

Comparison of Oral anticoagulants for extended Venous
Informed Consent Form

NCT03196349

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Consent to Participate in a Research Study

Title of Study: Comparison of Oral anticoagulants for extended Venous
Thromboembolism (COVET)

Investigator: *[name of site PI, contact information for PI and study team:]*

WHAT ARE SOME GENERAL THINGS TO KNOW ABOUT RESEARCH STUDIES?

You are being asked to take part in this research study because you have venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). Research studies include only those people who choose to take part. Your participation is voluntary. Please read this consent form carefully and take your time when making your decision about whether to participate. When your study doctor or a study staff member talks with you about this consent form, ask that person to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are described in this document.

Please tell the study doctor or a study staff member if you are taking part in another research study.

WHO WILL PROVIDE FUNDING?

Dr. Thomas Ortel of Duke University is the sponsor of the trial. The Patient-Centered Outcomes Research Institute (PCORI) is funding this trial. The funds from PCORI are paying *[Site PI]* and the doctor's research staff to do this study.

WHO WILL BE MY STUDY DOCTOR?

If you decide to take part in the study, *[Site PI]* will be your study doctor. The study doctor may be in contact with your regular doctor while you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?

Venous thromboembolism (VTE) is a medical problem involving blood clots forming in the veins. When a clot forms in in a deep vein (usually in the leg) it is called a deep vein thrombosis (DVT). When a clot breaks loose and travels to the lungs it is called a pulmonary embolism (PE). VTE is a common, potentially fatal, yet treatable condition,

and is the third leading cause of mortality by cardiovascular disease. You are being invited to participate in this study because you have been diagnosed with VTE and have received initial treatment with a blood thinner (anticoagulant).

Up to 5% of the population will experience VTE in their lifetime and the majority of these events will not be brought on by any specific event. VTE is primarily a disease of the elderly with incidence rates increasing with age for both men and women. The standard therapy for all patients with VTE is anticoagulation for 3-6 months; the most common oral anticoagulants used are vitamin K antagonists (for example, warfarin) and the direct oral anticoagulants (for example, apixaban and rivaroxaban). For patients who sustain VTE that is not associated with any specific event (for example, after surgery, following long plane flights), referred as an ‘unprovoked’ VTE, current guidelines recommend continuing anticoagulation indefinitely after the initial treatment period. Your doctor or healthcare provider has determined that you would benefit from long-term anticoagulation because of your risk for recurrent VTE. The purpose of the COVET study is to determine whether the direct oral anticoagulants apixaban and rivaroxaban are safer than warfarin (fewer bleeding complications) and still as effective as warfarin (no increase in recurrent blood clots).

All three of the anticoagulant agents included in this study (rivaroxaban, apixaban, and warfarin) are FDA approved and have been shown to be effective in the prevention of recurrent VTE. There have been no studies that have compared these three blood thinners for the purpose of preventing recurrent blood clots long-term.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A total of 3000 people to be evaluated at approximately 60 institutions in the US and Canada will be enrolled in this study.

WHAT IS INVOLVED IN THE STUDY?

If you agree to be in this study, you will be asked to sign this consent form. You will have the following assessments to make sure that you are eligible:

- Medical history (to assess your eligibility to participate in the study)
- A review of medication(s) you have taken and are currently taking to treat your DVT/PE.

If eligible, you will be randomly assigned (like drawing straws) to either receive warfarin (target INR of 2-3), apixaban (2.5mg twice daily) or rivaroxaban (10mg daily).

Participants should start on the assigned study drug within one week of randomization. Participants on once daily medications will have flexibility in determining the daily dosing timing. You will receive a prescription for the medication you are assigned to. All these medications are currently approved for treatment of the venous thromboembolism and pulmonary embolism.

The following test and procedures will be performed for this study:

- At the Screening/Randomization visit (Visit 1)
 - Review and sign the Informed Consent Document
 - Measure your height and weight
 - Review your Medical History
 - Review the medication(s) you have taken in the past and are currently taking to treat your DVT/PE
 - Complete the Anti-coagulant Treatment Scale (ACTS) patient satisfaction questionnaire that will ask you questions about your satisfaction with your anticoagulant treatment.
 - Complete the health questionnaire (EQ-5D-5L) that will ask you questions about mobility and usual activities after diagnosis of VTE.

- At the Follow-up phone Visits (Month 1, Month 6 and Month 12)
 - You will be contacted by the Duke Clinical Research Institute (DCRI) Call Center to talk with you about the following:
 - A review of medication(s) you have taken and are currently taking since the previous visit
 - Review of information on specific events you may have experienced.
 - Ask you questions from the Anti-coagulant Treatment Scale (ACTS) patient satisfaction questionnaire that will ask you questions about your satisfaction with your anticoagulant treatment.
 - Ask you questions from the Health questionnaire (EQ-5D-5L) regarding your mobility, usual activities, etc.

HOW LONG WILL I BE IN THIS STUDY?

Your participation in the study is anticipated to be 12 months from your screening/randomization visit.

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk with your doctor first.

WHAT ARE THE RISKS OF THE STUDY?

As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor, and you may choose to talk with your regular health care provider, too.

Apixaban may cause some, all, or none of the side-effects listed below.

- Bleeding is the most relevant adverse event.
- Major or severe bleeding may occur and, regardless of location of the bleeding, may lead to disabling, life threatening or even fatal outcomes.

Rivaroxaban may cause some, all, or none of the side-effects listed below.

- Bleeding is the most relevant adverse event.
- Major or severe bleeding may occur and, regardless of location of the bleeding, may lead to disabling, life threatening or even fatal outcomes.
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Warfarin may cause some, all, or none of the side-effects listed below.

- Bleeding is the most relevant adverse event.
- Major or severe bleeding may occur and, regardless of location of the bleeding, may lead to disabling, life threatening or even fatal outcomes.

In addition, you may experience unforeseeable risks and inconveniences associated with the use of the study drugs warfarin, apixaban and rivaroxaban. There is the potential risk of loss of confidentiality. Every effort will be made to keep your information confidential, however, this cannot be guaranteed.

Other Study Procedure Risks:

In addition, there may be uncommon or previously unknown problems that might occur. You should report any problems you have to the study team.

Reproductive Risks:

Taking study anticoagulant while pregnant may expose a fetus to significant risks. If you are of child-bearing potential and sexually active, you must agree to use appropriate contraception for as long as you are taking the study drug. Medically acceptable contraceptives include:

- surgical sterilization (such as a tubal ligation or hysterectomy)
- approved hormonal contraceptives (such as birth control pills, patches, implants or injections)
- barrier methods (such as a condom or diaphragm) used with a spermicide, or
- an intrauterine device (IUD).

Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

If you becomes pregnant during the course of the study and elect to carry the pregnancy to term, the following actions should be taken:

1. Notify your study doctor immediately.
2. Study doctor will discontinue your anticoagulant medication.
3. Study doctor will decide what (if any) ongoing anticoagulation therapy to be prescribed (off study).
4. You may continue with the follow-up telephone calls only.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may not be direct medical benefit to you. We hope that the information learned from this study will benefit other people with your condition in the future.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?

You do not have to participate in this study. You can get treatment or care for your illness even if you are not in a research study.

Please talk to your doctor about these options before you decide to take part in this study.

WHAT PERSONAL HEALTH INFORMATION ARE YOU ASKING PERMISSION TO GET FROM MY MEDICAL RECORD?

If you sign this consent form, you are giving your permission for the following people or groups to give the researchers certain information about you:

- Any health care providers, professionals or agencies who have provided your health services or treatment, such as physicians, clinics, hospitals, home health agencies, diagnostics centers, laboratories, treatment or surgical centers, or government health agencies
- Any agencies that provide payment for health care, such as insurers, or government agencies
- The Duke Clinical Research Institute and any third party vendors that are working with the sponsor during the course of the project.

This information may be shared with, used by, or seen by collaborating researchers, the sponsor of the research study, the sponsor’s representatives, and government agencies (like the FDA) if needed to oversee the research study. Anybody who receives your information from us could share it with others without your permission and would not be protected by US Federal Privacy Rules. We can use or share your information if we do so in a way such that nobody can tell it is your information.

If you want to participate in this study, you have to sign this authorization to allow access to your medical records. If you choose to not sign it, you are still able to receive your medical treatment not related to the study. If you do sign it, you can change your mind later by writing a letter that states you are taking back your permission. Mail the letter to *[Address]* or you can send us an email at *[List email address]*. Stopping your authorization will prevent sharing of information in the future, but will not affect any information that has already been shared.

Research information collected about you might be put in your medical record.

The permission you give us to access your medical record will last until the end of the study. You will be given a copy of this authorization.

If the results of this study are made public, information that identifies you will not be used.

HOW WILL MY PRIVACY BE PROTECTED?

Except when required by law, and as outlined in this consent, you will not be identified by name, Social Security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of your hospital. You will be assigned a unique code number so that any study data or samples sent outside of your hospital will only contain your unique study code. The key to the code will be kept at the hospital where you took part in the study. As part of the study, results of your study-related tests will be reported to the data coordinating center, Duke Clinical Research Institute (DCRI).

We ask that you provide your name and phone number so that DCRI may contact you during the follow-up period. We will also ask for the name and phone number of a family member that can answer health questions about you if we are unable to reach you.

A copy of this consent form will go into your medical record.

Representatives from DCRI will ask Dr. [add PI name] and his staff to send copies of parts of your record to DCRI to monitor the study. Monitoring means that DCRI staff may review study records to ensure that your information was entered correctly. A copy of this signed consent document, along with copies of your laboratory reports and records of important medical events that occur while you are in the study will be sent to DCRI via a secured electronic system. Trained personnel at the site will ensure that your name is removed from all medical record documents (but not your consent form) before they are sent and that you are identified only by your unique study code number on the documents that are sent. These documents will remain secured through DCRI's password protected electronic file system.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME IF I PARTICIPATE IN THIS STUDY?

You or your insurance provider will be responsible for all costs related to your medical care, including the cost of drugs used in this study. The study will provide co-pay assistance for up to \$60.00 per month if you are randomized to rivaroxaban or apixaban and \$10.00 per month if you are randomized to warfarin to help with out-of-pocket costs you may incur. Reimbursement for routine lab work such as INRs required to monitor the warfarin is not provided by the study and should be billed to your health insurance company or other third party payor. Your doctor or health care provider will help identify additional drug cost assistance programs. Your doctor or health care provider will also review the expected out-of-pocket/copay costs for each of the study drugs with you. If there is any expected out-of-pocket/copay cost for any of the three study drugs, either the full cost of the study drug, or a copy, that is not sufficiently off-set by the copay

provided through the study, and you are unable and/or unwilling to cover that cost, then you will not be eligible to participate in the study.

WHAT ABOUT COMPENSATION?

You will not be paid for participation in this study. The co-payment assistance is not considered compensation for study participation. Your participation in the study is voluntary.

WHAT IF I AM INJURED?

Immediate necessary medical care is available at *[medical center]* in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, PCORI, or your study doctor to provide monetary compensation or free medical care to you in the event of a study-related injury. Your health insurance company or other third party will be billed for the costs of this care. If your insurance company or third party payer does not pay for these costs, you will be billed for them.

For questions about the study or research-related injury, contact Dr. *[PI]* at *[phone number here with area code]* during regular business hours or at *[PI's 24-hour number with area code]* after hours and on weekends and holidays.

WHAT IF I WANT TO STOP BEFORE MY PART IN THE STUDY IS COMPLETE?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped. If you withdraw, no new information will be collected but we will use data that has already been collected.

NEW FINDINGS

If important new findings come up that might change your decision to be in this study, you will be given information about those findings as soon as possible. If you choose to stay in the study, you may be asked to sign a new version of the consent form.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, or if you have complaints, concerns or suggestions about the research, contact Dr. *[PI]* at *[PI's Number with Area Code]* during regular business hours and at *[PI's 24-hour Number with Area Code]* after hours or on a weekend or holiday.

For questions about your rights as a research participant, contact *[the IRB name and contact number]*

STATEMENT OF CONSENT

The purpose of this study, the procedures to be followed, the study’s risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to talk about problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form (or it has been read to me) and I agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a copy of this consent form and that a copy of this form will become part of my medical record.

I authorize the use and disclosure of health information from my medical record to the people or groups identified in this consent form for the purposes described in this document.

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

Signature of Research Subject

Date

Printed Name of Research Subject

Signature of Research Team Member Who Obtained Consent

Date

Printed Name of Research Team Member Who Obtained Consent