UNIVERSITY OF CALIFORNIA (UCI), IRVINE
CONSENT TO ACT AS A HUMAN RESEARCH SUBJECT

Sponsor / Study Title:	**American Heart Association / "Pragmatic Randomized Clinical Trial of Early Dronedarone versus Usual Care to Change and Improve Outcomes in Persons with First-Detected Atrial Fibrillation (CHANGE AFIB)"**
Protocol Number:	**4.0**
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Brief Summary

You are being asked to take part in a randomized pragmatic clinical trial called CHANGE AFib. A randomized clinical trial is a scientific research study in which the subjects are divided by chance into separate groups to compare different treatments.

The purpose of the study is to determine if early treatment with the study drug dronedarone improves cardiovascular and long-term outcomes in subjects presenting to the hospital with first-detected Atrial Fibrillation (AFib). Dronedarone, is a rhythm control medicine (antiarrhythmic drug) and has been approved by the U.S. Food and Drug Administration (FDA) in certain subjects with atrial fibrillation since 2009. The most common adverse reactions observed with dronedarone were diarrhea, nausea, abdominal pain, vomiting, and weakness or lack of energy. You are being asked to participate in this research study because you have newly-detected AFib, or AFib diagnosed in the past 120-days. The American Heart Association (AHA) is leading the study.

We expect 3,000 subjects with a new diagnosis of AFib from across the U.S. will take part in CHANGE AFib. If you choose to participate, you will take part in the study for approximately 12 months. There is no cost for you to participate in this study. While you will not get direct benefit from taking part in this study, the main reason you may want to join is to help researchers learn about treating subjects with newly diagnosed AFib. The results might benefit subjects like you in the future.

The information below explains the study so you can decide if you want to take part or not. Your participation in this study is completely voluntary. You do not have to take part in this study if you do not wish to do so.

You will be given a copy of the full signed and dated Informed Consent Form.

You are being asked to take part in this study because you have first-detected Atrial Fibrillation (defined as Atrial Fibrillation diagnosed in the previous 120 days). Atrial fibrillation (AFib) is an arrhythmia (abnormal heart rhythm) that causes the heart's upper chambers (the atria) to beat very fast and irregularly.

Participation in this study is voluntary and will include only people who choose to take part. Please read this consent form carefully and take your time in making a decision. As the study doctor or study staff discuss this consent form with you, please ask him/her 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 study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

If you are acting as a legally authorized representative to give consent for another person to participate in this study, 'you' throughout this consent form refers to that individual. The obligation of a legally authorized representative is to try to determine what the individual would do if competent, or if the subject's wishes cannot be determined, what the legally authorized representative thinks is in the person's best interest. If possible, an attempt should be made to obtain permission from the individual. Some persons may resist participating in a research study that has been approved by their legally authorized representatives. Under no circumstances may individuals be forced to participate.

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

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, the study doctor listed on page one will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHO IS DOING THIS STUDY?
The American Heart Association is the study sponsor. CHANGE AFib is a collaboration between the American Heart Association and the Duke Clinical Research Institute (DCRI) with support from Sanofi US Services Inc.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to determine if early study treatment with the medicine dronedarone is more effective than usual care alone for the prevention of unplanned cardiovascular hospitalization (such as hospitalization for heart failure, atrial fibrillation, stroke, coronary atherosclerosis, of acute myocardial infarction) or death (from any cause) in subjects presenting to the hospital with first-detected AFib.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 3000 subjects will take part in this study at approximately 200 different hospitals and medical facilities around the United States.

HOW LONG WILL I BE IN THIS STUDY?
You will be followed for at least 12 months. Study involvement is described in the following sections within this document.

WHAT WILL YOU ASK ME TO DO?
If you agree to participate in CHANGE AFib, here is what will happen:

1. <u>The research team will ask you a few questions to make sure you are a good fit for this study</u>. You are being asked to take part in this study because you have first-detected atrial fibrillation (defined as atrial fibrillation diagnosed in the previous 120 days). Atrial fibrillation (AFib) is an arrhythmia (abnormal heart rhythm) that causes the heart's upper chambers (the atria) to beat very fast and irregularly. The research team will need to make sure that you are a good candidate for the study and that you will be able to participate for the entire study period. Participation in this study is voluntary and will include only people who choose to take part.

   You cannot take part if you are pregnant, trying to become pregnant, or breastfeeding. If you are sexually active and could get pregnant, you should use birth-control during the study. If you do get pregnant, let your study doctor know right away.

2. The research team will ask a few things about you and your health. We will ask things like your birth date, sex, and race. We will also ask about your medical history, other medicines you take, and how your health and well-being affect your daily life. The study staff will also review your medical records. Information collected may include information about your medical history, vital signs (such as height, weight, and blood pressure), medications, and laboratory data as well as information about the types of health insurance (public or private) that you have.

   We will ask for your contact information so we can keep in touch during the study. We will also ask for contact information for a friend or relative. If we cannot reach you, we may call them to see how you are doing.

3. You will be assigned to one of two study groups. A computer will randomly assign you (like the flip of a coin) to receive either the study intervention or usual care. Both you and your study doctors will know to which group you have been assigned.

4. What is the study intervention? The study intervention is the oral medication dronedarone. Dronedarone is a heart rhythm medicine. If you are assigned to the study intervention group, you will be asked to take 400mg of dronedarone orally twice a day. You will also be prescribed any medicines that you would receive as part of your usual care as decided by your care team.

   The research team will work with you to provide the study medication, dronedarone, during your study participation (12 months). If you are assigned to the study intervention group, you will receive the study medication shipped directly to your address of choice.

5. What if you are assigned to the usual care group? The usual care group will be prescribed medicines that they would receive as part of their usual care (as decided by the care team) per routine clinical practice.
6. How long will you participate in the study? You will be in the study for approximately 12 months. You will be enrolled in the study while you are at the hospital. There will also be two follow-up visits. The first will take place between 3- and 9 months after your enrollment, and the second will take place approximately 12 months after your enrollment. These follow-up visits can be either virtual or in-person.

   The follow-up visits should take about 30 minutes and might include information about your vital signs (such as your height and weight) and medical encounters (such as routine care, hospitalizations, and ER visits) that you may have had since the last interview or follow-up visit.

7. We will ask you to fill out some short surveys. These will ask about any major things that have happened with your health, how you are getting along in daily life, and what medicines you are taking. You will fill them out during your enrollment visit and during your 12-month follow-up visit. The surveys should only take about 15 minutes.

8. We will get some information from other places from time to time as long as you are in the study. The research team needs to get a complete picture of your health. We will get certain information from your medical records. Examples include additional information about your health problems, health care visits, hospital stays, medical procedures, and lab results. In some cases, we might need you to sign and date a form saying it is okay for us to get the information we need for the study.

WHAT WILL YOU DO WITH MY INFORMATION?

Your study records, including confidential information about you collected during the study, will be kept at a secure location. Your name and other information that directly identifies you will be removed from your health information (see "What About My Privacy?").

If you are assigned to the study intervention group, you will receive a delivery of the study drug at your provided address of choice. For you to participate in this direct-to-home study drug shipment program, we will need to disclose your personal information, including health information, to Almac Clinical Services Limited (the Central Pharmacy ("Almac"), a contractor of the AHA, the study Sponsor. Almac understands that information about you and your health is personal and is committed to protecting the privacy of that information in accordance with applicable privacy and data protection legislation. By signing this consent form, you are authorizing the use and disclosure of your personal information for the purposes of study drug shipment, if you are assigned to the intervention group.

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.

FUTURE RESEARCH USE OF DATA

We may use the data collected in this study for future research or share it with other researchers. We will remove any information that may personally identify you from anything that is used or shared in the future. We will not inform you every time that your unidentified health information is used in a new research study.

We may share your de-identified health information for possible future cardiovascular research in atrial fibrillation. Before any de-identified health information is shared for future research, a research committee will review each research study for scientific value. If approved, any new research study will also have to be reviewed by a committee called an Institutional Review Board (IRB). The role of an IRB is to protect the rights and welfare of individuals that participate in research studies like you.

We will not inform you every time that your de-identified health information is used in a new research study, and you will not receive any direct benefits.

WILL I FIND OUT THE RESULTS OF FUTURE RESEARCH?
By signing and dating this consent form, you are giving your permission for us to collect and store your data so that researchers might use them in the future.

The studies that will be conducted in the future are for research purposes only. It is not the purpose of these studies to look for or provide you with any medical information or a diagnosis related to your present condition. The research that happens in the future is not a diagnostic test intended to help you, and it is not a substitute for your regular medical care or check-ups. It is possible that researchers could make a discovery in the future that there might be a risk to your health or well-being. If this happens, and if we have the ability to contact you, we will ask you if you want to learn more.

WHAT ARE THE MOST IMPORTANT SAFETY CONSIDERATIONS?
Dronedarone Therapy Safety Considerations and Drug Interactions

Dronedarone is approved by the FDA to reduce the risk of hospitalization for AFib in certain subjects with paroxysmal or persistent AFib. Dronedarone is subject to a boxed warning regarding increased risk of death, stroke and heart failure in subjects with decompensated heart failure or permanent atrial fibrillation. The most common adverse reactions observed with dronedarone are:

- Diarrhea
- Nausea
- Abdominal pain
- Vomiting
- Weakness or lack of energy.

The risks of dronedarone therapy include hepatic (liver) injury, new onset or worsening of heart failure exacerbation, renal (kidney) impairment and failure, QT interval prolongation, increased exposure to digoxin, increased plasma concentration of tacrolimus, sirolimus, and other drugs that are broken down in similar pathways (CYP 3A substrates), and very rare instances of lung injury. Dronedarone caused fetal harm in animal studies at doses equivalent to recommended human doses.

There are several medications that may interact with dronedarone and prevent it from working the way it should. Please make sure that your medical team knows about your participation in this study so that they can look for any possible drug interactions.

- Treatment with Class I or III antiarrhythmics or drugs that are strong inhibitors of CYP 3A must be stopped before starting dronedarone.
- Subjects should be instructed to avoid grapefruit juice beverages while taking dronedarone.

- Calcium channel blockers with depressant effects and beta-blockers could increase the bradycardia effects of dronedarone on conduction.
- Digoxin: In prior trials, (subjects who had recently decompensated heart failure or permanent AFib had an increased risk of arrhythmias or sudden death if they were treated with digoxin plus dronedarone. Digoxin can increase the effects of dronedarone, and dronedarone can increases the exposure to digoxin.
- Warfarin/coumadin: Cases of increased INR with or without bleeding events have been reported in warfarin-treated subjects initiated with dronedarone. Monitor INR after initiating dronedarone in subjects taking warfarin
- Statins: Avoid simvastatin doses greater than 10 mg daily.

If you have any questions or concerns, be sure to talk to your study doctor.

BIRTH CONTROL RESTRICTIONS

Taking dronedarone may involve risks to a pregnant woman, an embryo, or fetus (unborn baby), including an increased risk of birth defects. Therefore, if you are pregnant or planning to become pregnant, or breastfeeding you cannot participate in this study.

If you become pregnant while you are participating in this study, tell your study doctor or study staff immediately. The study drug will be stopped. Follow-up of the pregnancy will be requested until the outcome has been determined.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you promptly tell the study doctor if you believe that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at the number listed at the top of this form.

If you are injured as a result of being in this study, UCI will provide necessary medical treatment. The costs of the treatment may be covered by the University of California or billed to you or your insurer just like other medical costs, depending on a number of factors.

The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about this, you may call UCI Human Research Protections (949) 824-6068 or (949) 824-2125 or by e-mail at IRB@research.uci.edu.

You will not lose any of your legal rights or release the Sponsor, the study doctor, the study staff, or study site from liability for mistakes or intentional misconduct by signing and dating this consent document.

ARE THERE ANY ALTERNATIVES TO PARTICIPATION?
You do not have to be in this study to receive study treatment for your AFib. Please talk to the study doctor about your options before you decide whether or not you will take part in this study.

ARE THERE ANY BENEFITS TO PARTICIPATING?

This study is for research purposes only. There is no direct benefit to you from your participation in the study. The results might benefit subjects like you in the future.

We will provide general news and updates about CHANGE AFib from time to time. You can also get information about this study at www.clinicaltrials.gov.

ARE THERE ANY COSTS OR PAYMENTS?
There is no cost to you or your insurer for your participation in this study. You and /or your health plan/insurance will be billed for the costs of any standard medical care you receive to diagnose and/or treat any medical condition(s) outside of this study. You will also be billed for any deductibles or co-payments that would normally be associated with these standard medical costs.

You may however be required to cover the cost of the study drug (if assigned to the treatment group) depending on what your insurance company will cover. The study doctor and study team will work with you to confirm study medication coverage through your insurance, if applicable.

COMPENSATION FOR PARTICIPATION
You will not receive any monetary compensation for your participation in this study.

WHAT IF I CHANGE MY MIND?
Taking part in CHANGE AFib is your choice; participation is completely voluntary. No matter what you decide, now or in the future, it will not affect your benefits or future medical care.

If you decide to participate in CHANGE AFib, you can change your mind at any time. We will tell you if we learn anything new that might change your mind about being in the study. If you change your mind, you must let the study team know in writing. The study team contact information is on the first page of this consent form.

The study doctor or the Sponsor can stop your participation at any time without your consent for the following reasons:

- If it appears to be medically harmful to you;
- If you fail to follow directions for participating in the study;
- If it is discovered that you do not meet the study requirements;
- If the study is canceled; or
- For administrative reasons.

If you leave the study for any reason, the study doctor may ask you to have some end-of-study tests for your safety.

WHO WILL HAVE ACCESS TO MY STUDY DATA?

The research team, authorized UCI personnel, the study sponsor, the Institutional Review Board, and regulatory entities such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP), may have access to your study records to protect your safety and welfare.

While the research team will make every effort to keep your personal information confidential, it is possible that an unauthorized person might see it. We cannot guarantee total privacy.

ClinicalTrials.gov

ClinicalTrials.gov is a Web site that provides information about clinical trials. 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.

Medical Care

If you agree to participate in this research study, a signed copy of this consent document and the privacy authorization form may be filed in your electronic medical record (EMR) and your study participation may be added to your EMR. This information will be used for your care and treatment and for healthcare operations, which may include billing and payment.

Federal and state privacy laws give patients the right to access information about their care and treatment contained in their medical record. During this study, you may not be able to access certain information related to this study in your EMR until the study is complete to ensure that the study remains unbiased. By consenting to participate in this study, you are also consenting to this possible temporary withholding of your records. If necessary for your care, this information will be provided to you or your physician.

Investigator Financial Conflict of Interest

No one on the study team has a disclosable financial interest related to this research project.

If the results of this study are published or presented at meetings, you will not be identified.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Study Doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00057635**.**

If you have questions or concerns about:	***Please contact:***
Your health, including whether taking part in this study is a good idea for you	• Your doctor
The CHANGE AFib study, including any study-related injury	• Your study doctor, information listed on the first page of this consent.
The CHANGE AFib web site	• Changeafib.org

You may also contact UCI's Office of Research by phone, (949) 824-6068 or (949) 824-2125, by e-mail at IRB@research.uci.edu or by writing us at 160 Aldrich Hall, Irvine, CA 92697.

HOW DO I AGREE TO PARTICIPATE IN THIS STUDY?
You should not sign and date this consent form until all of your questions about this study have been answered by a member of the research team listed at the top of this form. You will be given a copy of this signed and dated consent form, and the attached "Experimental Subject's Bill of Rights" to keep. **Participation in this study is voluntary.** You may refuse to answer any question or discontinue your involvement at any time without penalty or loss of benefits to which you might otherwise be entitled. Your decision will not affect your future relationship with UCI or your quality of care at the UCI Medical Center.

Your signature below indicates you have read the information in this consent form and have had a chance to ask any questions you have about this study.

Note: If the research described in this form involves your protected health information (PHI), you will be asked to sign the UC HIPAA Research Authorization form for the use of your PHI.

I agree to participate in the study.

Printed Name of Subject

Signature of Subject Date

OR

Legally Authorized Representative Name (printed)

Legally Authorized Representative Signature Date

Relationship or Authority of Legally Authorized Representative to Subject

Printed Name of the Person Obtaining Consent

Signature of the Person Obtaining Consent Date

A witness signature is required on this consent form only if: ***(Researchers: check which one applies)***

☐Consent is obtained from the subject via the Short Form process, as approved by the IRB.
☐The subject has decision-making capacity, but cannot read, write, talk or is blind.
☐The subject's guardian/legally authorized representative (LAR) cannot read, write, talk or is blind.
☐The IRB specifically mandated a witness signature for this study (for example, high risk and/or invasive research procedures).

Note: The witness must be impartial (for example, not a member of the subject's family, not a member of the study team).

For the witness:
I confirm that the information in this consent form was accurately explained to and understood by the subject or legally authorized representative and that informed consent was given freely.

_____ _____

Witness Signature **Date**

(If no witness signature is required, this witness signature section of the consent form may be left blank).

_____

Printed Name of Witness

UNIVERSITY OF CALIFORNIA, IRVINE
Experimental Subject's Bill of Rights

The rights listed below are the right of every individual asked to participate in a research study. You have the right:

1. To be told about the nature and purpose of the study.

2. To be told about the procedures to be followed in the research study, and whether any of the drugs, devices, or procedures is different from what would be used in standard practice.

3. To receive a description of any side effects, discomforts, or risks that you can reasonably expect to occur during the study.

4. To be told of any benefits that you may reasonably expect from the participation in the study, if applicable.

5. To receive a description of any alternative procedures, drugs, or devices that might be helpful, and their risks and benefits compared to the proposed procedures, drugs or devices.

6. To be told of what sort of medical treatment, if any, will be available if any complications should arise.

7. To be given a chance to ask any questions concerning the research study both before agreeing to participate and at any time during the course of the study.

8. To refuse to participate in the research study. Participation is voluntary. You may refuse to answer any question or discontinue your involvement at any time without penalty or loss of benefits to which you might otherwise be entitled. Your decision will not affect your right to receive the care you would receive if you were not in the experiment.

9. To receive a copy of the signed and dated written consent form and a copy of this form.

10. To be given the opportunity to freely decide whether or not to consent to the research study without any force, coercion, or undue influence.

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact Advarra IRB at the address, phone, number, or email address listed in the WHOM TO CONTACT section of the informed consent form.

Please reference the following number when contacting the Study Subject Adviser: Pro00057635.

You may also contact UCI's Office of Research by phone, (949) 824-6068 or (949) 824-2125, by e-mail at IRB@research.uci.edu or by writing us at 160 Aldrich Hall, Irvine, CA 92697.