Patient Authorization and Consent to Participate in a Research Study

The Use of Ranolazine for Atrial Fibrillation and Diastolic Heart Failure
RAD-HF

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Sub-Investigators:	Brian Crandall, M.D. John Day, M.D. Pete Weiss, M.D. Jeffrey Osborn, M.D. Charles Mallendar, M.D. J. Brent Muhlestein, M.D., Rami Alharethi, M.D., Ritesh Dhar, M.D.
Sponsor:	RAD-HF is an investigator initiated research project and is partially funded by Gilead.
Location:	Intermountain Medical Center

You have been identified as potentially eligible for participation in the RAD-HF research study conducted by physician/investigators at IMC. You are being asked to participate in a research study called RAD-HF because you have because you have been diagnosed with:

- Atrial fibrillation (AF) Atrial fibrillation is a condition causing an irregular heartbeat. It may cause heart palpitations (irregular and/or racing heart beat), shortness of breath, chest pain, lightheadedness or fainting, and congestive heart failure. A person with atrial fibrillation can have other associated health conditions.
- Diastolic Heart Failure: is defined when signs and symptoms of heart failure (HF) are present, but left ventricular systolic (filling) function is preserved. It is characterized mainly by symptoms of fatigue, diminished exercise capacity, shortness of breath, lack of appetite or nausea, increased heart rate, and edema of the ankles, legs and/or abdomen.
- In addition, you have recently had an external electrical cardioversion. A cardioversion is the process of restoring the heart's normal rhythm by applying a controlled electric shock to the exterior of the chest

Background

Atrial fibrillation is a condition causing an irregular rapid heartbeat. It is common in our community and will affect between 6-10 percent of the population. Atrial fibrillation can cause stroke. Atrial fibrillation can also make the heart rate beat too quickly and less efficiently and as such cause heart failure symptoms which are shortness of breath, water or fluid retention in your abdomen or legs, chest discomfort, or feelings or tiredness or fatigue.

The most common cause of atrial fibrillation is high blood pressure. In people that have high blood pressure for many years, the lower muscular chambers of the heart (the ventricles) become thicker and stiffer. The upper chambers of the heart (the atrium) then become enlarged. The stretching and enlargement of the atrium cause these chambers to develop abnormal electrical impulses that become chaotic and result in atrial fibrillation.

When the ventricles of the heart become stiff and thick and then beat too quickly due to atrial fibrillation symptoms of heart failure can quickly develop. In this case, even though the pump function of the heart is strong, heart failure symptoms still develop. We call this situation diastolic heart failure. In patients with diastolic heart failure we need to approach the problem in two ways. First, we need a medication that helps the heart beat in a normal manner. Second, we need a medication that helps the heart be less stiff.

Ranolazine is approved by the U.S. Food and Drug Administration (FDA) and sold in the United States as Ranexa® for the treatment of recurrent, heart related chest pain called chronic angina.

Although ranolazine is approved by the FDA for recurrent chest pain, it is being used in this study to understand if it decreases AF in patients with Diastolic HF. Ranolazine has unique properties that also help treat abnormal heart rhythms and reduce the stiffness of the heart.

The testing of ranolazine in this study is investigational because the use of ranolazine as a treatment for AF or diastolic heart failure is not currently approved by the FDA. The FDA has granted permission to conduct this testing under the controlled conditions of a clinical research trial.

The purpose of this consent form is to provide you with information you and your family need to make an informed decision whether to take part in this study.

Why is this study being done?
The purpose of this study is to evaluate the efficacy of ranolazine in the prevention of recurrent AF in post-cardioversion patients with heart failure and preserved ejection fraction.

How many people will take part in this study?
110 patients will be enrolled in this study at Intermountain Medical Center.

What is involved in this study?
This research study is a double-blind study. This means that neither you nor your study team will know if you have been given study drug or placebo; however, the study doctor would be given this information if there was an emergent need for him/her to know.
You will be randomly assigned (like flipping a coin) into 1 of 2 treatment groups (ranolazine or placebo). There is an equal (1 out of 2 or 50/50) chance that you will receive ranolazine or placebo.
A placebo is a tablet or capsule containing material with no medicinal effect but which looks like an active study drug tablet or capsule. Placebo is the medication to which an investigational drug is compared in a scientific study to eliminate the possibility that the study team or the study patients may somehow influence the results by expecting the drug's effects.
Both ranolazine and placebo will be referred to as “study medication” in this document.

Study Procedures
Screening visit
After giving your informed consent to participate, we will perform some tests and ask questions to determine if you qualify for, and can safely participate in, the RAD- HF study.
The following items will be reviewed to determine whether you qualify for the study:

- Medical history and physical exam
- Review of medications (you will stay on your standard of care medications during this study)
- Assessment of heart failure status
- Heart failure questionnaire
- Laboratory tests (creatinine clearance, pregnancy test, basic metabolic panel, glucose, hemoglobin A1c, BNP brain natriuretic peptide)
- ECG (electrocardiogram)
- Transthoracic echocardiogram (TTE)—a probe is placed on your chest and images of your heart are recorded. The TTE does not require anesthesia.

Baseline visit
If you are eligible to participate in the RAD-HF study, you will then have a baseline visit in which you will be randomized. The following will occur at this visit:

- Laboratory tests (basic metabolic panel, glucose, hemoglobin A1c, BNP brain natriuretic peptide)
- ECG
- Randomization
- Dispense study medication
- Optional blood sample (DNA, plasma) Taken for long term storage described below.

Day 7 visit

You will need to return to the clinic for the Day 7 visit and the following will occur at this visit:

- Laboratory tests (basic metabolic panel, glucose, BNP brain natriuretic peptide)
- ECG
- Event monitor (A small, portable device you wear while you do your normal daily activities. This allows the monitor to record your heart for a longer time than an EKG.)
- Assess adverse events
- Dispense study medication

1 month visit:

You will need to return to the clinic for the 1 month visit and the following will occur at this visit:

- Laboratory tests (basic metabolic panel, glucose, BNP brain natriuretic peptide)
- ECG
- Event monitor
- Assess adverse events
- Dispense study medication

6 month visit:

You will need to return to the clinic for the 6 month visit and the following will occur at this visit:
Heart failure questionnaire
Laboratory tests (basic metabolic panel, glucose, BNP brain natriuretic peptide)
ECG
TTE
Event monitor
Assess adverse events
Dispense study medication: the investigator has the option to keep you on study medication until the last patient enrolled has completed their 6 month visit. (approx. 18 months)

As a part of this study, we would like to collect and store samples and health information for future research studies, from study participants who agree to give us these samples. Through these future studies, researchers hope to find new ways to detect, treat, and maybe even prevent or cure disease.

If you agree to provide samples for use in future research:

- At your baseline visit we will collect and store approximately 2 teaspoons (10 mL) of blood for future DNA testing. DNA is what makes up your genes that tell your cells what to do. DNA testing may tell us how a disease affects different types of people or it may help us find the type of person who will respond best to treatment.

The samples you give will be securely stored and labeled with a unique code number. The samples will be kept indefinitely (banked) and will only be identified by a number or code to protect your privacy.
Results from this research and the use of your samples will not be used to evaluate your medical condition or provide you with additional treatment
The sample you provide for future research will be used to test your DNA – also called genetic testing.

DNA is short for deoxyribonucleic acid. A gene, or DNA, contains information that determines in part the traits, such as eye color, height, or disease risk, that are passed on from parent to child. Genetic testing may tell us how a disease affects different types of people or it may help us find the type of person who will respond best to treatment.

The genetic studies described are for research purposes only. Therefore, you will receive no results from these genetic studies (except as described below). It is not the purpose of these studies to look for or provide you with any medical information or diagnoses relating to your present condition or any other disease or illness. These studies are not being used as diagnostic tests for any disease or illness. Your participation in this research project is not a substitute for your regular medical care or check-ups.

Potential Risks and the Genetic Information Non-Discrimination Act (GINA): There is a potential risk of loss of confidentiality. Every effort will be made to protect your confidential information, but this cannot be guaranteed. The genetic information obtained as a result of your participation in this research will not be included in your medical record. Information from which you may be personally identified will be maintained in a confidential, secure location at IMC accessible only by authorized members of the study team, and will not be disclosed to third parties except as described in this consent form, with your permission, or as may be required by law.

The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:

- Health insurance companies and group plans may not request genetic information from this research;
- Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premiums;
- Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Samples collected as part of this study may be valuable for scientific, research, or teaching purposes or for the development of a new medical product. The sponsor and/or the developers will assert all rights of ownership in the samples and all rights arising from use of the samples and may profit from this. In this event, there is no plan to compensate you.

If I agree to provide samples, can I request that my samples be destroyed?
If you decide later that you would like your samples destroyed, you must let T. Jared Bunch MD know you are withdrawing your permission for your samples to be stored and used for future research.

- During the main study, please contact T. Jared Bunch MD in writing. The mailing address is T. Jared Bunch MD c/o Cardiology Department, Intermountain Medical Center, 5121 South Cottonwood Street, Murray, UT 84157-7000.
- After the main study, please contact T. Jared Bunch MD in writing. The mailing address is T. Jared Bunch MD c/o Cardiology Department, Intermountain Medical Center, 5121 South Cottonwood Street, Murray, UT 84157-7000.

If the information linking your coded samples to you has already been destroyed, your samples can no longer be linked to you and we will be unable to locate them for destruction.

Also, even though your samples will be destroyed,

- We cannot get back samples or information that we have already given out to researchers

- You cannot withdraw your samples and information from studies that have already begun

What are the risks of this study?
Risks or discomforts that may be expected include:
Risks associated with ranolazine
Ranolazine has been studied in a total of 2,018 subjects with chronic angina. Of these subjects, 1,251 subjects received treatment with ranolazine in open-label, long-term studies: 1,227 subjects were exposed to ranolazine for more than 1 year, 613 subjects for more than 2 years, 531 subjects for more than 3 years, and 326 subjects for more than 4 years.

In these studies, about 6% (3 in every 50 subjects) of subjects who received ranolazine (at doses up to 1000 mg twice daily) stopped taking the medication because of side effects compared to 3% of subjects taking placebo. The most common side effects that led to stopping ranolazine were dizziness, nausea, weakness (asthenia), constipation, and headache. Doses above 1000 mg twice daily are poorly tolerated.

The most frequently reported side effects (4% or greater [2 or more in every 50 subjects] and more common on ranolazine than on placebo) were dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). Dizziness may be dose-related. In open-label, long-term treatment studies, similar side-effects were observed.

Less frequently reported side effects (0.5 to 4.0% [up to 2 in every 50 subjects]) included the following: slow heart beat (bradycardia), palpitations (of the heart), ringing in the ears (tinnitus), blurred vision, vertigo, abdominal pain, dry mouth, vomiting, indigestion (dyspepsia), swelling of hands and feet (peripheral edema), shortness of breath (dyspnea), abnormally low blood pressure (hypotension), low blood pressure and dizziness upon standing (orthostatic hypotension), feeling weak (asthenia), loss of appetite (anorexia), fainting (syncope), confusion, blood in the urine (hematuria), excessive sweating (hyperhidrosis).

Other uncommon (< 0.5% [less than 1 in every 200 subjects]) but potentially medically important side effects observed included: forgetfulness (amnesia), a rare, but potentially serious rash and swelling of the face, lips, and/or tongue (angioedema), abnormal color in the urine (chromaturia), high white blood cell count of eosinophils (eosinophilia), decreased sensitivity to touch (hypoesthesia), increased urea in the blood, kidney failure, low white blood cell count (leukopenia), low red and white blood cells and low platelets (pancytopenia), numbness/tingling (paresthesia), low platelet count (thrombocytopenia), tremor, and damage to the lungs (pulmonary fibrosis).

There are other events that have been reported and it is not possible at this time to estimate the frequency or establish a causal relationship with ranolazine. These events are known to include: hallucinations, skin rash, and itchy skin (pruritus).

Other risks
The treatment and procedures involved in the study may involve risk to you (or to an embryo, fetus or nursing infant) which are currently unknown, unforeseen or unanticipated. In one animal study ranolazine given twice a day for 30 days increased the number of tumors formed in a special type of mouse specifically bred to grow tumors. What this means in humans is not clear. Based on other studies an increased risk of tumors to you in this study is not expected.
Ranolazine affects how the body removes some drugs, and other drugs have an effect on how the body removes ranolazine. During this study, it is important that you tell your study team about all drugs or

medications that you are taking. This study may require that you not use or take certain products. For example, the consumption of grapefruit juice or Seville orange juice or products which contain grapefruit or Seville oranges, digitalis preparations (such as digoxin), use of a greater than 1000 mg total daily dose of metformin, dabigatran, and St. John's Wort are prohibited throughout the study, in that these substances may interfere with the effectiveness of the drug you are taking.

Unknown/unforeseeable risks or discomforts

In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these study drugs, including severe or life threatening allergic reactions, unexpected interactions with another medication or interaction between study drugs. Some symptoms of allergic reactions are: rash, difficulty breathing, wheezing, sudden drop in blood pressure, swelling around the mouth, throat or eyes, a fast pulse, and sweating. Please alert the study team immediately if you have any of these symptoms, or any other side effects, during the study.

Risks associated with procedures done in this research study

Electrocardiogram (ECG) and Event monitor

An ECG and an event monitor are tests that measure the electrical activity of the heartbeat using electrodes (disposable adhesive discs placed on the skin). There is no pain or risk associated with having an ECG. When the electrodes are removed, there may be some minor skin discomfort or irritation. Your chest may be shaved in spots to make a smooth surface for electrode placement for this procedure.

Risks associated with having **blood drawn** from an arm vein include:

• discomfort	• bruising	• infection
• bleeding or clotting	• fainting is also possible, although unlikely	

Pregnancy risk

Inadequate information is available regarding the effect of ranolazine on the human fetus or newborn breastfed infant; therefore, ranolazine should not be used by anyone who is pregnant or breastfeeding. Women of childbearing potential must have a negative pregnancy test at the time of screening. Women of childbearing potential must agree to use a reliable form of contraception during this study, which your study doctor will discuss with you. Medically acceptable birth control methods for this study include:

- hormonal methods (birth control pills, or injected or implanted contraceptive)
- intrauterine device (IUD) with spermicide,
- condom with spermicide or
- diaphragm with spermicide.

Even if you use a medically acceptable birth control method, you could still become pregnant. It is important to the safety of your unborn child that if an accidental pregnancy occurs, you tell your physicians immediately. If you become pregnant while participating in RAD-HF, you will be discontinued from study treatment, you will be immediately referred to the physician or other provider of your choice for obstetrical care, and, for safety reasons, the investigator will request your permission to collect data regarding the outcome of the pregnancy.

How long will I be in the study?

You will participate in this study for 6 months. The investigator may decide to take you off the study at any time if he/she feels your continued participation would in any way impair your health. The investigator has the option to keep you on study medication until the last patient enrolled has completed their 6 month visit. (approx. 18 months)

What are the benefits to taking part in the study?

Possible benefit to you

Personal benefit may or may not result from participation in this study.

Potential Benefit to Others

Your participation in the RAD-HF trial may help future patients by providing physicians with better treatment options for atrial fibrillation and diastolic heart failure.

What other options do I have?

Instead of being in this study, you may choose not to enroll in this study and receive the standard appropriate atrial fibrillation care provided all patients with your condition (s).
Choosing not to participate in this study will not result in any penalty or lost benefits to which you are otherwise entitled and the medical care you receive will not be affected in any way.

What are the costs?

- You or your insurance carrier will be billed in the usual manner for the normal standard of care all patients with your condition(s) would receive if treated outside of this study.
- You will not be billed for activities performed solely for participation in the RAD-HF study (non-standard of care testing).
  These activities are:
  Screening Visit: Creatinine clearance, pregnancy test
  Baseline Visit: Hemoglobin A1c, study medication, optional blood sample
  Day 7: Basic metabolic panel, glucose, BNP (brain natriuretic peptide), study medication
  1 Month: Basic metabolic panel, glucose, BNP (brain natriuretic peptide), electrocardiogram, study medication
  6 Month: Hemoglobin A1c, study medication, electrocardiogram
- You will not be paid for participating in this study
- You will not be charged to enroll in this study.

What if I get hurt or ill from my participation?

As a research subject, you may be harmed as a result of your participation. It is the nature of medical research that all adverse events are not preventable or foreseeable. In the event you sustain injury resulting from your participation in the research project, Intermountain Healthcare can provide to you, emergency and temporary medical treatment and will bill your insurance company. Since this is a research study, payment for any injury resulting from your participation in this research study may not be covered by some health insurance plans.

If you believe that you have sustained an injury as a result of your participation in this clinical investigation, we ask that you contact the investigator as soon as possible. You may also contact the Office of Research at (800) 321-2107.

What about confidentiality?

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Intermountain Healthcare has a commitment to protect your confidentiality. Federal regulations require that you understand how your protected health information (PHI) is used for this study.

This is the information we will use:

☒ Your **initials** may be attached to a study identification code (for example ABC-123).

☒ Your **name**, **initials, date of birth**, **address** and **telephone number(s)** will be placed into a study document entitled "confidential enrollment log". This log is not available to anyone except regulatory agencies with oversight for the protection of human subjects and Intermountain Healthcare staff members who are conducting this clinical trial at Intermountain Medical Center. There are several reasons investigators keep the confidential enrollment log:

- we may need to contact you with information regarding the trial or results of the trial after your participation has ended and/or

regulatory agencies may request to examine all records generated during a clinical trial.

☒ Your **previous medical history** may be reviewed to determine your eligibility to participate in this trial. Hospital admission and discharge summaries placed in your hospital chart(s) give us the most reliable information.

☒ Your **most current medical history** or information specific to the event for which you have been hospitalized (for example, a heart attack) may be reviewed to determine your eligibility to participate in this trial. Hospital admission and discharge summaries placed in your hospital chart(s) give us the most reliable information.

☒ It is important that we know about any **allergies** you may have as this may affect your safety while participating in this clinical trial.

☒ **Current and past medications or therapies/results** which may affect your eligibility for this trial or your safety while participating in it may be reviewed to determine your eligibility to participate in this trial.

☒ Information (results) from **tests, procedures and physical examinations**, such as blood pressure readings, heart rate, breathing rate, and temperature at specified times, may be reviewed for the purpose of establishing your baseline condition and to continue monitoring your progress and/or safety while participating in this trial.

☒ We may need to review your prior medical history (**PMI)/medical records kept by other physicians** you may see for your medical conditions(s) to establish eligibility, to document any adverse events/side effects you may have during the trial and to assure that you can safely participate in this trial. If this information is needed we will ask you to give us permission to ask your doctor for it by signing a medical release of information form.

☒ **Dates** of surgeries, device implants, or procedures related to this clinical trial.

☒ The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

☒ A description of this clinical study will be available on http://www.ClinicalStudys.gov, as required by US 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 any time.

Others who will have access to your identifiable PHI for this research project include:

- (Intermountain Healthcare) Intermountain Medical Center's Institutional Review Board (the committee that oversees research studying people) and authorized members of Intermountain Healthcare's workforce who need the information to perform their duties (for example: provide treatment, to ensure integrity of the research, and for accounting or billing matters),
- the Food and Drug Administration (FDA), and
- others as required by law.

As part of the study requirements, T. Jared Bunch MD and his study team will report the overall results (in which no individual will be identified) of this clinical investigation to representatives of Gilead, the company that is providing partial funding for this investigation.

Except as addressed in this authorization form, 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 Intermountain Healthcare. Information received during the study will not be placed on any mailing lists or sold to anyone for marketing purposes. For records disclosed outside of Intermountain Healthcare, your information will be assigned a unique code number (for example 123-ABC). The key to the code will be kept in a password protected file stored in the Intermountain Healthcare computer network.

Signing this document means you allow us, the researchers in this study, and others working with us to use PHI about your health for this research study. You can choose whether or not you will participate in this research study; however, in order to participate you have to sign this consent form.

You may change your mind later, and ask us to stop using or disclosing your PHI. You must either give this notice, called a revocation, in writing to the principal investigator, T. Jared Bunch, M.D. the principal investigator's staff, or mail it to T. Jared Bunch, M.D. c/o Cardiology Department, Intermountain Medical Center, 5121 South Cottonwood Street, Murray, UT 84157-7000. If you revoke this authorization, we will not be able to collect new information about you, and you will not be able to participate in the study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

If we send PHI about you outside Intermountain Healthcare, based on this or any other authorization you sign, we cannot guarantee that the recipient will not redisclose your PHI to a third party. The recipient of the information may not be required to abide by this authorization or applicable federal and state law governing the use and disclosure of your PHI.

You have a right to information used to make decisions about your health care; however, your information from this study will not be available to you during the study. It will be available after the study is finished and the results are made available. This authorization does not have an expiration date.

What are my rights as a participant? Where can I get more information?
A copy of this form will be given to you as a participant in this study if you agree to enter the RAD-HF study.

Taking part in this study is your choice and your participation is voluntary. If you agree to take part and then decide against it, you can withdraw for any reason. If you decide to stop taking part in the study, you should talk to the researcher so it can be done safely. Leaving the study will not result in any penalty or lost benefits to which you are otherwise entitled and the medical care you receive will not be affected in any way.

If you have any questions now or at any point during the study concerning the research or related matters, or, if you think you have had study related injury, you should call the principal investigator, T. Jared Bunch, M.D**.** at (801) 507-4701 (24 hour voicemail).

If you would like to speak to someone not associated with the study about your rights as a participant, or any other matter related to clinical research conducted at Intermountain Healthcare facilities, contact the Intermountain Healthcare Office of Research at (800) 321-2107.

Sometimes during the course of a research project, new information becomes available about the treatment/drug/procedure/data that is being studied or there is a change in the trial protocol (directions on how to conduct the trial). If this happens, your research doctor will tell you about how it will affect your participation in the trial and discuss with you whether you want to continue in the study. If you decide to withdraw from study treatment, the investigator will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form, which will contain the new information. (You may sign more than one consent document throughout the duration of the trial.) Also, upon receiving new information the investigator might consider it to be in your best interest to withdraw you from participation in the study. He/she will explain the reasons and arrange for your care to continue.

Signatures

For more information about my rights to my PHI, how to revoke this authorization, and how (Intermountain Healthcare) Intermountain Medical Center uses my health information, I may ask to see or obtain a copy of the Intermountain Healthcare Notice of Privacy Practices. I hereby acknowledge that I have received or been offered a copy of Intermountain Healthcare's Notice of Privacy Practices.

My signature below indicates that I have read or had read to me and understand all of the information given to me in this document. The information in this document has been explained to me and I have had the opportunity to ask questions. My signature below indicates that I voluntarily agree to participate in the study described in this document and I have received a copy of my signed/dated consent.

_____	_____	_____
Patient's Printed/Typed Name	***Patient's Signature***	***Date***

Please initial your choice as to whether you agree to have your blood sample stored and used for future genetic (DNA) sampling:

_____ I agree to allow my blood sample to be stored and used for future genetic (DNA) sampling.

_____ I DO NOT agree to allow my blood sample to be stored and used for future genetic (DNA) sampling

If the patient is unable to give consent and authorization, consent and authorization is given by the following authorized personal representative of the individual:

_____
Name of Authorized Personal Representative

_____	_____
Signature of Authorized Personal Representative	***Date***

If the participant is unable to give authorization and consent, describe the legal representative's authority to act for the individual: _____

I, the undersigned, certify that I have fully explained this clinical investigation to the patient (and to the patient's legal/personal representative(s), if the patient wishes) signing this consent form and the patient/representative (if applicable) has been given the opportunity to ask questions regarding the contents of this consent form and the expectations associated with his/her participation in this research study.

_____	_____
Signature of Person Obtaining Consent	D***ate***