenteeism and presenteeism in paid work.

Given the significant burden for CVT patients and their families including time away from work, societal costs are relevant for this population as well as their healthcare utilization post-discharge from hospital.

5 Study Design

5.1 Study Overview

This is a prospective, randomized, controlled, open-label with blinded outcome assessment (PROBE) trial with a modified internal pilot design to assess feasibility and

inform sample size estimation, refinement of the primary endpoint, and randomization minimization algorithm.

Randomization will be 1:1 to a) rivaroxaban 20 mg daily (experimental group), or b) a Vitamin K antagonist (INR target 2.0-3.0) or therapeutically-dosed low-molecular weight heparin (control group). Sample size, the primary endpoint, and the minimization algorithm will be reviewed following completion of the 180-day follow-up for 50 participants.

5.2 Safety Outcomes

5.2.1 Primary

a) Composite proportion of participants who die from any cause, experience symptomatic intracranial bleeding, or experience major extracranial bleeding by Day 180.

Note: Symptomatic intracranial bleeding is defined as a new symptomatic intracranial hemorrhage OR worsening existing intracranial hemorrhage with a $\geq$33% change in hematoma volume, AND either an NIH Stroke Scale (NIHSS) score increase of 4 or more points, or a change in level of consciousness as per NIHSS item 1a, AND the clinical change is thought to be attributable to the hemorrhage. Major extracranial bleeding is defined as bleeding in a critical area or organ, including intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a drop in hemoglobin by 20 g/L or more, leading to transfusion of 2 or more units of whole blood or red cells.

5.2.2 Secondary

a) The individual components of the composite safety outcome
b) Proportion of participants with recurrent venous thromboembolism (any thrombosis at a new site including CVT in a separate location from index event) at Day 180 or end of anticoagulation, whichever is sooner
c) Proportion with major bleeding or clinically relevant non-major bleeding at Day 180 or end of anticoagulation, whichever is sooner. A clinically relevant non-major bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of: (a) a hospital admission for bleeding, or (b) a physician guided medical or surgical treatment for bleeding, or (c) a change in antithrombotic therapy (including interruption or discontinuation of study drug)
d) Proportion of participants who have partial or complete venous recanalization by Day 180 and 365
e) Proportion of participants with functional independence (mRS 0-1) at Day 365 or the last rating
f) Shift of one or more categories to reduced functional dependence analyzed across the whole distribution of scores on the mRS at Day 365 or the last rating
g) Societal costs (lost productivity [absenteeism and presenteeism for paid or

unpaid work] and out-of-pocket expenses) and health care resource utilization including number of hospitalizations (e.g., length of stay, critical care unit use), emergency room visits, unscheduled outpatient consultations, post-acute care (e.g., home care, rehabilitation stays, long-term care) at Day 365

h) Improvement on each of Quality of Life Assessment (EQ-5D-5L), Fatigue Assessment Scale, The Headache Impact Test (HIT-6™), components of cognitive screen (NIH Toolbox), Montreal Cognitive Assessment (MoCA©), spontaneous speech (Cookie theft picture) and Patient Health Questionnaire (PHQ-9) at Day 365 (refer to Section 8.2)

5.3 Feasibility Outcomes

5.3.1 Primary

a) Rate of recruitment, defined as number of participants providing informed consent per year

5.3.2 Secondary

a) Rate of refusal, defined as the proportion of eligible patients declining informed consent
b) Rate of retention, defined as the proportion of participants withdrawing informed consent before the end of their 365-day follow-up period

6 Selection and Enrolment of Participants

6.1 Inclusion criteria

a) Patients aged 18 and above
b) New diagnosis of symptomatic CVT as confirmed on CT/CT venogram (CTV) or MRI/MR venogram (MRV)
c) Ability to randomize within 14 days of neuroimaging-confirmed diagnosis
d) The treating clinician is of the opinion that the patient is appropriate for oral anticoagulation as per standard of care
e) Patient of legally acceptable representative is able to provide signed informed consent

6.2 Exclusion criteria

a) Patient has known antiphospholipid antibody syndrome (APLS; lupus anticoagulant, anti-beta 2-glycoprotein I antibodies, and anticardiolipin antibody) by Sapporo-Sydney criteria* with a previous history of venous or arterial thrombosis
b) Patient is anticipated to require invasive procedure (e.g. lumbar puncture, thrombectomy, hemicraniectomy) prior to initiation of oral anticoagulation**
c) Patient is unable to swallow due to depressed level of consciousness†
d) Impaired renal function (i.e., CrCl < 30 mL/min using Cockroft-Gault equation)
e) Pregnancy; if a woman is of childbearing potential a urine or serum beta human chorionic gonadotropin (β-hCG) test is positive

f) Breastfeeding at the time of randomization
g) Bleeding diathesis or other contraindication to anticoagulation
h) Any concurrent medical condition requiring mandatory antiplatelet or anticoagulant use
i) Concomitant use of strong CYP3A4 inducers (e.g., ongoing use of dilantin, carbamazepine, HIV protease inhibitors) or CYP3A4 inhibitors (e.g., diltiazem, ketoconazole)
j) Patient has a severe or fatal comorbid illness that will prevent improvement, or cannot complete follow-up due to the same, or cannot complete follow-up due to co-morbid non-fatal illness, non-residence in the city, or for any other known reason for which follow-up would be impossible.

*At least one *clinical* AND one *laboratory* criterion of:

Clinical: (1) Arterial, venous or small vessel vascular thrombosis, (2) Pregnancy morbidity (one or more unexplained deaths of a morphologically normal fetus at 10 weeks' gestation or later; one or more premature births of a morphologically normal neonate prior to 34 weeks' gestation due to eclampsia, severe pre-eclampsia, or placental insufficiency; or three or more unexplained spontaneous abortions before 10 weeks' gestation with normal maternal anatomic and hormonal and parental chromosomal causes excluded).

Laboratory (present on 2 or more occasions ≥12 weeks apart): (1) Lupus anticoagulant in plasma, (2) Anticardiolipin antibodies (IgG and/or IgM) in serum or plasma in moderate or high titer, (3) Anti-beta2-glycoprotein-I antibody (IgG and/or IgM) in serum or plasma.

**Patients who have received an invasive procedure and/or whose level of consciousness improves such that it does not interfere with their ability to take oral medication may be subsequently enrolled into the trial if the investigator deems that the patient is otherwise eligible within the first 14 days of enrollment.

†A patient without depressed level of consciousness requiring an NG tube for dysphagia who is otherwise eligible does not meet exclusion criterion b).

6.3 Selecting Patients

The principles of patient selection are based upon the broad criteria of:

a) Symptomatic presentation with a diagnosis of CVT
b) Imaging proof of CVT or cortical vein thrombosis relevant to the presenting symptoms
c) Suitable for therapeutic anticoagulation as per standard of care

The most challenging of these principles is (c) since it requires clinical judgment and imaging interpretation. There are exceptional circumstances where a patient with CVT may not be appropriate for therapeutic anticoagulation, including but not limited to: malignancy with severe thrombocytopenia (Plt <50), CVT related to significant brain and/or polytrauma, or CVT with massive hemorrhage. However, we anticipate that such cases are extremely rare. Approximately 5% of patients with CVT in previous series are unsuitable for this primary treatment strategy due to massive hemorrhage and require

alternative treatments, such as mechanical thrombectomy and/or hemicraniectomy.[52] To further illustrate the rarity of such cases unsafe for anticoagulation, the TO-ACT trial, which enrolled those rare CVT patients requiring heroic therapy, including but not limited to those with massive hemorrhage, recruited only 67 patients over 5 years from 14 centres in 5 countries[53].

6.4 Enrolment

Patients will be screened within 14 days of diagnosis using the usual stroke team process of care at the site.

Candidates for enrolment will be approached for consent. Since less than 10% of patients with CVT present with severe neurological deficits such as coma, many/most will be able to provide consent themselves. Patients who are unable to give informed consent, who otherwise meet criteria, may still be enrolled with the consent of a surrogate or legally authorized representative. All patients or their surrogate must provide written informed consent prior to any study procedure.

All patients will be evaluated clinically and then undergo brain imaging using CT, followed immediately by a CTV. If they remain eligible, after review of clinical, imaging, and laboratory testing, they will be enrolled and treated. All participants will be treated within 14 days of their first scan confirming diagnosis of CVT. In sites where MRI/MRV is routinely used, CT/CTV can be substituted. In all parts of the protocol, MRI/MRV can be substituted for CT/CTV.

A participant is considered enrolled into the trial at the point (date and time) of randomization. Randomization is considered time 0, and should receive the study drug immediately (i.e., <24 hours). A patient who provides consent but is not enrolled into the trial is considered a screen failure.

7 Study Interventions

Randomization will be 1:1 to rivaroxaban (experimental) or a Vitamin K antagonist (target INR 2.0-3.0)/therapeutic low molecular-weight heparin (control).

7.1 Experimental

Participants randomized to rivaroxaban therapy will be treated using 20 mg daily. Dose adjustments to 15 mg daily for patients with CrCl 30-49 mL/min will be made as per the Cockroft-Gault equation. Treatment will be for a minimum of 180 days, with an option to extend therapy to 365 days at the discretion of the treating physician. If anticoagulation is indicated past 365 days, the treating physician can determine which anticoagulant is most appropriate for the patient.

7.2 Control

There is equipoise regarding choice of initial anticoagulant in patients with CVT.[12,13] In general and as per guideline recommendations, either UFH or LMWH is initiated at diagnosis followed by transition to oral VKA or ongoing LMWH for maintenance anticoagulation.[8] If a participant is randomized to the control arm, the local investigator can choose either a Vitamin K antagonist (target INR 2.0-3.0) **OR** therapeutically-dosed low molecular-weight heparin. Regardless of patterns of practice at certain centres (e.g., where DOACs may be routinely used in CVT patients), **a DOAC is not an acceptable choice of antithrombotic for the control arm.**

Anticoagulation should be started immediately upon randomization. As with the experimental group, treatment will be for a minimum of 180 days, with an option to extend therapy to 365 days at the discretion of the treating physician. If anticoagulation is indicated past 365 days, the treating physician can determine which anticoagulant is most appropriate for the patient. Guidelines for anticoagulation in the control group are further outlined Section 10.1.

All patients will have standard of care medical management on an acute stroke unit.

7.3 Randomization

Patients must undergo a CT head or MRI (repeat CTV/MRV is optional) ≤72 hours ***prior*** to randomization as features such as intracranial bleeding or thrombus burden may have changed from the time of the initial diagnostic scan on clinical presentation.

For the internal pilot phase, randomization will be 1:1, completed by a fully concealed computer algorithm. The sample size of the pilot study prevents stratification for multiple covariables. Given that standards of care are similar throughout major stroke centres in Canada with implementation of Canadian Best Practice guidelines, we will not stratify by site. We will stratify by age (i.e., ≤37 and >37 years) as older age is associated with worse prognosis and this age cut-off was identified in the second-largest series of CVT patients to date.[7]

Other significant adverse prognostic factors in large studies of CVT will likely be lesser concerns in our study population. Although males have a worse prognosis, this is accounted for at least in part by the fact that CVT associated with the pregnancy and puerperium tends to have a better prognosis, and this group would be excluded from the trial because rivaroxaban is contraindicated in pregnant and nursing women. Similarly, those who present with depressed level of consciousness and/or very large hemorrhages, which are both associated with poorer early prognosis, would not be enrolled in the trial unless they were to improve clinically and meet study criteria.

Demographic information from participants enrolled during the internal pilot phase will be used to generate a minimization algorithm with minimal sufficient balance randomization following the internal pilot phase. This will ensure balance throughout the trial, based on key variables. This algorithm will be developed centrally and the

details will not be available to participating sites. Randomization will be dynamic and generated in the moment via a web-based system; thus, a randomization list does not exist. The result will be random allocation that is fully concealed. Randomization will be biased coin that will vary from fully balanced (50:50) to biased (65:35) dependent on characteristics of participants that have been previously enrolled. The system will be enabled for smart-phone, tablet, laptop or desktop computer use.

7.4 Study Drug

The trade name for rivaroxaban is Xarelto®.

7.4.1 Storage and Stability

Store Xarelto at 15-30°C. Store in a safe place out of the reach of children.

7.4.2 Dosage Forms and Packaging:

15 mg Tablets:

Film-coated, round, biconvex, red immediate release tablets of 6 mm diameter for oral use. Each tablet has the Bayer Cross on one side and 15 and a triangle on the other side. XARELTO tablets 15 mg are supplied in HDPE bottles of 90 and blisters of 28, 42 and 100.

20 mg Tablets:

Round, biconvex, white to yellow white coated tablet immediate release tablets of 6 mm diameter for oral use.

7.5 Schedule of Assessments

Table 1: Schedule of assessment completion.

	Screening	Random-ization	Day 30 (±5 d)	Day 90 (±14 d)	Day 180 (±14 d)	Day 365 (±14 d)
Informed consent	X					
Attempt at regained capacity informed consent[Ω]		X	X	X	X	X
History and examination, demographics		X				
Review of risk factors		X	Collected to Day 365 visit*			
Height and weight		X (Actual)				
Telephone follow-up			X			
Vital Signs (BP, HR, Temp)		X		X	X	X
Randomization/ Study drug administration		X				
Mortality/Vital statistics review			X	X	X	X
NIHSS		X		X	X	X
mRS	X[¶]	X	X	X	X	X
PHQ-9, Fatigue assessment Scale, EQ-5D-5L, HIT-6[#]		X	X	X	X	X

Cognitive assessments†		X		X	X	X
CT/CTV, MRI/MRV **	X	X		X^	X	X^^
CBC, INR, aPTT, serum creatinine, blood urea nitrogen and serum glucose	X‡					
Pregnancy test	X‡‡					
Societal costs and health care resource utilization assessment including COVID-19 form (as of Aug 2020)		X	X	X	X	X
AE and SAE assessment		Collected to Day 365 visit + 30 days				
Prior medications	X§					
Concomitant medications	Collected to Day 365 visit					

Ω For subjects for whom the LAR completed the original consent (and if required), research staff will make ongoing efforts until (1) regained capacity consent is obtained from subject, (2) death, or (3) completion of the Day 365 assessment.

¶ Historical (pre-stroke) score

* Re-review with availability of additional investigations as per the treating physician's clinical judgement (e.g., thrombophilia workup, malignancy workup)

Patient Health Questionnaire-9 (PHQ-9) to assess for depression, Fatigue Assessment Scale, EuroQoL-5-dimensional score (EQ-5D-5L), The Headache Impact Test (HIT-6™)

† NIH Toolkit Cognitive Battery, Montreal Cognitive Assessment (MoCA)©, Boston Cookie theft picture

**CT or MR imaging will be done as per standard of care at the institution. The diagnostic scan can be the randomization scan as long as it is within 72h prior to randomization.

^ At the discretion of the investigator

^^ Day 365 CTV/MRV is not performed if there is complete recanalization on Day 180 scan

‡ Blood should be drawn prior to randomization and then subsequent draws following standard of care at the institution.

‡‡ If the subject is female and of childbearing potential, a pregnancy test (urine or serum point-of-care pregnancy test) must be completed and the result must be negative in order to be eligible for study participation

§ Prior medications should be documented prior to randomization.

d = days; h = hours, CTV = CT venogram, MRV = MR venogram

8 Evaluations

8.1 Time points

8.1.1 Baseline

Past medical history, assessment of risk factors, medication review, height and weight, vital signs, NIHSS, mRS, baseline CT/CTV or MR/MRV, standard of care bloodwork, pregnancy test in women of childbearing potential, cognitive assessments (i.e., MoCA©, NIH toolbox, Cookie theft picture), headache impact (i.e., HIT-6™), depression (i.e., PHQ-9), fatigue, health-related quality of life (i.e., EQ-5D-5L), and societal costs/health care resource utilization assessment.

8.1.2 30 (±5) days

Telephone follow-up with mRS, review of any additional standard of care bloodwork and medications, mortality/vital statistics review, compliance check, EQ-5D-5L, PHQ-9, fatigue, HIT-6™, and societal costs/health care resource utilization assessment.

8.1.3 90 (±14), 180 (±14), 365 (±14) days

Mortality/vital statistics review, vital signs, review of standard of care bloodwork and medications, compliance check, NIHSS, mRS, cognitive assessments (refer to Section 8.2.1), Day 90 repeat CTV/MRV (if deemed necessary by treating physician), Day 180

repeat CTV/MRV, Day 365 repeat CTV/MRV if not fully recanalized on Day 180, HIT-6, PHQ-9, EQ-5D-5L, fatigue, and societal costs/health care resource utilization assessment.

8.1.4 Continuous

Concomitant medications, adverse event (AE) and serious adverse event (SAE), hospitalizations, and protocol deviations/violations.

8.1.5 Safety visit (Post 30 days)

Telephone follow-up with (S)AE and hospitalization reports if applicable.

8.2 Assessments

Note: The investigator completing the 90, 180 and 365-day outcome assessment should be a blinded site trial investigator, sub-investigator or coordinator defined as absence of involvement in the first 24 hours of treatment of the patient. If not feasible to complete in person, these assessments can be completed by telemedicine.

8.2.1 Cognitive assessments

Processing speed, working memory and attention are the most common domains affected in young stroke patients[54] and the "ceiling effect" of common screening tools such as the MoCA© may be more pronounced in this generally young cohort. In addition to the MoCA©, cognitive function will be assessed using the NIH toolbox cognitive battery. For participants outside of Vancouver, trained examiners from the Coordinating Centre will administer the NIH toolbox (using an iPad) remotely over videoconference with assistance from the on-site research coordinator. The Boston Aphasia Cookie Theft description task is considered a valid test of spontaneous discourse. Participants will be asked to describe the Boston Cookie Theft Picture and speech will be audiorecorded and subsequently transcribed for analysis of linguistic features (e.g., lexical features [part-of-speech, word types and frequencies], syntactic complexity, grammaticality, fluency, vocabulary richness, and acoustic features), using a previously validated algorithm from our group.

8.2.2 Quality of life assessment

Potential mitigating effects of depression and fatigue will be assessed using the Patient Health Questionnaire-9 (PHQ-9) and the Fatigue Assessment Scale which have been validated for post-stroke depression and fatigue, respectively.[55,56] The Headache Impact Test (HIT-6™) is a six item tool to assess the impact of headaches on daily life and function. We will include the European Quality of Life-5 Dimensions Questionnaire (EQ-5D-5L), a standardized instrument for measuring health outcomes validated for a wide range of health conditions.

8.2.3 Neuroimaging

Modality for baseline and follow-up imaging (i.e., CT/CTV or MRI/MRV) will be performed as per clinical practice at each site. In keeping with standards of care, no pre-specified imaging protocol will be required. If randomization occurs >72 h from diagnosis, brain and vascular imaging (CT or MRI, CTV/MRV are optional) must be

repeated within 72 h as burden of intracranial blood, size or presence of venous infarct/edema or other findings may have evolved. Follow-up neuroimaging with CT/CTV or MR/MRV will occur at Day 90 (if deemed necessary by the treating physician), Day 180, and if complete recanalization is not attained, Day 365. As per standard of care, neuroimaging by standard site protocol will be obtained urgently if there is any clinical worsening or if the treating physician feels additional imaging is otherwise indicated.

8.2.4 Assessment of recanalization

Quantitative and qualitative assessments of recanalization will be performed. Change in thrombus volume will be measured using Quantomo (Calgary, AB) and recanalization scores to assess no/partial/complete recanalization at anatomical site will be derived and validated during the lead-in phase of the trial[57].

8.2.5 Societal costs and healthcare resource utilization

The societal costs and healthcare utilization questionnaire will be conducted in-person or by phone. Both self-complete and coordinator-administered options will be available. There will be three parts to the questionnaire in total. The first part is the baseline questionnaire that will be administered during enrollment. The "Societal Costs" and "Outpatient Healthcare Utilization and Patient Costs" questionnaires will be completed during subsequent follow-ups. The Societal Costs section includes two parts: previous paid or unpaid work. The questions in both sections are designed to determine levels of absenteeism and presenteeism from this work, and are based on the Valuation of Lost Productivity Questionnaire (VOLP) that has previously been tested for face validity, construct validity, and reliability.[50,58-60] The Healthcare Utilization and Patient Cost section includes questions to determine the amount of healthcare resource consumed, and the time patients must spend to consume those resources. It also includes questions to determine out-of-pocket costs for patients related to their CVT. While these methods are subject to recall bias, without an administrative database including utilization of these resources, patient responses remain the most valid option for data collection. The questionnaire will be administered at each follow up period within the trial, and responses will be used to inform societal cost of lost productivity. The mitigating circumstances of COVID-19 on disruptions to work and school will be collected as of August 2020.

8.3 Modifications for telemedicine assessment

In an effort to enroll patients living in remote areas and prevent loss to follow-up, telemedicine can be utilized. A NIHSS-certified assessor can perform the NIHSS over telemedicine in lieu of the on-site study coordinator. QoL measures, including the PHQ-9, EQ-5D-5L, HIT-6, and the fatigue assessment scale can be completed over the phone if necessary. A computerized version of the cognitive battery will be developed and validated during the first year of the study and will be subsequently used for remote and in-person cognitive assessments. One chief advantage of a computerized assessment is the ability to measure time elapsed for each task in addition to test scores, which increases sensitivity for baseline deficits and improvement on follow-up.

9 Prohibited medications and procedures

In the control group, DOAC is not acceptable for "standard of care" antithrombotic – only a vitamin K antagonist (INR 2.0-3.0) **OR** therapeutic low molecular-weight heparin are acceptable.

In the experimental group, no antiplatelet agent or additional antithrombotic medicines should be given during the study. Participants who require antithrombotic treatment during the course of follow-up for a separate indication (e.g., cardiac stent) will be considered a protocol violation, as would patients for whom the site investigator otherwise determines that a change in anticoagulation is required. Similarly, patients requiring medications that interfere with the metabolism of either experimental or control group medications (i.e., relevant enzyme inducers or inhibitors) for which there are no suitable alternatives will be considered a protocol violation.

Note: If clinically indicated, one additional antiplatelet drug or a brief (≤ 3 month) period of dual antiplatelet medication is acceptable for continuing on study medication, though we would encourage using single antiplatelet or the shortest possible course of dual antiplatelet therapy.[61] If the site investigator determines that a change in anticoagulant management is required, then the study medication will be discontinued. Medications that interfere with metabolism of experimental or control medications for which there are no suitable alternatives would require discontinuation of the study medication. Even if study medication is withdrawn, every effort will be made to continue with study follow-up procedures, though a participant may choose at any time to withdraw informed consent for overall study participation.

Patients should not undergo any invasive procedure (e.g., lumbar puncture, thrombectomy, thrombolysis, hemicraniectomy) outside of the trial protocol. This is considered a protocol violation. In addition, if it is anticipated that a patient will undergo any invasive procedure, they should not be enrolled into the trial pre-procedure. However, patients who have received these procedures prior to enrolment may be subsequently enrolled into the trial following their procedure provided they are otherwise eligible for the trial. Endovascular thrombectomy or thrombolysis preceding enrollment is also not grounds for exclusion and these patients may be enrolled following their procedure provided they are otherwise eligible for the trial.

Adverse events that occur related to use of any prohibited medications and procedures will be recorded and adjudicated accordingly.

10 Guidelines for Clinical Care

It is expected that participants will receive the best usual standard of stroke unit care. Participants are expected to be admitted to hospital as part of routine standard of care.

Most patients will have mild symptoms and recover in 1-2 days and will likely be subsequently discharged home.

It is expected that all patients will undergo a routine work-up for the mechanism of their CVT and be treated appropriately and definitively, including appropriate monitoring of INR in standard of care patients taking an oral VKA. Patients in whom there is a high clinical suspicion for criteria-defined antiphospholipid antibody syndrome should not be enrolled in the trial. Otherwise, it is not necessary to await results of antiphospholipid antibody testing prior to randomization.

We wish to prevent adverse events related to supra- or sub-therapeutic anticoagulation from confounding the 180-day clinical outcome, such that patients who are well at discharge remain that way for the duration of the follow-up period.

10.1 Guidelines for antithrombotic therapy – control group

Patients who are randomized to the control group should receive initial anticoagulation with UFH or LMWH with transition to maintenance oral anticoagulation with an oral VKA (e.g., warfarin) or with ongoing LMWH as per accepted standard of care with guidelines below for dosing and monitoring as needed:

a) Warfarin – target INR 2.0 – 3.0[62,63]

Initial dose of warfarin is typically 5 mg/day in most patients. A starting dose of < 5 mg may be considered for patients > 70 years of age, elevated baseline INR > 1.1, hypoalbuminemic patients (e.g., malnourished, liver disorders, post-operative), impaired nutrition (e.g., weight < 45 kg), heart failure, known to take medications that increase sensitivity of warfarin, or previously documented increased sensitivity to warfarin.

Whenever feasible, a single strength warfarin tablet (i.e., recommend 1 mg only for safety and dose flexibility) should be prescribed such that doses are multiples of one tablet strength. Patients should take their warfarin once a day at the same time in the evening, and have their INR test performed in the morning. This limits diurnal variations and provides the physician with a same day window for dosage adjustment in the event of an unanticipated INR change.

The optimal maintenance dose for warfarin varies from patient to patient and at different times in the same patient. There are no maximal or minimal doses to maintain a therapeutic range. The actual dose can range from 0.5-20 mg or higher, daily. Persons of Asian origin tend to require lower doses while those of Black origin tend to use higher doses because of differences in genetic polymorphisms in these populations.

The narrow therapeutic index and a high risk/benefit ratio necessitate close and long-term monitoring. During the first few days of treatment, the INR rises without concomitant clinical anticoagulant effect. Moreover, during the maintenance phase,

dose changes may not be reflected in INR for 4-5 days. For these reasons, **frequent dose changes are not recommended**.

During the induction or initiation phase, it is recommended that INR be monitored with first INR check on day 3-4 and then every 2-4 days (initially daily if on therapeutic heparin) until the INR is in the patient's target range for two consecutive values. Once the INR is stabilized within the patient's target range, it can be monitored weekly. The interval can be gradually increased up to every 4 weeks if the INR remains stable and within the therapeutic range. Monitoring frequency of up to 12 weeks can be considered in patients with stable and therapeutic INRs whose doses have been unchanged for at least 3 months. For more information INR dosing and monitoring, refer to Tables 2-3 below.

Table 2: Recommended warfarin initiation dosing (clinical judgment should supersede the monogram) [http://www.hematology.org/Clinicians/Guidelines-Quality/Quick-Reference.aspx]

Day	INR	DAILY DOSE
1-3	Not required	5 mg*
3 or 4	1.0-1.3	7.5 mg
	1.4-1.5	5 mg
	1.6-1.8	5/2.5 mg alternating
	>1.9	2.5 mg
	≥2.0	Hold x 1 day, then 2.5 mg†
7 & 10	≤ 1.5	Increase by 15% of ADD
	1.6-1.9	Increase by 10% of ADD
	2.0-3.0	**No Change**
	3.1-3.5	Decrease by 10% of ADD
	3.6-4.0	Decrease by 15% of ADD
	> 4.1	Hold 1 day, decrease by 15% (or more)†
	≥ 6.0	Consider Vitamin K†

Abbreviations: ADD = average daily dose

* 2.5 mg for frailty, liver disease, malnutrition, drugs that enhance warfarin activity, or Asian ethnicity; 5-7.5 mg for young healthy patients

† Check INR more frequently

Dosage adjustment is not required for minor fluctuations of INR as long as the results remain within the patient's target range. INR fluctuations beyond the patient's target range should always prompt a direct communication with patient to determine cause; consider causes such as a change in dosage of warfarin, patient adherence, medications including over-the-counter (OTCs), dietary changes, unusual alcohol consumption and intercurrent illness. For further chronic dosage adjustment information, refer to the

table below.

Table 3: Chronic warfarin dose adjustments (Target INR 2.0 – 3.0), no significant bleeding (INR – international normalized ratio. Clinical and professional judgment may allow variation in the application of the nomogram[64])

Goal of INR 2.0–3.0	
INR	Action
≤ 1.5*	Increase weekly dose by 15%; repeat INR determination in 7–14 days
1.51–1.99*	If falling or low on two or more occasions, increase weekly dose by 10%; repeat INR determination in 7–14 days
2.00–3.00	No change
3.01–3.99*	Do not hold warfarin. If rising or high on two or more occasions, decrease weekly dose by 10%; repeat INR determination in 7–14 days
4.00–4.99	Hold for 1 day. Decrease weekly dose by 10%; repeat INR determination in 7–14 days
5.00–8.99	Hold warfarin. Consider oral vitamin K 2–4 mg† if at increased risk of bleeding. If INR still high 24 h later, consider giving 1–2 mg of additional oral vitamin K† and restart at lower dose (decrease weekly dose by 15%) when INR is therapeutic. Check INR weekly until stable
≥ 9.0	Hold warfarin and give oral vitamin K 5.0–10.0 mg.† Monitor more frequently and repeat vitamin K if necessary
Serious bleeding regardless of INR	Hold dose and give intravenous vitamin K 10 mg and fresh frozen plasma, recombinant factor VIIa, or prothrombin complex concentrates, depending on the urgency of the situation

b) Unfractionated heparin[65]

IV: 80 units/kg (or alternatively 5,000 units) IV push followed by an initial continuous infusion of 18 units/kg/hour (or alternatively 1,000 units/hour). Infusion rate adjusted based on partial thromboplastic time (PTT) readings (target PTT 60-90 seconds). Alternatively, heparin dosing based on site-specific, weight-based heparin nomogram/protocol to achieve target PTT of 60 to 90 seconds.

The use of a UFH dosing nomogram is encouraged because it helps achieve and maintain the activated PTT (aPTT) in the therapeutic range efficiently. aPTT reagents

vary in their sensitivity to UFH; therefore, each laboratory should establish a local therapeutic range. A reasonable estimate of an adequate therapeutic effect would be achieved by an aPTT ratio of 2.0-3.0 times control.

Prior to starting IV UFH, a baseline complete blood count (CBC), prothombin time (PT) and aPTT should be done. Monitoring of the aPTT is required every 6 hours to guide adjustment of the infusion rate. Once a therapeutic range is achieved, then the aPTT can be checked once daily. Daily monitoring of the platelet count in patients receiving full-dose IV UFH is advised.

c) Dalteparin

200 units/kg subcutaneously every 24 hours.

d) Enoxaparin

1 mg/kg subcutaneously every 24 hours.

e) Tinzaparin

175 anti-Xa units/kg subcutaneously every 24 hours.

Note: Product monographs for the LMWHs recommend that, at a minimum, patients receiving LMWH have their platelets checked twice weekly while in hospital and then weekly for the first month or until LMWH is stopped.

Overlap with warfarin

In most cases, warfarin can be started on the same day as UFH or LMWH. Warfarin and UFH or LMWH should overlap for at least 5 days and until the INR value is within therapeutic range for 2 consecutive days.

10.2 General care considerations

Patients with seizures should receive acute and maintenance anticonvulsive therapy with duration of treatment per the investigator, and patients with visual deficits and/or papilledema should be treated with acetazolamide and receive appropriate follow-up to prevent visual loss and to decide on duration of therapy and/or required adjunctive treatments. Symptomatic treatment for headache and nausea should be given as required. Work-up and treatment of underlying pro-coagulable states should be managed appropriately with specialist follow-up as indicated.

For patients that are disabled from their event and require a longer in-patient stay and/or rehabilitation, it is expected that they will receive standard stroke unit care to prevent complications.

These include:

- Hydration
- Swallowing assessments and prevention of aspiration pneumonia

- Early mobilization and physiotherapy to prevent skin breakdown, pneumonia, DVT/PE
- Early diagnosis and treatment of fever

Patients with dysphagia requiring parenteral administration of medication may take study medication that has been crushed within the preceding four hours.

10.3 Hypercoagulability

Based on results from RAPS[66] and TRAPS[67] trials, rivaroxaban treatment may not be as effective compared to warfarin for recurrent thromboembolic events in high-risk patients with triple-positive antiphospholipid antibody syndrome (APLAS). While APLAS in CVT patients is uncommon (6-17%), the prevalence of "true" APLAS in this cohort is uncertain. Routine screening is not required prior to study enrollment but a hypercoagulability workup is warranted in cases with a high clinical index of suspicion.

Criteria-defined APLAS with a previous arterial or venous thrombotic event would be an indication for warfarin and these patients would not be suitable for trial participation. **APLAS is an exclusion criterion.** Otherwise, it is at the discretion of the treating physician. If a patient enrolled is subsequently found to have APLAS, the study drug can be discontinued and transitioned to an alternative therapy. In patients where there is no high clinical index of suspicion for APLAS, randomization can occur while awaiting results of APLAS testing. Even if antibodies are present, study drug can be continued until a criteria-defined diagnosis is confirmed. It should be noted approximately 4% of the general population will have antiphospholipid antibodies present and lupus anticoagulant testing is expected to be abnormal while on anticoagulation.

If indicated, a hypercoagulability workup should be drawn prior to initiation of anticoagulation, in particular, protein C and S, and antiphospholipid antibodies. Genetic tests such as antithrombin, prothrombin gene mutation, and Factor V Leiden are not affected.

11 Criteria for Study Drug Disruption/Discontinuation

The study drug may be withdrawn temporarily at the discretion of the investigator in cases of planned or emergent treatments. Adherence to best practice as per the most recent American College of Clinical Pharmacy guidelines with regards to risk stratification for disruption of anticoagulation and timing of restarting therapy is encouraged.[68]

The study drug may also be withdrawn temporarily or permanently at the discretion of the investigator in cases of: major hemorrhage or clinically significant non-major bleeding, development of a separate indication for different antithrombotic therapy, development of an intercurrent health issue requiring medications that interfere with the metabolism of either experimental or control group medications (for relevant drug

interactions, refer to product monographs) for which there are no suitable alternatives, or if a participant chooses to stop study medication.

If clinically indicated, one additional antiplatelet drug or a brief (≤3 month) period of dual antiplatelet medication is acceptable for continuing on study medication, though we would encourage using single antiplatelet or the shortest possible course of dual antiplatelet therapy.[61] If the site investigator determines that a change in anticoagulant management is required such that study medication is no longer a suitable treatment for a participant, then the study medication will be discontinued. Medications that would interfere with metabolism of experimental or control medications for which there are no suitable alternatives would require discontinuation of the study medication.

Even if the study medication is withdrawn, every effort will be made to continue with study follow-up procedures, though a participant may choose at any time to withdraw informed consent for overall study participation.

In the event a participant withdraws consent for follow-up in the study, the participant will be discontinued from the trial on the date of their withdrawal of consent. Data collected prior to this date will be included in the final study report.

12 Seizures

Seizures may occur in up to 40% of patients with CVT and the majority occur at presentation[69], while a minority may have late seizures. After benzodiazepines, phenytoin is the primary first-line agent available for IV loading in Canada; available alternatives may include IV valproate or IV levetiracetam. Drug-drug interactions occur between DOACs and phenytoin through the CYP3A4 pathway and can result in decreased DOAC levels. In the event of acute presentation with seizures, while IV valproate or levetiracetam are favoured and there is no interaction with DOACs, any available loading agent should be used at presentation. Acceptable agents for maintenance antiepileptic therapy in the DOAC group include levetiracetam, valproic acid, and lamotrigine.

13 Imaging

Diagnosis on neuroimaging at enrollment will be based upon the Site PI's interpretation of the imaging. Detailed assessment of baseline and follow-up scans will be centrally performed at the core imaging lab in Calgary (1403 29 St NW, Calgary, AB T2N 2T9). All imaging completed of the brain (i.e., CT/CTV, MRI/MRV) will be de-identified and sent for central adjudication. At a minimum, the diagnostic scan, randomization scan (if different from diagnosis), Day 180, and Day 365 (if performed) scans should be included. Assessments will include burden and location of venous thrombus, qualitative and quantitative measures of recanalization of follow-up imaging, and presence, location

and volume of venous infarct and venous hemorrhage on baseline and follow-up imaging.

14 Event definitions and reporting

14.1 Adverse event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug -related. AEs can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. AEs are collected after enrollment and are defined as not being present prior to enrollment. AEs should be managed according to the best current standard of care.

Example: A patient with known episodic gouty arthritis of the great toe, who develops an attack of gout, is not considered to have suffered an AE; the event was known prior to enrollment. A patient who develops a new diagnosis of gout during the study period is judged to have suffered an AE. This is reportable as an AE even though it is most likely entirely unrelated causally to the study drug, but is instead only associated with study drug use temporally.

14.2 Serious adverse event

SAEs are those AEs that require in-patient hospitalization or prolongation of existing hospitalization, which cause congenital malformation, result in persistent or significant disability or incapacity, are life-threatening or result in death. An SAE can also be an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. An SAE is also an event that results in a congenital anomaly or birth defect. SAEs should be managed according to the best current standard of care.

The primary adverse events of interest are symptomatic intracranial bleeding or other major bleeding. The other major adverse events of interest are death and clinically relevant non-major bleeding.

The DSMB may recommend to the SC to stop the trial or amend the protocol at any point based on the rates of symptomatic intracranial or other major bleeding. Potential changes may include altering inclusion criteria or changing timing of initiation of therapy. The DSMB may also recommend stopping the trial or amending the protocol for any other serious medical concerns, including death rate.

14.2.1 Severe adverse event definitions

a) Symptomatic intracranial bleeding

A new symptomatic intracranial hemorrhage OR worsening existing intracranial hemorrhage with a $\geq$33% change in hematoma volume, AND either an NIHSS score

decline of 4 or more points, or a change in level of consciousness as per NIHSS item 1a, AND the clinical change is thought to be attributable to the hemorrhage.

b) Other major bleeding

Bleeding in a critical area or organ, including intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a drop in hemoglobin by 20 g/L or more, leading to transfusion of 2 or more units of whole blood or red cells.

c) All-cause death

Death from any reason.

d) Clinically relevant non-major bleeding

A clinically relevant minor bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of: (a) a hospital admission for bleeding, or (b) a physician guided medical or surgical treatment for bleeding, or (c) a change in antithrombotic therapy (including interruption or discontinuation or study drug).

14.3 Reporting and Review

When AEs are captured on the Adverse Event Report Form of the Case Report Form (CRF), its seriousness, duration, relationship to study drug, action taken, and outcome must be addressed. SAE is defined as an event that results in death, is life threatening, results in hospitalization or prolongs hospitalization, causes severe disability or incapacity, is a congenital anomaly or birth defect, or is medically important.

The reporting period for SAEs includes the entire treatment duration plus 30 days. In cases of permanent discontinuation of study medication, AEs other than outcome events must be reported up to 1 month after the last dose of study medication intake (Safety Visit).

All SAEs, all non-serious AEs leading to permanent discontinuation of study-drug treatment, and any non-serious AEs of particular concern to the investigator will be captured on the CRF. Other non-serious AEs will not be collected due to the large amount of available safety data for the study drugs.

SAEs and all other relevant safety information (as defined in the Investigator Institution Initiated Research [IIR] Agreement) must be reported **immediately by the investigator to the sponsor regardless of severity or causality as soon as possible and no later than 24 hours following knowledge of the SAE**. SAEs will be recorded on the SAE CRF and will be reviewed by the trial medical monitor. SAEs will be reported to the Institutional Research Ethics Board (REB) and Health Canada in accordance to relevant regulations. The sponsor will prepare any required safety reports for regulatory authorities and all active investigators.

Pregnancies occurring in study participants after giving informed consent will be treated procedurally as SAEs and should be reported on the Pregnancy CRF. The pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. For the pregnancy of a male participant's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent. For all pregnancy reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE (i.e., within 24 hours of awareness).

The investigator is responsible for continuing follow-up on all reported SAEs (whether or not related to study drug) until resolution or until the event is considered chronic and/or stable by the investigator, and/or another physician is responsible for the patient's medical care. Follow-up SAEs will be reported according to the same timelines as initial reports, as soon as new significant information becomes available.

The assessment of the causal relationship between an AE and the use of study drug is a clinical decision made by the investigator, who is a qualified physician, based on all available information at the time of CRF completion. The assessment is based on the question whether or not there was a *"reasonable possibility"* that the study drug caused the event. Possible answers are *"yes"* or *"no."*

An assessment of *no* would include the existence of a clear alternative explanation. Other reason for an assessment of *no* may be lack of plausibility (e.g., the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration).

An assessment of *yes* indicates that there is a reasonable suspicion that the AE is associated with the use of the study drug. Factors in assessing the relationship of the AE to study drug include the temporal sequence from drug administration (i.e., the event should occur after the drug is given) and the length of time from drug exposure to event, and should be evaluated in the clinical context of the event. Furthermore, recovery on drug discontinuation (de-challenge), and recurrence on drug re-introduction (re-challenge, if available), underlying, concomitant, or intercurrent diseases should be evaluated in the context of the natural history and course of the disease being treated. In addition, concomitant medication or treatment, the pharmacology and pharmacokinetics of study drug should be considered.

The intensity of an AE is assessed as mild (usually transient in nature and generally not interfering with normal activities), moderate (sufficiently discomforting to interference with normal activities), and severe (prevents normal activities).

Any action on study treatment to resolve the AE is to be documented as: study drug withdrawn, interrupted, dose not changed, not applicable, or unknown. Other specific treatment of AEs will be documented as: none, remedial drug therapy, or other. The outcome of the AE is to be documented as: recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, or unknown.

The sponsor will determine the expectedness of AEs according to the applicable reference document, which for this study is the most current version of the investigator's brochure (IB)/product monograph.

An unexpected AE is any AE whose specificity or severity is not consistent with the IB or product monograph. Also, reports that add significant information on specificity or severity of an already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered "unexpected".

15 Expected Drug Reactions

For expected adverse drug reactions (i.e., with relationship to rivaroxaban or standard of care medications including: UFH, dalteparin, enoxaparin, tinzaparin and warfarin), investigators are directed to the product monographs.

16 Treatment Guidelines for Bleeding/Suspected Bleeding

Participants with bleeding or suspected bleeding will undergo confirmatory laboratory or other testing (e.g., US, CT, MRI) and a (S)AE CRF must be completed. The date and time of bleeding event onset will be recorded on the CRF. Treatment guidelines as outlined here generally conform to normal standards of practice.

For participants with minor bleeding, the study drug may or may not be held at the discretion of the local physician and investigator. A risk/benefit determination should be made (as would be normally done with warfarin) weighing the participant's risk of further bleeding against the participant's risk of thromboembolism and benefit from continued anticoagulation. Minor bleeding should otherwise be managed according to local standard of care.

For participants with clinically significant bleeding, the study drug should generally be held. Bleeding should be managed according to local standard of care and may include measures such as:

- Local measures to stop the bleeding
- Volume resuscitation, and transfusion of blood products as appropriate
- Standard laboratory tests (e.g., hemoglobin, hematocrit, platelet count, INR, PTT)
- Subjects receiving warfarin, UFH and LMWH should be managed according to the local standard of care. The anticoagulant effects of warfarin will be reflected in

the PT/INR and will generally take 3-5 days to return to normal. Warfarin can be reversed with IV vitamin K and prothrombin concentrate complex as per local protocols. UFH may be reversed if necessary using 1 mg protamine sulfate/100 units heparin. With LMWH, protamine will not completely abolish the anti-Xa activity but may neutralize higher molecular weight fractions of heparin at the following doses:

- Enoxaparin within 8h: 1mg protamine/1 mg enoxaparin
- Enoxaparin greater than 8h: 0.5 mg protamine/1 mg
- Dalteparin or tinzaparin: 1 mg protamine per 100 anti-factor Xa units of LMWH

Andexanet alfa, a reversal agent for rivaroxaban, has completed Phase II testing but is not yet approved by Health Canada.[70] Another agent, Ciraparantag (PER977), a small molecule antidote that binds directly and specifically to direct thrombin inhibitors, factor Xa inhibitors, and heparins, has completed Phase I testing but is also not approved.[71]

In the interim, management is as follows:
Given rivaroxaban's half-life of ~5-9 hours, five half-lives, the expected time to full resolution of anticoagulation will have elapsed ~1.5 days after the last dose. Participants receiving rivaroxaban with major bleeding that do not respond to local measures or requiring urgent surgery may be treated with activated 4-factor PCC at 50 units/kg if available, or unactivated 4-factor PCC at a dose of 50-80 units/kg. If a 4-factor PCC is unavailable, a 3-factor PCC can be used; supplementation of 3-factor PCC with Fresh Frozen Plasma has been used to supply factor VII, which is present at minimal levels in 3-factor PCCs.

For participants with life threatening bleeding and significant thrombocytopenia, transfusion of platelets can be considered.

17 Anticipated challenges

CVT is a rare disease and a proportion of patients with CVT (i.e., those pregnant or breastfeeding; approximately 10% of cases[7,72]) are ineligible for the study as DOAC use is contraindicated in these patients. To optimize recruitment, we have: (1) made the eligibility criteria as inclusive as possible, (2) engaged a large number of stroke sites across Canada, with the site PIs' commitments to liaising with additional specialists who may be involved in the care of CVT patients to best ascertain all potential subjects (e.g., stroke neurologist site PI liaising with hematology group); additionally we have liaised with CanVECTOR, a national network of thrombosis investigators, and will invite their membership to participate as PIs for additional sites, and (3) are piloting a model for remote recruitment and follow-up (refer to Section 17.1) at non-tertiary sites using Telemedicine (refer to Section 8.3).

17.1 Beacon-and-satellite Model

Given that only a small percentage (i.e., 5%) of CVT patients need heroic therapy[73] (e.g., endovascular therapy, hemicraniectomy), tertiary stroke centres only receive a proportion of patients with this rare condition. Thus, inclusion of peripheral sites will help to recruit and retain eligible candidates. Approximately 20 tertiary care sites with clinical research infrastructure (i.e., "beacons") will participate, and those peripheral sites with established clinical/Telestroke relationships with beacon sites will be approached to serve as "satellite" sites, where eligible patients will be identified, but recruitment and follow-up will be performed either in person with local travel or over telemedicine by a beacon study coordinator. **This is a novel recruitment model that facilitates engagement from sites that do not have a clinical trials infrastructure, while maximizing ascertainment of a rare condition and optimizing recruitment**. During the lead-in feasibility phase, we will pilot this model in British Columbia (Beacon: Vancouver General Hospital, Satellites: *In-person assessments* – St. Paul's Hospital, Lion's Gate Hospital, Royal Columbian Hospital; *Teleneurology assessments* – Kelowna General Hospital, University Hospital of Northern British Columbia). We hope to extend this strategy to other provinces with a well-established telemedicine network, including Alberta and Ontario.

18 Steering Committee

The SC will meet at least every six months or more often as needed. The Executive SC (i.e., Drs. Field, Hill and Ms. Villaluna) will confer weekly to discuss recruitment, execution, budget and other issues.

19 Statistics and data analyses

A general description of the statistical methods to be used to analyze the feasibility and safety of the study drug is outlined below. A detailed statistical analysis plan (SAP) will be provided in a separate document that will be finalized following the internal pilot period. The SAP will accommodate protocol amendments or unexpected issues in study execution or data that affect planned analyses, and will provide more details on the analytic approaches, coding guidelines, censoring of any time-to-event variables, and output tables and figures.

The primary outcomes for the internal pilot phase are measures of feasibility and will be described with descriptive statistics.

The sample size for the internal pilot will be too small to determine event rates and differences between the arms. However, we will seek to explore any evidence of relative safety or efficacy to justify primary outcome refinement at the time of sample size recalculation. We will perform an exploratory analysis using intention-to-treat with primary hypotheses tested using stratified log-rank test and relative risk estimated with Cox proportional hazards models at study completion.

Receiver operating characteristic curves will be used to determine the degree by which complete vs. partial vs. no venous recanalization is able to discriminate those at risk for the primary outcome (i.e., mRS of 2-6, and "Cognition Total Composite" T-score of -2.5 or below on the NIH Toolbox).

19.1 Measures of Success - Internal pilot phase

1 – Recruitment of 90% of target study sample at 12 months
2 – Retention of 90% of study patients at 365-day follow-up
3 – Demonstration of $\leq$5% rate of the primary outcome in rivaroxaban-treated patients

19.2 Sample Size - internal pilot phase

For the internal pilot period, a convenience sample of 50 patients has been chosen. This sample will allow for the early identification of any major safety concerns and will help to determine more precise rates of the primary safety outcome. Here we are primarily excluding an unacceptably high rate of the primary outcome as compared to current standards of care that would preclude further studies of DOACs for CVT. The designated feasibility sample of 50 patients in the current feasibility study will provide data on recruitment rates, operational feasibility and exploratory treatment effect estimates to refine our calculations.

At present, 16 additional Canadian sites have committed to participating, and recruitment of 50 patients during the first year at Canadian sites would reflect a recruitment rate of 1-3 patients per year per site. We anticipate rates that are 2-3 times higher than this based on the commitment letters from participating sites, and we are also in the process of engaging additional Canadian and international sites.

We expect that the primary outcome for the full study will be the primary safety outcome, although this outcome may be refined following the end of the internal pilot phase.

19.3 Societal Cost and Healthcare utilization valuation

The following equations describe how societal costs will be calculated using the questionnaires. This first equation describes the overall calculation for societal costs. Lost productivity from paid and unpaid work will be multiplied by their respective wage rates and summed over all follow up periods within the trial. Wage rates for paid work will be calculated using B3, B4, B5 *(What was your average income (before taxes)?)* and an average wage rate for unpaid work will be used based on childcare and cleaning.

$$S_c = \sum_a [(LP_p * WR_p) + (LP_u * WR_u)]$$

Where, S_c is the societal cost, a is the follow up periods for each patient, LP_p is the lost productivity over the study period from paid work, LP_u is the lost productivity over the study period from unpaid work, WR_p is the wage rate for paid work, WR_u is the wage rate for unpaid work.

Lost productivity for paid work will be calculated by adding absenteeism and presenteeism. Absentee days will be calculated will be calculated by subtracting the date from PSC2 *(If yes, on what day did you return to work? ___ date)*, from the date of the patient's last follow up assessment. Presenteeism will be calculated by subtracting the date of the next follow up with the date from SC2 *(If yes, on what day did you return to work?),* and then multiplying this by the percent present from PSC3 *(Since you have returned to work, has your performance at work been affected by your CVT or by the residual effects of your CVT?)* or by the ratio of hours worked in perfect health vs. hours worked with a CVT from question PSC4.

Paid:

$$LP_p = D_a + (D_p) * (P)$$

Where LP is the lost productivity over the study period, D_a is the days absent, D_p are the days present at work, and P is the percentage that individuals are present at work.

Unpaid:
To calculate lost productivity for unpaid work, the number of days that individuals were unable to perform unpaid work from USC2 *(On how many days did you feel that way?)*, will be multiplied against USC3 *(How many hours on average would that person spend doing this on these days?).*

$$LP_u = D * H$$

Where LP is the lost productivity over the study period, D_r are the number of days where an individual is unable to perform their unpaid work, and H is the number of hours of unpaid work that they were unable to perform that day.

Informal Care:
To determine the lost productivity from informal care, the hours from USC5 or PSC7 (*Since you were discharged or the last time we spoke, how many hours of care have you received from informal givers? __ hours*) will be multiplied against an average Canadian wage rate.

$$S_{ci} = H_i + WR_G$$

Where S_{ci} is the societal cost due to informal care, H_i is the hours of informal care received by the CVT Patient, and WR_G is the average Canadian wage rate.

Healthcare Utilization Costs:
In order to measure healthcare utilization costs, the amount of healthcare resource consumed by each patient from HU2, HU5, HU8, and HU14 *(How many times have you used this resource since your discharge form hospital or the last time we spoke?)* will be multiplied against the unit cost of that resource for all follow up time periods.

$$HCUC = \sum_{a,i} (HR_i + UC_i)$$

Where $HCUC$ is the healthcare utilization cost, a is the follow up periods for each patient, *i* is each healthcare resource, HR_i is the amount of healthcare resource *i* consumed, UC_i is the unit cost of healthcare resource *i.*

Lost Productivity:
As previously stated, lost productivity as a result of a health condition is relevant when taking a societal perspective to health economic analysis. When patients have returned to work, time taken to attend appointments and perform tests are considered lost productivity. In order to calculate this lost productivity, the amount of healthcare resource will be multiplied by the amount of time it takes a patient to utilize that resource that will be in turn multiplied by the patient's wage rate. Note that Home Care will not be included in this equation since a patient will already be at home, and will not need to travel for their appointment. We are particularly interested in the bloodwork for INR utilization since this will be an incremental difference between the study groups in the trial. To avoid double counting absenteeism and lost productivity due to healthcare resource consumption, the units on healthcare resource consumption will be equally distributed across the follow up period. If a patient returned to work in that follow up period, the number of units consumed post return to work will be estimated and counted as lost productivity. If the patient has not returned to work, they will not experience any lost productivity due to healthcare resource consumption. If they have returned to work in a previous follow up period, all of their healthcare resource consumption will be counted as lost productivity.

$$LP_T = \sum_{a,i} (HR_i * t * WR)$$

Where LP_T is the lost productivity due to travel to healthcare utilization appointments, a is the follow up periods for each patient, *i* is each healthcare resource, HR_i is the amount of healthcare resource *i* consumed, *t* is the amount of time a patient

would have to spend to consume resource HR_i, and WR is the wage rate for the patient.

19.4 Handling of missing data

Every effort will be made to keep missing data, particularly the Day 180 outcome assessments, to a minimum. However, some missing data may be inevitable due to, for example, loss to follow-up, or inability to complete all assessments at a follow-up visit. For the primary analysis for regulatory submission, we will assume that participants missing the primary endpoint data will have not sustained a primary safety outcome. Sensitivity analyses using various imputation techniques will be specified prospectively in the SAP before the database lock for the interim analysis if more than 5% of subject randomized are missing the primary endpoint.

20 Ethics and Confidentiality

20.1 Human Subjects

The Sponsor-Investigator (and any Participating Site Investigators) will ensure that this study is conducted in full conformance with the principles of the Declaration of Helsinki. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the participant.

20.2 Ethics approval

Any subsequent modifications to this protocol and ICF are reviewed and approved by the local REB responsible for oversight of the study. Approval from the committee must be obtained before starting the study, and should be documented in a letter to the Sponsor-Investigator (and any Participating Site Investigators) specifying the date on which the committee met and granted the approval. A signed ICF must be obtained from the participant. For participants who cannot provide consent themselves, a legally authorized representative, or person with power of attorney, may sign the ICF. The ICF describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the ICF must be given to the participant, the legally authorized representative, or the person with power of attorney; and this fact must be documented in the participant's record.

If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated if necessary. All participants (including those already being treated) should be informed of the new information, given a copy of the revised ICF, and give their consent to continue in the study.

20.3 Confidentiality

All imaging, evaluation forms, reports, and other records that leave the site are identified only by the site and participant number to maintain participant confidentiality. All records are kept in a locked file cabinet. Clinical information is not released without written permission from

the participant, except as necessary for monitoring by the REB, regulatory bodies, the sponsor, or the sponsor's designee. The list that links participants to their study ID will be kept securely by the Sponsor.

All study investigators at the clinical sites must ensure that personal identity and medical information of study participants is kept confidential at all times. Country specific privacy regulations, where applicable, must be followed. On CRFs, other study documents, or image materials submitted to the CRU, participants are identified only by study identification codes.

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRFs by the site monitors. Other properly authorized persons, such as the regulatory authorities, may also have access to these records. Personal medical information is always treated as confidential.

21 Conditions for Terminating the Study

The Sponsor-Investigator reserves the right to terminate the study at any time. If this is necessary, the Sponsor-Investigator will work with any Participating Site Investigators to arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor-Investigator (and any Participating Site Investigators) will assure that adequate consideration is given to the protection of the participants' interests.

22 Data Collection, Management, and Monitoring

Data will be housed and managed in a custom database at the Hotchkiss Brain Institute Clinical Research Unit at the University of Calgary (3300 Hospital Drive NW, Calgary AB, T2N 4N1) using regulatory compliant data systems. Only the clinical and research staff directly involved in the study will have access to this data, unless required by a regulatory agency. Study personnel will require a username and password to access the database, approved by the Sponsor-Investigator and respective Site Investigator.

Data from the CRFs will be either faxed or electronically-transferred into DataFax, which is an Electronic Data Capture clinical trial management system. The DataFax application will be downloaded and installed on approved electronic devices, only accessible with an individually-assigned username and password. All study personnel who have database access will receive training on DataFax use and how to comply with security and privacy safeguards.

Designed for studies subject to regulatory review, DataFax includes: electronic signatures, password aging, reuse, complexity and lockout rules, fine-grained user permissions, audit trails, and secure 128 bit SSL encryption of all data and document transmissions over the internet. This is the same encryption process as the majority of secure, global web services like online banking.

All study participants' data and source documents will be kept in a study binder in a locked cabinet inside a locked office at each site. Participants will be assigned a unique study number as a participant in the study. This number will not include any personal identifying information (e.g., Personal Health Number, SIN, initials). Only this study number will be used on any research-related information collected. Only the PI will have access to the list that matches a participant's name to their unique study number and will not be removed or released without the participant's consent, unless required by law. Data will be de-identified as quickly as possible.

22.1 Study Documentation, CRFs and Record Keeping

22.1.1 Investigator's Files/Retention of Documents

The Sponsor-Investigator and Site Investigators must maintain adequate and accurate records to enable the conduct of the study to be fully documented and study data subsequently verified. These documents should be classified into two different separate categories: a) Investigator's Study File, and b) Patient Clinical Source documents.

a) **Investigator's Study File:** The Investigator's Study File will contain protocol/amendments, Case Report and Query Forms, ethics correspondence and governmental approval with correspondence, sample ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents/correspondence. Some or all of these files may be stored electronically.

b) **Patient Clinical Source documents:** Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, diagnostic imaging, pathology and special assessment reports, signed ICFs, consultant letters, and patient screening and enrollment logs.

The Sponsor-Investigator (and any Participating Site Investigators) must keep these two categories of documents on file for 25 years after completion or discontinuation of the study. After that period of time, the documents may be destroyed, subject to local regulations.

22.1.2 Source Documents and Background Data

Site Investigators shall supply the Sponsor-Investigator on request with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In cases of particular problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that participant confidentiality is protected.

22.1.3 Case Report Forms

For each participant enrolled, a CRF must be completed and signed by the Sponsor-Investigator/Site Investigator (or authorized delegate from the study staff). This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the CRF.

All forms should be filled out clearly and legibly. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the Sponsor-Investigator/Site Investigator (or their authorized delegate). The Sponsor-Investigator/Site Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor-Investigator in the CRFs and in all required reports.

22.2 Site Monitoring and Audits

The central trials staff will use trained employees familiar and experienced with clinical trial administration to conduct data monitoring. Data will be checked for completeness, logic, and validity. Queries will be sent to sites to verify data as required. Risk-based monitoring will be used. Details of monitoring will be in a separate site-monitoring plan.

The Sponsor-Investigator and Site Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor-Investigator or designee or to health authority inspectors after appropriate notification. Verification of CRF data must be by direct inspection of source documents.

22.2.1 Data Safety and Monitoring Board

The DSMB will provide periodic safety reviews of the clinical data and will review all outcomes/(S)AEs in real time. A preliminary interim analysis for feasibility will be conducted after 365 days of the launch of the first 8 sites or after 50 patients have been enrolled, whichever occurs first. A second interim analysis for safety will be conducted at approximately two-thirds patient enrolment (n=256). Members of the DSMB will be acknowledged publicly but will not be considered authors for any manuscripts that arise from this trial. The DSMB charter will include the approach to handling feasibility and overwhelming differences in safety and potential imbalance in key prognostic variables. Firewalls will be in place at the Statistical Center to sequester interim results.

23 Patient Engagement Strategy

We will engage people who have experienced CVT and their family members in consultation forums, and will work together to develop a patient advisory group and patient website to support integrated and end-of-study knowledge translation (KT) activities for the study. In addition, we wish to connect patients and their families with one another and with clinicians for information exchange and peer support.

23.1 Patient Forums

We will hold a series of patient/citizen forums to:

a) Consult with people who have experienced CVT and their loved ones to determine those symptoms and outcomes that are most impactful on their QoL
b) Identify barriers to engagement in clinical research for stroke patients in their peak productive years, and/or who reside outside cities with academic research centres, and discuss methods to improve study participation and engagement in clinical research
c) Pilot a telemedicine remote engagement model to engage members at remote sites and seek feedback to optimize this strategy

Potential participants (i.e., patients with an admission diagnosis of CVT) will be identified using clinical practice databases at participating centres and ethics approval will be sought for permission to contact patients for the forum. In order to better understand barriers to engagement, those who decline informed consent will be asked to provide their rationale if they feel comfortable doing so.

23.1.1 Pre- and post-survey

Incorporating feedback from knowledge users (i.e., Dr. Nadeau and Ms. Sadeghi, who are young stroke survivors), we have created a pre-forum survey that will be completed by forum participants prior to the event to help facilitate and prioritize discussion. The survey aims to identify symptoms most relevant to daily function, duration of symptoms after diagnosis, and impact on QoL, and will help to guide forum discussion. Following the forum, participants will be able to revise their responses and give additional feedback about the forum structure and content and remote telemedicine engagement initiative.

23.1.2 Patient forum

We will hold a one-day forum for people who have had CVT and their family members. Given the financial constraints of joining patients from across the country at one forum and to maximize in-person patient engagement we will hold separate one-day forums in six cities across the country: Vancouver, Calgary, Ottawa, Toronto, Montreal (in French) and St. John. Participants unable to travel to the forum will have the opportunity to participate by videoconference.

Each forum will begin with a local patient-citizen or family member discussing their experience after CVT, and then followed by a brief physician-led lay discussion about CVT and opportunities for future and ongoing research. The results of the pre-survey will be presented as a means to facilitate discussion around patient-oriented outcomes for the upcoming clinical trial and clinical practice. We will discuss strategies to optimize patient engagement in research initiatives and discuss potential content for online education, support and engagement resources on the website.

23.2 Patient Advisory Core

Patient-citizens (i.e., Dr. Nadeau, Ms. Sadeghi, Ms. Canfield, and interested participants from the patient forum) will form a patient advisory group that will liaise with the PIs, Steering Committee and publications committee of the study. They will have quarterly videoconferences via WebEx to review ICFs, medication and follow-up instructions, lay content for online resources and suggested content for future patient forums. They will advise on issues related to recruitment, retention, and other patient-centered challenges. They will join the PI in planning meetings with policy-makers (i.e., health services collaborators including Ms. White and Ms. Ramsay from the BC Provincial Stroke Strategy) to discuss patient-centered priority-setting for knowledge dissemination for policy makers and health care professionals at the end of the trial, and will also advise on end-study knowledge dissemination for patient-participants.

23.3 Patient Website

We will develop a patient website integrating feedback from patients and family members to facilitate ongoing KT and research initiatives for patients, clinicians and researchers. Site content will be linked where appropriate to resources from the Canadian Partnership for Stroke Recovery and Canadian Stroke Best Practices. Original content will be developed by interested patients, family members, pharmacists and trainees (i.e., interested residents and postgraduate fellows) and will be peer-reviewed and vetted by the SECRET Patient-citizen advisory committee.

Content will include:

a) Patient and clinician education resources in multiple languages (e.g., English, French, Punjabi, Farsi, Chinese) around CVT, prognosis and pharmacological (e.g., anticoagulants) and symptomatic pharmacological (e.g., antidepressants, seizure medications, analgesics) and non-pharmacological (e.g., wellness strategies including meditation, social engagement and exercise) management
b) Study updates and information regarding clinical research and consultation opportunities
c) Access to treatment guidelines and other peer-reviewed resources
d) Patient discussion forums for online peer support and coordination of face-to-face peer mentorship and support meetings

24 Ancillary Studies Policy

Ancillary or sub-studies may be considered by the trial Executive Committee. Important principles that guide the addition of ancillary studies are:

a) No patient shall be enrolled in a concurrent investigational drug/device trial during the study period.
b) Concurrent enrollment of a SECRET study participant in a site-specific observational cohort study is allowable, where the following conditions are met:
    i. the Executive Committee is notified

ii. the concurrent study does not interfere with any study follow-up procedures or potentially confound the outcome of the SECRET trial
iii. the site PI of the concurrent study explicitly acknowledges that the treatment given in the SECRET trial may confound the outcome of the site-specific concurrent study
iv. the patient may not be included in any publication or report until the SECRET study has been concluded and published.

c) Ancillary or sub-studies shall be vetted and approved by the trial executive committee.

25 Data-sharing plan

The Executive SC will follow the spirit of the NIH policy on data-sharing [http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm]. In addition, the Executive SC will follow the CIHR guidelines on public access to trial results and make the results available as free-access using PubMed. Upon completion of the SECRET trial, a public use database will be prepared by stripping any and all personal identifiers. The public use database, consisting of several data files, should contain: (1) baseline and demographic characteristics; (2) outcomes assessments; (3) CT/MRI data; (4) concomitant medications and procedures; and (5) (S)AEs. Each data file is made available as a formatted SAS dataset or other electronic format. The data files are distributed along with the data dictionary and a brief instruction (i.e., Readme) file. These data files will be made available to the public only after all major manuscripts (i.e., including secondary analysis papers) of the trial are accepted for publication in peer-reviewed journals.

26 Publication and Presentation Policy

The trial executive SC will be co-authors on all publications and presentations. The primary author list for the primary publication will consist of the executive SC and the site PI at each of the sites. The results of this study may be published or presented at scientific meetings.

27 References

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