Informed Consent Form for Participation in a Research Study

STUDY TITLE: *The Fourth Left Atrial Appendage Occlusion Study (LAAOS-4)*

SPONSOR/Funder: *Hamilton Health Sciences Corporation through its Population Health Research Institute (PHRI)*

INVESTIGATOR: *Dr Stephen Wilton 403-210-7102*

INTRODUCTION

Dr Stephen Wilton and associates from the Cumming School of Medicine at the University of Calgary are conducting a research study.

This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something described here, or information not included here, please ask. Take the time to read this carefully and to understand any accompanying information. You will receive a copy of this form for your records.

You were identified as a possible participant in this study because you are taking anticoagulant medications, have atrial fibrillation and have been identified as being at an increased risk of stroke. Your participation in this research study is voluntary.

This consent form provides you with information to help you make an informed choice. Please read this document carefully and ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether to participate.

Please take your time in making your decision. You may find it helpful to discuss it with your friends and family.

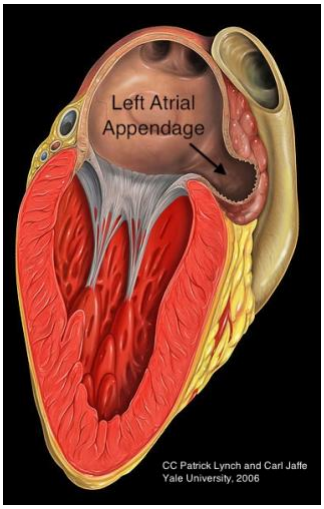
You have the option to not participate, or you may choose to leave the study at any time. Whatever you choose, it will not affect the usual medical care that you receive.

IS THERE A CONFLICT OF INTEREST?

There are no conflicts of interest to declare related to this study.

WHY IS THIS STUDY BEING DONE?

Atrial fibrillation is a common heart condition that happens when the top two chambers of the heart, the atria, beat too fast and with an irregular rhythm (fibrillation). This condition can decrease the heart's pumping capacity, which can cause blood cells to pool and stick together, forming clots in a small pouch on the heart called the left atrial appendage. If a clot escapes from the appendage and gets into your arteries, it may block the blood supply to your brain and cause a stroke. Atrial fibrillation is associated with a 3-5 times increased risk of stroke.



Research studies have found that the risk of stroke can be reduced by taking medications called "oral anticoagulants" (often known as blood thinners), that help to prevent blood clots. Studies have also found that the risk of stroke can be reduced by closing off the left atrial appendage with a device permanently implanted into the heart, or by removing the appendage during heart surgery.

The purpose of the LAAOS-4 study is to determine if closure of the left atrial appendage using a device called the WATCHMAN FLX™,or FLX PRO™, in addition to taking oral anticoagulant medications, is more effective at reducing strokes and blood clots in your body, than taking oral anticoagulant medications on their own.

The WATCHMAN FLX™ and FLX PRO™ devices (shown below) are manufactured by Boston Scientific Corporation. It is a permanent parachute-shaped implant about the size of a quarter, designed to close off the left atrial appendage in the heart in an effort to reduce the risk of stroke by preventing blood clots from forming in the left atrial appendage. The device is made of a metallic frame and covered with a thin layer of fabric. The device is available in five different sizes. If you are randomized to receive a WATCHMAN FLX™ or FLX PRO™ device, testing (A CT scan and/or special heart ultrasound) will be done to determine what size will be best for you.

WATCHMAN FLX™ device

The WATCHMAN FLX™ device has been approved for use by the U.S Food and Drug Administration (FDA), Health Canada, the European Medicines Agency (EMA) and other regulatory authorities internationally to prevent blood clots from forming in the left atrial appendage. There is a second FDA-approved WATCHMAN FLX ™ device in use in the USA and in Canada, the WATCHMAN FLX PRO™, and both the FLX and FLX PRO models are used in the LAAOS-4 study in the USA and in Canada.

Although the WATCHMAN FLX™ and FLX PRO ™ LEFT ATRIAL APPENDAGE CLOSURE devices are approved for use in Canada, LAAOS-4 is currently studying the combination of device implantation with continuation of anti-coagulation medication therapy after the procedure. The continuation of oral anti-coagulants therapy after implantation of the device is not commercially approved by Health Canada. The WATCHMAN FLX™ and FLX PRO™ LEFT ATRIAL APPENDAGE CLOSURE devices used in the LAAOS-4 study in Canada will only be used at the direction of Qualified Investigators who are approved to lead the study at the respective research hospital site.

The comparison being tested in this study is whether or not having a WATCHMAN FLX™ device implanted will help in preventing strokes and blood clots in people taking anticoagulant medication, compared to people taking anticoagulant medication without a device.

The Boston Scientific Corporation is providing the money for this study to Hamilton Health Sciences Corporation through its Population Health Research Institute who designed and will carry out the study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that about 4000 people will take part in this study, from research sites located in North America and other countries internationally. We hope to enrol 25 subjects at the University of Calgary.

WHAT WILL HAPPEN DURING THIS STUDY?

ASSIGNMENT TO A GROUP

If you decide to take part in this study, you will be asked to sign and date this informed consent form. You will then be "randomized" into one of the groups described below. Randomization means that you are put into a group by chance (like flipping a coin). There is no way to predict which group you will be assigned to. You will have *an equal* chance of being placed in either group. Neither you, the study staff, nor the study doctors can choose what group you will be in. You will be told which group you are in.

Group 1 - Intervention (Device and Anticoagulation group): If you are randomized to this group, you will have a WATCHMAN FLX™ or FLX PRO™ device implanted, AND continue to take anticoagulant medications prescribed by your doctor.

Group 2 -Standard (Anticoagulation group): If you are randomized to this group you will continue to take anticoagulant medications prescribed by your doctor.

STUDY PROCEDURES

Information at the visits described below will be collected through in-person visits; telephone calls or video/virtual call with you or a family member; or from your medical records.
For your safety, please check with the study doctor before starting, stopping, or changing your current medications or supplements at any time during the study.

Baseline Procedures

- Medical record and medication review

- Brief physical exam
- Questionnaires about your health, brain function and quality of life

Randomization

- The study team will use a computerized system to determine which study group you have been assigned to
- *Intervention group* will be scheduled for device implant within 15 calendar days. Medications may be adjusted and/or antibiotics used. Imaging (CT scan) will also be scheduled to determine which size device you will need
- *Standard group:* will continue anticoagulation medications for the duration of the trial as directed by the study doctor. NO implant or imaging.

DEVICE Implant

If you are in the device arm of the trial, the following will occur:

- You will be admitted to a day-cardiology unit and have an IV started
- Your doctor will review your health status and answer any questions you may have
- You will be brought to specialized cardiac procedure room at Foothills Medical Center laboratory where the procedure will be done

The implant procedure will be done while under general anesthetic, supervised by an anesthesiologist. Cardiac ultrasound imaging will be done to help guide the device implant procedure. This imaging may be called either a "transesophageal echocardiogram (TEE)" or an "intra-cardiac ultrasound (ICE)". TEE is performed by inserting an ultrasound probe into your mouth and advancing it into your esophagus (food tube) to take pictures of your heart from inside your chest. ICE is performed by inserting a flexible tube (ultrasound catheter) through the blood vessel in your groin and directing it through your blood vessel to your heart to take pictures from inside your heart. Your doctor will discuss the recommended option with you prior to the procedure.

To place the WATCHMAN FLX™ or FLX PRO™ device into your left atrial appendage, the study doctor will insert a flexible tube (catheter) through a vein in your groin and direct it into your heart. Then, a needle device is used to access the left atrium. Once the tube is in position, your study doctor will take pictures of your heart in order to measure your appendage. These measurements will determine which size WATCHMAN FLX™ or FLX PRO™ device to use. The device will then be guided to your heart through this same tube. After the device is put in place, additional heart measurements and pictures will be taken by TEE or ICE to make sure the device is securely in the correct position. Once your study doctor is satisfied, the device will be released and left permanently in your heart. This procedure takes about 60-90 minutes. You may need to stay in the hospital 1-2 days after the procedure to recover and be monitored.

- After the implantation procedure you will return for follow-up exams so your study doctor can check your health status and the status of the device with additional cardiac images. Your doctor will tell you what the timing and assessments for this follow up will be.

ANTICOAGULATION Group

If you are assigned to the Anticoagulation Group, you will continue treatment with oral anticoagulant medications for the duration of the trial as directed by the study doctor.

For the purposes of your safety and this research, it is very important that you attend each study visit no matter which group you are in.

Follow-up visits
You will have a study visit 45 days after randomization . You will then be asked to have contact with your clinic (either in person, via video or virtual call or by telephone) every 6 months until study end.

You may be seen more often if the study doctor determines that this is necessary.

No matter which group you are randomized to, we would like to keep track of your health for the duration of the study. We would do this by having someone from this centre call you to see how you are doing, if you are not able to come into the clinic. If something should happen to your health and we need to get information regarding your medical condition, we may contact your health care provider, next of kin or another provider/facility where you may have been treated.

Questionnaires
You will be asked to complete questionnaires regarding your health and thinking 3 times during the study. The purpose of these questionnaires is to understand how the study intervention affects your brain health and your quality of life. Each questionnaire will take about 5-10 minutes to complete.

People who have a stroke during the study will also be contacted about 3 months after the stroke occurred to ask about health status and recovery progress.

The information you provide is for research purposes only. Some of the questions are personal. You can choose not to answer questions if you wish.

HOW LONG WILL I BE IN THE STUDY?

This study should take about 6 years to complete. Participation in the study is expected to last an average of 51 months (or 4.25 years), but this period may be shorter or longer for each individual, depending on whether they were enrolled early or later on in the overall study to reach 4000 participants

ARE THERE ANY POTENTIAL RISKS OR DISCOMFORTS THAT I CAN EXPECT FROM THIS STUDY?

You may experience side effects from participating in this study. Some side effects are known and are listed below, but there may be other side effects that are not expected. You should discuss these with the study doctor, who will watch you closely to see if you have side effects. When possible, other medicine will be given to you to make side effects less serious and more tolerable. Many side effects go away quickly, but in some cases be serious, long-lasting, permanent, or may even cause death.

The implant procedure and the WATCHMAN FLX™ or FLX PRO ™ device risks:

- Minor bruising under the skin of the groin where the vein is accessed to insert the device. (20%)
- Less common complications (3-20%) include:
  - irregular heartbeats
  - allergic reaction to the contrast dye
  - anesthesia risks

- chest pain/discomfort
- low blood pressure
- damage to your blood vessels
- bleeding
- fainting (vasovagal reactions)
- bleeding or pain at the groin puncture site,
- non-healing of the hole in the heart wall between the atria from the implant procedure
- reduced red blood cell count requiring transfusion.

❖ Uncommon complications (less than 3%) may include
- an accidental hole in your heart which could cause blood to collect in the sac around the heart (this could require a procedure to drain the excess blood or surgery to repair the tear)
- blood clots
- air bubbles in the blood stream
- abnormal connection between an artery and a vein (AV fistula)
- heart attack
- infection
- stroke
- collection of blood around a vessel puncture site
- blood clot in the vessels of the lung (pulmonary embolism)
- fluid in or around your lungs
- kidney dysfunction or failure
- damage to the valves in your heart
- bleeding requiring transfusion
- misplacement, fracture or dislodgment of the device
- inability to remove the device (if necessary)
- bleeding
- device infection
- allergic reaction to the implant materials
- scarring or clotted veins or chronic irritation from the device in the heart that could lead to erosion or death
- Potential blood clots on the device when taking an anticoagulant

All efforts will be made to minimize risks. There is a risk of dislodgement or migration of the device in your heart if it does not fit properly, which could lead to another procedure or major surgery to remove the device.

Additionally, there are risks associated with imaging tests required to insert the WATCHMAN FLX™ or FLX PRO ™ device. If a trans-esophageal echo (TEE) is done, risks include problems with breathing or heart rhythm, infection of the heart valves, and bleeding or tear of the esophagus (food pipe). If intra-cardiac echocardiography (ICE) is used, risks remain similar to the overall procedure to insert the WATCHMAN FLX™ device. If a Cardiac CT scan is used to image the heart, there's some exposure to x-ray radiation, however the levels of radiation are considered safe for adults.

You and your study doctor should carefully discuss in detail all of the possible risks involved with this study before you volunteer to participate. By agreeing to volunteer in this study you agree that you have read, understood and accepted the potential risks involved with this study.

There may also be additional risks or side effects which are unknown at this time.

WHAT ARE THE REPRODUCTIVE RISKS?

The treatment and medications used in this study may pose a risk to developing fetuses. If you become pregnant while you are in this study, you should immediately notify the study doctor. The study doctor will ask if you are willing to provide information about the pregnancy as part of this study. You may choose not to give consent for the collection of this information or may withdraw consent at any time without giving a reason. This will not impact your participation on the study and will not result in any penalty or affect your current or future health care.

ARE THERE ANY POTENTIAL BENEFITS IF I PARTICIPATE?

There may or may not be any direct benefits to you if you decide to take part in this study. However, previous studies have found that the risk of stroke can be reduced by closing off the left atrial appendage with a device permanently implanted into the heart. Therefore, there could be less chance of stroke or blood clots in your body.
Your participation in this study is also expected to add to the medical knowledge about the use of this device in people with atrial fibrillation and at increased risk of stroke.

WHAT OTHER CHOICES DO I HAVE IF I CHOOSE NOT TO PARTICIPATE?

You do not have to take part in this study in order to receive treatment or care. Other options include, but are not limited to:

- no therapy at this time
- other research studies may be available if you do not take part in this study

Please talk to your usual doctor or the study doctor about the benefits and risks of these other options before you decide to take part in this study. Your usual doctor or the study doctor can also discuss with you what will happen if you decide not to undertake any treatment at this time.

CAN I STOP BEING IN THE STUDY?

You can choose to end your participation in this research (called withdrawal) at any time without having to provide a reason. If you choose to withdraw from the study, you are encouraged to contact the study doctor or study staff.

You may be asked questions about your experience with the study intervention, and to have laboratory tests and physical examinations considered necessary to safely stop your study involvement.

CAN THE RESEARCHERS REMOVE ME FROM THIS STUDY?

The study doctor may stop your participation in the study early, and without your consent, for reasons such as:

- New information shows that the study intervention is no longer in your best interest
- The study doctor no longer feels this is the best option for you
- The Sponsor decides to stop the study

- The Regulatory Authority/ies (for example, Health Canada) or research ethics board withdraw permission for this study to continue
- If you plan to or become pregnant

If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form.

If you are removed from this study, the study doctor will discuss the reasons with you and plans will be made for your continued care outside of the study.

WITHDRAWAL OF STUDY DATA

You may withdraw your permission to use information that was collected about you for this study at any time by letting the study doctor know. However, this would also mean that you withdraw from the study.

Information that was recorded before you withdrew will be used by the researchers for the purposes of the study, but no new information will be collected or sent to the sponsor after you withdraw your permission.

WHAT IF RESEARCHERS DISCOVER SOMETHING ABOUT ME?

During the study, the researchers may learn something about you that they didn't expect. For example, the researchers may find out that you have another medical condition.

If any new clinically important information about your health is obtained as a result of your participation in this study, you will be given the opportunity to decide whether you wish to be made aware of that information.

WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?

You will not be paid for taking part in this study.
In the case of research-related side effects or injury, medical care will be provided by your doctor or you will be referred for appropriate medical care.
The WATCHMAN FLX™ or FLX PRO™ device will be supplied at no charge while you take part in this study.
The costs of your medical treatment will be paid for by your provincial medical plan to the extent that such coverage is available.

Parking costs for study specific visits to the Foothills Hospital site will be covered or reimbursed.

HOW WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT CONFIDENTIAL?

The researchers will only collect the information they need for this study and do their best to make sure that your private information is kept confidential, unless required by law. Information about you will be handled as confidentially as possible, but there is always the potential for an unintended breach of privacy. The research team will handle data according the Data Management Plan as outlined below:

Records identifying you at this centre will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this

consent document.

Authorized representatives of the following organizations may look at your original (identifiable) medical/clinical study records at the site where these records are held, to check that the information collected for the study is correct and follows proper laws and guidelines.

- Hamilton Health Sciences Corporation through it's Population Health Research Institute, the Sponsor of this study
- The University of Calgary and the Conjoint Health Research Ethics Board
- The monitors for this study
- Health Canada (because they oversee the use of the WATCHMAN FLX™ and FLX PRO™ device in Canada)
- U.S. Food and Drug Administration (because they oversee the use of the WATCHMAN FLX™ and FLX PRO™ device in the United States)

The records received by these organizations may contain the following identifiers: participant code, sex, hospital admission and discharge dates, date of your implant procedure, and date of death if applicable.

Studies involving humans sometimes collect information on race and ethnicity as well as other characteristics of individuals because these characteristics may influence how people respond to different interventions. Providing information on your race or ethnic origin is required.

Communication via e-mail is not absolutely secure. We do not recommend that you communicate sensitive personal information via e-mail.

In the unlikely event of your death, it would be helpful for the researchers to have access to any information available. If an autopsy is performed with the consent of your next of kin, a copy of the report will be provided to the study doctor, and included in the study data.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be used in analyses and will be published/ presented to the scientific community at meetings and in journals. This information may also be used as part of a submission to regulatory authorities around the world to support the approval of the study intervention.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated.

Any information, sent outside of Canadian borders may increase the risk of disclosure of information because the laws in those countries dealing with protection of information may not be as strict as in Canada. However, all study data, that are transferred outside of Canada will be coded (this means it will not contain your personal identifying information such as your name, address, medical health number or contact information). Any information will be transferred in compliance with all relevant Canadian privacy laws. By signing this consent form, you are consenting to the disclosure of your coded information to organizations located outside of

Canada.

The Sponsor of this study will share your study data, including full dates of medical events that are important for statistical analyses of the study, in pseudonymized form (personal information is replaced with artificial identifiers to prevent your identification) with Boston Scientific Corporation, the manufacturer of the study product and collaborator of the Sponsor. Boston Scientific is a medical device company that is located in the United States and is considered a data controller. Boston Scientific may use the pseudonymized study data that it receives about you for the purposes of internal development and analysis of the study product and for submission to Regulatory Authorities. The legal basis for the processing of your pseudonymized data is Boston Scientific's legitimate interest in collecting regulatory evidence and conduct internal analysis for product development, as well as the need to conduct scientific research. Boston Scientific will retain your pseudonymized data as needed to perform the purposes mentioned above, and as necessary to comply with our legal obligations and to resolve disputes. The Sponsor of this study may additionally share your study data, in coded form, with Regulatory Authorities at the request of Boston Scientific.

Because this study also falls under U.S. regulations, in the event of an investigation of the study, the US Food and Drug Administration (US FDA) may need to copy and take away records that contain your personal information. If possible, the study doctor will inform you and confirm your consent at that time. By signing this consent form you are agreeing to this release of information. You should be aware that privacy protections may differ in other countries.

HOW LONG WILL INFORMATION FROM THE STUDY BE KEPT?

The researchers will keep the research *records* until the research is published and/or presented. After this time it will be securely stored for 15 years as per University of Calgary policy and then destroyed.

WILL MY FAMILY DOCTORS/HEALTH CARE PROVIDERS KNOW I AM PARTICIPATING IN THIS STUDY?

Your family doctor/health care provider may be informed that you are taking part in a study so that you can be provided with appropriate medical care. If you do not want your family doctor/health care provider to be informed, please discuss this with the study team.

IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?

It is important that you tell the researchers if you believe that you have been injured because of taking part in this study.
In the event that you suffer injury as a result of participating in this research, no compensation will be provided to you by Hamilton Health Sciences, PHRI, Boston Scientific, the University of Calgary, Alberta Health Services or the Researchers. However, you still have all your legal rights. Nothing said in this consent form alters your right to seek damages.

WHO CAN I CONTACT IF I HAVE QUESTIONS ABOUT THIS STUDY?

The Research Team:
You may contact Dr Stephen Wilton at 403-210-71-2 or 403-210-6047 with any questions or concerns about the research or your participation in this study.

Conjoint Health Research Ethics Board (CHREB):
If you have any questions concerning your rights as a possible participant in this research, please contact the Chair, Conjoint Health Research Ethics Board, University of Calgary at 403-220-7990.

Public Information about this Study: ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

HOW CAN I FIND OUT ABOUT THE STUDY RESULTS?

We will send you a letter/email with study results after the study has been completed and all data analyzed.

WHAT ARE MY RIGHTS and RESPONSIBILITIES IF I TAKE PART IN THIS STUDY?

If you choose to participate in this study, you will be expected to:

- Tell the study doctor about your current medical conditions, and any significant health events
- Tell the study doctor about all prescription and non-prescription medications and supplements, including vitamins and herbal supplements, and check with the study doctor before starting, stopping or changing any of these. This is for your safety as these may interact with the intervention you receive on this study.
- Tell the study doctor if you are thinking about participating in another research study
- Tell the study doctor if you become pregnant while participating on this study

Taking part in this study is your choice. You can choose whether or not you want to participate. Whatever decision you make, there will be no penalty to you.

- You have a right to have all of your questions answered before deciding whether to take part.
- Your decision will not affect the standard medical care you receive
- If you decide to take part, you may leave the study at any time.

SIGNATURES

- All of my questions have been answered,
- I understand the information within this informed consent form,
- I allow access to medical records and related personal health information as explained in this consent form,
- I do not give up any legal rights by signing this consent form,
- I understand that my family doctor/health care provider may be informed of study participation
- I agree to take part in this study.

Name of Participant

Signature of Participant | Date

SIGNATURE OF PERSON OBTAINING CONSENT

Name of Person Obtaining Consent | Contact Number

Signature of Person Obtaining Consent | Date

SIGNATURE OF THE WITNESS

Name of Witness

Signature of Witness | Date

A signed copy of this consent form has been given to you to keep for your records and reference.