Protocol Title: A pilot study assessing the feasibility of a randomized controlled trial investigating primary thromboprophylaxis with rivaroxaban in patients with malignancy and central venous catheters: TRIM-Line

Protocol #20180357

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Sponsor	Ottawa Hospital Research Institute
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NCT #	03506815

Confidentiality agreement

This protocol contains confidential information belonging to Drs. Rick Ikesaka and Marc Carrier. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law) nor use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, Dr. Rick Ikesaka or Marc Carrier, The Ottawa Hospital should be promptly notified.

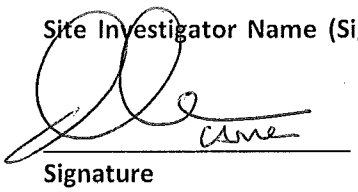
Signature

Dec 12 2019
Date

SIGNATURE PAGE

I have read and understand the protocol and I agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I will work according to the principles of Good Clinical Practice (GCP) as described in the Food and Drug Act, Division 5, Health Canada regulations, The Declaration of Helsinki (2004), and Good Clinical Practice (GCP) as described in the International Council on Harmonisation (ICH) document. Further, I will conduct the study in keeping with local regulatory requirements.

I will provide copies of the protocol and access to all relevant information to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

Site Investigator Name (Printed)	Site Investigator Name (Signature)	
Dr. Marc Carrier		Dec 12 2019
	Signature	Date

Trial Personnel

Investigators

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STEERING COMMITTEE

A Steering Committee comprised of the trial's co-investigators will manage the overall conduct of the trial. Drs. Ikesaka and Dr. Carrier, will regularly review the progress of the trial. The Steering Committee will review how the trial was conducted and review the various outcomes of the trial to determine if the evidence justifies a full randomized trial.

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1. ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ASA	Aspirin
bid	Twice Daily
BP	Blood Pressure
CBC	Complete Blood Count
CVC	Central Venous Catheters
DVT	Deep Vein Thrombosis
LMWH	Low Molecular Weight Heparin
od	Once Daily
po	by mouth
PE	Pulmonary Embolism
SAE	Serious Adverse Event
U/S	Ultrasound
ULN	Upper Limit of Normal
VTE	Venous Thromboembolic Event

2. STUDY SYNOPSIS

Title: A pilot study assessing the feasibility of a randomized controlled trial investigating primary thromboprophylaxis with rivaroxaban in patients with malignancy and central venous catheters (CVC)

Short Title: The TRIM-Line
Protocol Version: 28Feb2018 Version 1.1

Principal Investigators: Dr. Rick Ikesaka and Dr. Marc Carrier
Sponsor: OHRI
Study Centres:

The Ottawa Hospital, General Campus, Ottawa, ON
QEII Health Sciences Centre, Halifax, Nova Scotia
University of Alberta Hospital, Edmonton, Alberta

Timeline: February 2019-September2019

Purpose of Pilot Trial
To determine the feasibility of conducting a multicentre randomized open label-controlled trial evaluating the use of prophylactic dose rivaroxaban to prevent CVC associated venous thromboembolism(VTE) among cancer patients.

Purpose of Full Trial
The purpose of the full trial is to determine the efficacy and safety of prophylactic dose rivaroxaban to prevent CVC associated VTE among cancer patients.

Pilot Trial Endpoints
The primary feasibility outcome for the pilot study is the number of participants recruited per centre per month. We will obtain baseline details of the patient's type, location and treatment of cancer, comorbidities and medications. Secondary feasibility outcomes of the pilot study will include, consent rates, loss to follow up, adherence to therapy defining 80% or greater medication taken as having good adherence to study drug, proportion of screened patients who meet eligibility criteria.

We will document reasons for non-consent in order to assist recruitment for the larger multicentre trial.

Full Trial Endpoints
For the full multicentre trial the outcomes would be as follows: primary outcome symptomatic, radiographically confirmed VTE. Secondary outcomes include major and clinically relevant non-major bleeding (CRNMB), CVC life span, premature CVC removal, CVC lumen occlusion, CVC associated infection and death.

Design
This is a pilot study to be conducted at 3 Canadian Centres. The Ottawa Hospital, QEII Health Science Centre and University of Alberta Hospital. It is an open label randomized controlled trial.

Consenting participants, meeting eligibility criteria will be randomized at the time of enrollment to one of two groups.

Rivaroxaban 10mg po daily x 90 days
OR
Observation

Participants in the treatment arm will have study drug dispensed at Day 1 and take medication for 90 days. Follow up visits (in person or phone) will occur at Day 30 (+/- 3 days) and Day 90 (+/- 3 days) month and 3 months post enrollment. Overall, participants will be followed for 3 months. Adverse events will be collected for the first 90 days.

Number of participants

100

Inclusion and Exclusion Criteria

Inclusion criteria:

Patients 18 years of age or older with a new or existing diagnosis of cancer with a CVC inserted in the last 72 hours.

Exclusion criteria:

1) CVC in place for >72 hours
2) Patient requires anticoagulation for other indication
3) Concomitant use of dual antiplatelet therapy
4) Prior VTE
5) Major bleeding event in the last 6 weeks
6) Patient on concomitant medication with known interaction with rivaroxaban (eg. CYP3A4 inhibitor)
7) Pregnancy (documentation of use of effective contraception if sexually active or negative B- Hcg required)
8) Known renal failure, based on Creatinine clearance <30 mL/min (Cockroft-Gault) (in the previous 3 months)*
9) Documented severe liver disease (eg. acute clinical hepatitis, chronic active hepatitis, cirrhosis or ALT >3ULN) (in the previous 3 months)*
10) Known thrombocytopenia < 50x 10^9/L (in the previous 3 months)*
11) Allergy to rivaroxaban
12) Life expectancy <6 months
13) History of condition at increased bleeding risk including, but not limited to:
    a) Major surgical procedure or trauma within 30 days before the randomization visit
    b) Clinically significant gastrointestinal bleeding within 6 months before the randomization visit
    c) History of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding
    d) Chronic hemorrhagic disorder
    e) Known intracranial neoplasm, arteriovenous malformation, or aneurysm
    f) Sustained uncontrolled hypertension: systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg
14) Primary malignancy diagnosis of basal cell or squamous cell carcinoma of the skin or acute leukemia or myelodysplastic syndrome
15) Geographic inaccessibility
16) Refused or unable to obtain consent

* Baseline platelet count for inclusion/exclusion to be drawn within 2 weeks of enrolment.

SCHEDULE OF MANDATORY EVENTS

	Screening, Baseline and Randomization	Day 30 +/- 3 days	Day 90 +/- 3 days
Consent	√		
Inclusion/Exclusion	√		
Demographic	√		
Randomization	√		
Labs	√		
History	√		
Cancer Treatments	√		
Dispense IP (Group 1)	√		
Concomitant Medications	√	√	√
IP Compliance		√	√
Outcome Information (Section 4.5)		√	√
Adverse Events		√	√

3. STUDY RATIONALE AND BACKGROUND

3.1 WHY IS A RANDOMIZED CONTROLLED TRIAL NEEDED?

Venous thromboembolism is a common but potentially fatal disease. A subtype of VTE, upper extremity deep vein thrombosis (UEDVT) accounts for approximately 4-11% of all VTE but unlike lower extremity deep vein thrombosis, UEDVT are poorly described and their risk and optimal treatment are not known (1). Many patients with cancer require insertion of a CVC in order to maintain venous access, administer chemotherapy, draw blood work and provide supportive care. UEDVT seems to be a frequent complication of CVC in this patient population receiving chemotherapy (3).

Pharmacologic thromboprophylaxis has been shown to be effective in reducing VTE in other high-risk populations such as hospitalized medical patients, those that have had hip or knee arthroplasty and in myeloma patients receiving immunomodulatory drugs (4, 5). While thromboprophylaxis is recommended in high risk cancer subgroups (e.g. hospitalized medically ill, post-major abdominal surgery, etc.) (6), it is not routinely recommended for the prevention of CVC associated VTE in outpatients with cancer. Previous comparative studies have not shown consistent clinical benefits (7-9).

3.2 WHY IS A CLINICAL TRIAL NEEDED NOW?

A recent meta-analysis by D'Ambrosio et al. suggests that prophylactic anticoagulation might reduce the risk of UEDVT in this high-risk patient population but notes heterogeneity in study results and highlights the need for a large prospective randomized trial in order to definitively answer this question (10).

Rivaroxaban is an oral factor Xa inhibitor with predictable pharmacokinetics that obviates the need for routine laboratory monitoring (11). The use of prophylactic rivaroxaban has been studied and proven efficacious to reduce VTE complications in other high-risk populations (post hip and knee arthroplasty, secondary prevention of VTE, etc.) (12). Furthermore, it is also currently under investigation in other high-risk cancer subgroups (CASSINI-Clinicaltrials.gov NCT02555878) (13). Until recently, the only options for pharmacologic prophylaxis were either a costly daily injection or warfarin which is difficult to manage safely in the context of cancer and chemotherapy. The convenience of an oral medication which does not require laboratory monitoring and its relatively short half-life are positive attributes which position rivaroxaban very well as an ideal agent for thromboprophylaxis of patients with cancer and a CVC (11). These qualities may potentially alter the risk versus benefit ratio of thromboprophylaxis use in favor of anticoagulation.

3.3 PRINCIPAL RESEARCH QUESTION

To assess the feasibility of conducting a multicentre randomized open label trial using Canadian centres and to assess the safety and efficacy of rivaroxaban to prevent CVC associated VTE among cancer patients.

3.4 WHY IS A PILOT RCT NEEDED BEFPRE A FULL RCT CAN BE COMPLETED?

Recruitment of patients to a prophylaxis study which would add an additional medication and potentially further burden or complicate their care, may be challenging as patients may feel overwhelmed or be unwilling to accept the bleeding risks for a condition which they currently do not have. Thus, a pilot trial to assess feasibility of the larger RCT is needed first.

3.5 WHY IS AN OPEN-LABEL TRIAL DESIGN CHOSEN?

The current standard of care in most cancer patients is to not use outpatient thromboprophylaxis. Patients often receive thromboprophylaxis only when admitted to hospital or subject to additional risks. Not using a placebo tablet reduces study expense and complexity while improving patient acceptance and potentially enrollment into the trial. Since the primary endpoints in the larger planned multicentre study are objective, imaging confirmed thrombosis and bleeding outcomes and not expected to be adversely affected with an open label design.

4. TRIAL OBJECTIVES AND DESIGN

4.1 TRIAL PURPOSE

To determine the feasibility of conducting a multicentre randomized controlled trial comparing rivaroxaban at a prophylactic dose of 10mg daily versus standard of care (no prophylaxis) in patients with confirmed malignancy and insertion of a central venous catheter.
With the large sample size calculated to be required to demonstrate a difference using this intervention, confirmation of the ability to meet minimum recruitment rates is required prior to a launch of a large multicentre trial.

The overall goal of the full randomized trial is to demonstrate the safety and efficacy of using low dose rivaroxaban prophylaxis at preventing upper extremity venous thrombosis in patients with a diagnosis of malignancy and insertion of a central venous catheter.

4.2 TRIAL DESIGN

TRIM-Line is an open-label, randomized controlled feasibility pilot trial comparing rivaroxaban 10mg po daily vs standard of care (no treatment) in patients with active cancer and indwelling CVC. This will involve 3 centres, Ottawa as the coordinating centre, Halifax and Edmonton. Cancer patients with insertion of CVC will be eligible.
While the primary outcome is feasibility based clinical data will be collected using the same methodology as the proposed full-sized trial. Should there be no major changes to the trial design based on the findings of this pilot study's feasibility data that would render the collected data inappropriate for inclusion, the clinical data collected during this trial will be included in the primary and secondary analysis for the full trial.

4.3 TRIAL INTERVENTION

Eligible and consenting patients will receive rivaroxaban 10 mg tablets to be taken once daily, starting within 72 hours of CVC placement. Randomization will occur in a 1:1 ratio via a central web-based randomization system.

The study drug will be continued until the CVC is removed, until one of the study outcomes is achieved, or until the end of the follow-up (90 Days +/- 3 days). Study medication will be held if the platelet count is 50 x 10^9/L or less, the CrCl falls below 30mL/min, the patient experiences bleeding or the patient is required for treatment of cancer to start on a medication or chemotherapy which has a major interaction with rivaroxaban. All patients will be followed for 90 days (+/-3 days), unless they die or withdraw permission for follow up. At the end of the trial, VTE prophylaxis will be left to the discretion of the local investigator.

4.4 ELIGIBILITY

Inclusion and Exclusion Criteria

Inclusion criteria:

Patients 18 years of age or older with a new or existing diagnosis of cancer with a CVC inserted in the last 72 hours.

Exclusion criteria:

17) CVC in place for >72 hours
18) Patient requires anticoagulation for other indication
19) Concomitant use of dual antiplatelet therapy
20) Prior VTE
21) Major bleeding event in the last 6 weeks
22) Patient on concomitant medication with known interaction with rivaroxaban (eg. CYP3A4 inhibitor)
23) Pregnancy (documentation of use of effective contraception if sexually active or negative B- Hcg required) **
24) Known renal failure, based on Creatinine clearance <30 mL/min (Cockroft-Gault) (in the previous 3 months)*
25) Documented severe liver disease (eg. acute clinical hepatitis, chronic active hepatitis, cirrhosis or ALT >3ULN) (in the previous 3 months)*
26) Known thrombocytopenia < 50x 10^9/L (in the previous 3 months)*
27) Allergy to rivaroxaban
28) Life expectancy <6 months
29) History of condition at increased bleeding risk including, but not limited to:
    g) Major surgical procedure or trauma within 30 days before the randomization visit
    h) Clinically significant gastrointestinal bleeding within 6 months before the randomization visit
    i) History of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding
    j) Chronic hemorrhagic disorder
    k) Known intracranial neoplasm, arteriovenous malformation, or aneurysm
    l) Sustained uncontrolled hypertension: systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg
30) Primary malignancy diagnosis of basal cell or squamous cell carcinoma of the skin or acute leukemia or myelodysplastic syndrome
31) Geographic inaccessibility
32) Refused or unable to obtain consent

** Women of child-bearing potential will be asked to have a baseline pregnancy test done. She must agree to ongoing pregnancy testing during the study, and after end of study therapy. This applies even if the subject practices true abstinence from heterosexual contact. She must either commit to true abstinence from heterosexual contact (which must be reviewed at subsequent study visits and source documented) or agree to use and be able to comply with highly effective

contraception without interruption, during the study therapy (including dose interruptions), and for 30 days after discontinuation of study therapy.

Male subjects must practice true abstinence (reviewed at subsequent study visits) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 30 days following investigational product discontinuation, even if he has undergone a successful vasectomy.

Acceptable methods of contraception include: combined (estrogen and progestogen containing) hormonal contraception: oral; Intravaginal; transdermal; progestogen-only hormonal contraception associated with inhibition of ovulation: oral; Injectable hormonal contraception; Implantable hormonal contraception; placement of an intrauterine device; placement of an intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner.

4.5 WHAT ARE THE MEASURED OUTCOMES FOR THE PILOT STUDY?

The primary feasibility outcome for the pilot study is the number of participants recruited per centre per month. We will obtain baseline details of the patient's type, location and treatment of cancer, and medications. Secondary feasibility outcomes of the pilot study will include, consent rates, loss to follow up, adherence to therapy defining 80% or greater medication taken as having good adherence to study drug, proportion of screened patients who meet eligibility criteria. We will document reasons for non-consent in order to assist recruitment for the larger multicentre trial.

For the full multicentre trial the outcomes would be as follows: primary outcome of symptomatic, radiographically confirmed VTE. Secondary outcomes include major and CRNMB, CVC life span, premature CVC removal, CVC lumen occlusion, CVC associated infection and death.

4.6 SCREENING

Participants will be screened within 72 hours of CVC insertion.

4.7 RANDOMIZATION

Consenting subjects will be randomized at 1:1 ratio to treatment or non-treatment arms at study enrollment with treatment allocation determined by central web-based randomization. Randomization will be stratified by gender and the type of central venous catheter (Peripherally Inserted Central Catheter or Hickman/Port-a-Cath/Central line).

Participants will be randomized once the participant has consented and all eligibility criteria have been confirmed.

Randomization will be conducted using a customized web-based program developed for this study. The randomization process will be initiated by the local study coordinator who will access

the web-based system and enter the patient's unique identifier and confirmation of eligibility and informed consent. Specific patient allocation will then be electronically delivered, to the research pharmacy who will prepare and dispense trial medication.

4.8 TREATMENT ARMS

Treatment Arm 1: Experimental

Rivaroxaban 10 mg po daily for 90 (+/-3) days. After the Day 90 follow up, the study treatment will be discontinued, and subsequent treatment will be at the discretion of the attending physician.

Treatment Arm 2: Standard of care

No rivaroxaban prophylaxis. Management will be at the discretion of the attending physician.

4.9 PROHIBITED MEDICATIONS DURING THE STUDY

Systemic treatment with strong CYP 3A4 and P-glycoprotein inhibitors (such as ketoconazole, itraconazole, posaconazole, or ritonavir) is a contra-indication to treatment with rivaroxaban and is therefore an exclusion criterion for study entry.

If a participant in the rivaroxaban arm requires initiation of treatment with strong CYP 3A4 and P-glycoprotein inhibitor while on study treatment the participant will be withdrawn from study treatment. The participant may then be switched to an alternative anticoagulant treatment at the discretion of the attending physician.

4.10 PRODUCT LABELLING

Rivaroxaban will be purchased through the research pharmacy and relabeled for this trial according to the template below. Each participant in the treatment arm will be given a 93-day supply of study drug (according to the randomization scheme) at Day 1.

Product information for each of the study medications is listed in Appendix 4.

Rivaroxaban 10 mg Expiration: DD-MMM-YYYY Store at room temperature between +15°C and +25°C Lot # ------- Protocol : TRIM-Line Trial Sponsor: The Ottawa Hospital Research Institute, 725 Parkdale Ave, Ottawa ON K1Y 4E9 Investigational drug -- to be used only by a qualified Investigator	Rivaroxaban 10 mg Expiration: JJ-MM-AAAA Conserver à l'air ambient, entre +15°C et +25°C, Lot # ------- Nom du Protocole: TRIM-Line Trial Commanditaire: Institut de recherche de l'Hôpital d'Ottawa 725 Parkdale Ave., Ottawa ON K1Y 4E9 Médicament expérimental -- à être utilisé seulement par un Investigateur qualifié

4.11 ACCOUNTABILITY AND STORAGE

Study drug will be stored and maintained by the Clinical Trial pharmacy technicians at The Ottawa Hospital. Bulk accountability logs and individual accountability logs will be completed and maintained by the pharmacy technicians. Participants will keep a medication diary. Drug accountability (pill count & review of diary) will be done on Day 90 +/- 3 days when the medication is returned.

Participants will be counseled to keep the study drug in room temperature conditions. The study medication which they take home should not be exposed to extreme temperatures.

4.12 INDIVIDUAL PARTICIPANT COMPLIANCE

Participants will be given a diary and will record the date and time of administration of each dose. If a dose is missed the participant should take it as soon as it is remembered and record the time. The next dose should be taken at the new time. Non-adherent participants may be removed from the study at the discretion of the primary investigator. In order to allow drug accountability by research staff participants will be instructed to return all bottles of study medication.

4.13 CONCOMITANT MEDICATIONS

Concomitant use of antiplatelet agents or NSAIDS must be documented in the patient's study record and carefully monitored by the treating physician/site investigator. The use of dual antiplatelet therapy is an exclusion to participation in this study.

4.14 PROPOSED FREQUENCY AND DURATION OF FOLLOW UP

In addition to the initial enrollment visit, patients that are enrolled will receive a telephone follow up at Day-30 +/- 3 days and an in person follow up at Day 90 +/- 3 days.

Post-enrollment follow up visits will include assessment and history for major and minor bleeding, CVC life span, premature CVC removal, CVC lumen occlusion, CVC associated infection and death and assessment of adherence to study drug. Patients will be followed for 90 days +/- 3 days.

4.15 WITHDRAWAL OF SUBJECTS

A subject has completed the study once all follow-up procedures have been completed. Study drug is discontinued, and appropriate clinical management is initiated in the case of the following outcome events (as defined in section 4.5).

For the subjects who reach a study endpoint, subsequent treatment will be left up to the discretion of the treating physician and documented.

If the subject is prematurely discontinued from participation in the study, the study personnel will make every effort to obtain, and record, information about the reasons for discontinuation and any adverse events and if possible perform all safety assessments.

A subject may voluntarily withdraw participation in this study at any time, including for future data collection. If the subject does not return for a scheduled visit, every effort will be made to contact the subject. In any circumstance, every effort will be made to document the reason for withdrawal and when possible, all safety assessments will be done.

All data will be reported for any subject randomized and not completing the study. Subjects withdrawn as a result of an adverse event thought to be related to the study drug will not be replaced. All safety data collected from all subjects during the study will be analyzed.

5 SAFETY

The adverse event reporting period will begin with the first dose of study medication and end on Day-90 +/- 3 days. Adverse events may be collected from participant report or by review of the clinical chart. Adverse events will be documented in the CRF.
Clinical investigators and ultimately the Qualified Investigator (QI) have the primary responsibility for adverse event identification, documentation, grading, assignment of attribution and reporting.

5.1 DEFINITIONS

Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a participant administered at least one dose of study medication; the event does not necessarily have a causal relationship with that treatment or usage. All adverse events (see exception for cancer-related chemotherapy below) will be reported

An adverse event can therefore be:

- All suspected adverse medication reactions.
- All reactions from medication abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness (definition below).
- Injury or accidents.
    - **Note** that if a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) will be reported as two separate AEs.
- Abnormalities in physiological testing or physical examination (findings that require clinical intervention or further investigation beyond ordering a repeat [confirmatory] test).

- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g., elevated liver enzymes in a subject with jaundice) will be described as a separate AE.

Serious Adverse Events

Serious Adverse Event (SAE)

- An event that results in death
- An event that places the participant at immediate risk of death (a life-threatening event). This does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires participant hospitalization or prolongation of existing hospitalization. For this study, the following exceptions apply to the index hospitalization:
  - Hospitalization for routine administration of chemotherapy/radiation therapy or monitoring of chemotherapy/radiation therapy side effects will not be recorded as a serious adverse event.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/ birth defect
- Other medically important events that, in the opinion of the Site Investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above.

Some conditions may not be immediately life threatening or require hospitalization. Should the investigator feel that the event may jeopardize the participant or may require intervention to prevent more serious outcomes, then it should be treated as serious.

Pre-Existing Conditions

In this trial, a pre-existing condition (i.e., a disorder present before the adverse event reporting period started) should not be reported as an adverse event unless the condition worsens during the adverse event reporting period.

Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event.

Laboratory Test Abnormalities

Laboratory test value abnormalities will be reported as an AE if they satisfy one or more of the following conditions for clinical significance:

1. Accompanied by clinical symptoms
2. Leading to a change in study medication (e.g. Dose modification, interruption or permanent discontinuation)
3. Requiring a change in concomitant therapy (e.g. Addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

Please note: any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an adverse event in the CRF.

GRADING OF ADVERSE EVENTS

All adverse events will be graded by the Investigator using the scale below.

1=Mild	Discomfort noticed but no disruption of normal daily activity
2=Moderate	Discomfort sufficient to reduce or affect daily activity
3=Severe	Inability to work or perform normal daily activity

CAUSALITY

Relationship of all adverse events and serious adverse events to the study interventions (causality) should be assessed by the investigator as follows:

- **Unrelated:** There is not a reasonable possibility that the adverse event may have been caused by the study drug.
- **Possibly related**: The adverse event may have been caused by the study drug, however there is insufficient information to determine the likelihood of this possibility.
- **Related**: There is a reasonable possibility that the adverse event may have been caused by the study drug.

EXPECTEDNESS

Adverse events and serious adverse events will also be assessed according to the following categories:

- **Expected (anticipated):** the event is identified in nature, severity, or frequency in the investigator brochure, product monograph or in the protocol.
- **Unexpected (unanticipated):** the event is not identified in nature, severity, or frequency in the investigator brochure, the product monograph or in the protocol.

CANCER RELATED AES

For this study, adverse events that are possibly related or related to cancer and its treatment will not be recorded as an adverse event. However, if the cancer related event meets the criteria of a SAE, the event will be recorded and reported accordingly regardless of the causality. These include but are not limited to:

- Nausea
- Vomiting
- Changes in bowel function – including constipation, diarrhea, bloating or flatulence
- Abnormal white blood cell count
- Urinary symptoms
- Appetite changes
- Fatigue or lethargy
- Hair loss
- Mouth or throat changes
- Weight loss
- Confusion or altered level of consciousness
- Progression of cancer

5.2 RECORDING, REPORTING AND FOLLOW -UP OF ADVERSE EVENTS

Adverse Events Recording

Adverse events will be recorded on the CRF.

The investigator and delegates will record all directly observed adverse events and all adverse events spontaneously reported by the participant. In addition, each participant will be questioned about adverse events at each visit.

Adverse Events Reporting

The QI or delegate will be responsible for reporting the AEs to the OHSNREB, and the Data and Safety Monitoring Board (DSMB) as follows:

- Adverse events will be reported to the OHSNREB as per their guidelines
- Adverse events will be summarized in a table and provided to the Data and Safety Monitoring Board (DSMB) before DSMB meetings.

Serious Adverse Events Reporting

SAEs require prompt or immediate reporting to the QI or delegate. The QI is ultimately responsible for reporting the SAEs to Health Canada, the OHSNREB, the Data and Safety Monitoring Board and Bayer.

Reporting to Health Canada

Serious adverse events that are both unexpected and related or possibly related are subject to expedited reporting to Health Canada. SAEs that are expected or that are unrelated to the study drug are not reportable.

All sites will report to the coordinating centre and the sponsor of the trial will be responsible for reporting the SAE to Health Canada

Report must be filed in the cases:

I. where the SAE is neither fatal nor life-threatening; within 15 days after becoming aware of the information
II. where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information

Within 8 days after having informed Health Canada of the SAE, the Qualified investigator will submit as complete as possible, a report which includes an assessment of the importance and implication of any findings.

Each SAE which is subject to expedited reporting should be reported individually using the TRIM-Line form (see Appendix).

Any updated follow up information that becomes available regarding the SAE should be reported in a follow up report.

Reporting to the OHSNREB

All SAEs will be reported to the OHSNREB as per their guidelines.

Reporting to the Data Safety Monitoring Board (DSMB)

SAEs that are related or possibly related and unexpected will be reported immediately to the Chair of the DSMB.

All SAEs, whether related to the study interventions or not will be summarized in a table, and provided to the DSMB before each scheduled DSMB meeting.

Reporting Procedures for Adverse Events by all sites			
Gravity	**Reporting Time**	**Report to**	**Type of Report**
Serious (fatal or life-threatening) if unexpected and	Immediately	1) Local REB 2) PI (Ottawa/coordinating Centre) by fax and email	Initial Report
	Within 7 days post initial		Follow-up/Final Report
related/possibly related)	report then every 15 days if		
Serious (non-fatal or non-life-threatening) whether expected/unexpected or related/unrelated)	Within 24 hours	1) Local REB 2) PI (Ottawa/coordinating Centre) by fax and email	Initial Report
	Within 15 days post initial report then every 15 days if ongoing until end of event		Follow-up/Final Report
AEs	7days	1) PI (Ottawa/coordinating Centre) by entering in	Adverse Event Form in eCRFs

NOTE: In the rare event that the investigator does not become aware of the occurrence of a SAE immediately (e.g., if a trial participant initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document his/her first awareness of the AE.

Adverse Events Follow-Up

Follow-up of adverse events considered related or possibly related to study drugs should continue until they have returned to baseline status or stabilized, or the causal relationship has been changed from related to unrelated to study drug.

Stopping Rules

The study has no formally defined stopping rules. Data will be monitored as they accumulate, and the use of the experimental therapy will cease if there is clear evidence of rivaroxaban-related adverse events or of a lack of efficacy. This decision will be at the discretion of the DSMB

5.3 MANAGEMENT OF MAJOR BLEEDING

All participants with major bleeding (ISTH definition) will have study drug held until judged safe to resume by the investigator.

Treatment Arm

In the event of hemorrhagic complications in a participant receiving rivaroxaban, treatment should be temporarily discontinued, and the source of bleeding investigated. Rivaroxaban has a half-life of approximately 5 to 13 hours. Consideration should be given to the resumption of anticoagulant therapy at the discretion of the treating physicians, when clinically appropriate to adequately control risk of underlying thrombosis.

Management of bleeding should be individualized according to the severity and location of the bleeding. Appropriate symptomatic treatment should be used as needed, such as mechanical compression (eg, for severe epistaxis), surgical hemostasis with bleeding control procedures, fluid replacement and hemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anemia or coagulopathy) or platelets.
If bleeding cannot be controlled by the above measures, consider administration of prothrombin complex concentrate (PCC). However, there is currently only very limited experience with the use of these products in individuals receiving rivaroxaban. A specific antidote for rivaroxaban is not available.

Non-treatment arm

Management of bleeding will be at the discretion of the attending physician.

6 STUDY MONITORING

6.1 MONITORING

The investigator/institution will permit trial-related monitoring, audits, REB review and regulatory inspections(s), and will provide direct access to source data/documents as required.

The multicentre research coordinator will be responsible for the training of research staff and conducting monitoring visits in the anticipated 3 centers. Remote monitoring methods will be used. An initiation teleconference will be performed in each center before commencement of the trial. Monitoring at each center will be performed to ensure that patient safety, study procedures, and data collection are performed in accordance with the research protocol and GCP/ICH guidelines. The detailed monitoring plan can be found in the resource manual.

7.2 DATA AND SAFETY MONITORING BOARD

The DSMB will be comprised of clinicians and methodologists who are independent of the sponsor and study investigators but have experience with clinical trials and can be relied upon to exercise good judgment in weighing the potential risks and benefits to patients as data accumulate in the trial. The committee will review data on a regular basis for monitoring safety

of the patients exposed to the study medication. The DSMB will have an independent associated statistician who will receive study data from the central database and will remain independent of the trial management team.

7 PROTOCOL DEVIATIONS/VIOLATIONS

Study related procedures must be conducted in compliance with the protocol, amendments, regulations and guidelines, in order to ensure participant safety and data integrity. Any deviations from the protocol, or violations of the protocol, will be accurately documented, reported and reconciled.

7.1 PROTOCOL DEVIATIONS

Protocol deviations refer to incidents involving non-compliance with the protocol that are unlikely to have a significant impact on the participant's rights, safety or welfare, or on data integrity. Examples of deviations include: forgetting to complete a procedure at a specified visit (weight, missing lab value, etc.).

If a protocol deviation occurs the following procedures will be followed:

- The local investigator or delegate will document and explain any deviation from the approved protocol
- Deviations from the protocol must be reported in the study source document
- Deviations will be reviewed during monitoring visits.

7.2 PROTOCOL VIOLATIONS

Protocol violations refer to more serious incidents involving non-compliance with the protocol that may result in significant effect on the participant's rights, safety, or welfare or data integrity.

Protocol violations could result in the participant being excluded from the eligibility analysis and/or result in the participant being discontinued from the trial. Examples of violations include: non-compliance with inclusion/exclusion criteria and dosing administration.

If non-compliance is identified, the following procedures will be followed:

- All protocol deviations will be recorded in a log
- The site investigator or delegate will notify the coordinating centre in Ottawa as soon as possible after discovering the violation.
- The site investigator or delegate will document: the details and reason for the protocol violation. The documentation will also include an assessment by the site investigator with regards to the impact of the protocol deviation on the participant or trial data. Follow-up procedure and corrective action to prevent future violations will also be documented.
- Violations will be recorded in the study source document and on the protocol violation form

- All violations will be reported to the local research ethics board (according to local policies)
- All violations will be reported and reviewed by the Data and Safety Monitoring Board.

8 STATISTICS

8.1 STATISTICAL AND ANALYTIAL PLANS

8.1.1 ANALYSIS OF BASELINE CHARACTERISTICS

Descriptive statistics will be used to examine the baseline characteristics of excluded subjects and those in the experimental and standard of care arm. Standard deviations will be reported for all characteristics expressed as continuous variables. Medians and ranges will be presented for discrete data.

8.1.2 PILOT TRIAL PRIMARY ANALYSIS

The primary analysis will involve a simple estimate of the mean monthly recruitment rate per site along with the 95% confidence interval of the mean.

8.1.3 PILOT TRIAL SECONDARY ANALYSES

Proportions with 95% confidence intervals will be calculated using Wilson's score method for the following secondary analyses: 1) proportion of screened subjects who meet eligibility criteria, 2) proportion of eligible subjects who provide consent, 3) proportion of withdrawals/losses to follow-up among randomized subjects, 4) proportion of sites requiring >18 months to obtain all required approvals/contracts from time of delivery of all study documents, and 5) proportion of crossover between study arms. Reasons for non-consent will be collected and analyzed using qualitative thematic analysis.

8.1.4 FULL TRIAL ANALYSES

Primary analysis: Analysis will be performed by intention to treat. Intention to treat analysis will be supplemented by a sensitivity analysis that excludes subjects who did not complete the allocated treatment plan. Primary outcome event rates will be compared in the experimental and standard of care arm by an unadjusted Fisher's test of proportions, with 95% confidence intervals provided.

Secondary analysis: Analysis will be performed by intention to treat. Intention to treat analysis will be supplemented by a sensitivity analysis that excludes subjects who did not complete the allocated treatment plan. Proportions will be compared between study arms by an unadjusted Fisher's test, with 95% confidence intervals reported. The following outcomes will be analyzed:

symptomatic VTE, symptomatic ATE, major bleeding, CRNMB, non-major non-CRNMB, medication intolerance/reaction, and all-cause mortality.

8.2 DETERMINATION OF SAMPLE SIZE

Using an alpha=0.05, 80% power and event rate estimates of 6.8% in the untreated and 3.7% in the treated population, the estimated sample size would be 860 patients per arm or 1720 patients in total for the full trial. Estimating a 10% lost to follow up this would lead to a required sample of 1892 patients. Enrollment data, event rates, and study drop out will be assessed in this pilot trial will aid in the calculation of the required sample size for the full trial. Due to the low event rates, small differences in the event rates in either patient population will lead to large changes in the sample size required.

For the purposes of the pilot the target sample size is 100 patients with plans to run the pilot trial for1 year. This would involve 4-6 enrollments/month at the coordinating centre in Ottawa, and 2 enrollments per month at the sites of Halifax and Edmonton.

9 ETHICS

9.1 ETHICAL CONDUCT OF THE TRIAL

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly (Helsinki, Finland, 1964 and later revisions), the Tri-Council Policy Statement and the ICH GCP Guidelines.

9.2 RESEARCH ETHICS BOARD (REB)

This study will be and approved with annual renewal by the Ottawa Health Science Network Research Ethics Board. REB approval will be obtained from all other participating centres prior to initiating the study at these sites.

9.3 SUBJECT INFORMATION AND CONSENT

The investigator, or his designee, will inform each subject (or the subject's acceptable representative) prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The subjects must be informed about their right to withdraw from the trial at any time. Written subject information will be given to each subject before enrolment.

Furthermore, it is the responsibility of the investigator or his designee to obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from all subjects prior to inclusion in the trial.

10 DATA HANDLING AND RECORD KEEPING

10.1 PERSONAL HEALTH INFORMATION

Personal health information including Case Report Forms, evaluation forms, reports, etc. will be kept strictly confidential. All records will be stored on-site in a secure, locked facility. Records will be destroyed after 25 years, in accordance with Health Canada Regulations.

10.2 CASE REPORT FORMS

A Case Report Form (CRF) is required and will be completed for each randomized subject. The completed original CRFs are the sole property of The Ottawa Hospital and are not to be made available in any form to third parties, except for authorized representatives of appropriate Regulatory Authorities.

10.3 RECORD RETENTION

To enable evaluations and/or audits, the investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs and detailed records of drug disposition. To comply with international regulations, the records are to be retained for 25 years.

11 STUDY DISSEMINATION PLAN

The results of our trial will be used by the investigators to evaluate the feasibility of a larger trial evaluating the role of the prophylactic dose rivaroxaban to reduce upper extremity DVT in cancer patients with central venous catheters. The results will provide justification to external funding agencies before a commitment is made to fund a full trial. Regardless of the results of the trial, we will strive to publish and present our data and conclusions about feasibility such that future researchers might benefit from this work.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. It is the responsibility of the QI to register this trial in an acceptable registry on or before patient enrollment.