CONSENT TO PARTICIPATE IN RESEARCH

Sponsor / Study Title: **University of Alabama at Birmingham / "A REAL-WORLD COMPARATIVE EFFECTIVENESS TRIAL OF TREATMENT STRATEGIES IN PATIENTS WITH RHEUMATOID ARTHRITIS: THE RA-PRO (PATIENT-REPORTED OUTCOMES) PRAGMATIC TRIAL (RA-PROPR)"**

Protocol Number: **05312021**

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General Information	You are being asked to take part in a research study. This study is voluntary, meaning you do not have to take part in it. The procedures, risks, and benefits are fully described further in the consent form.
Purpose	The purpose of the study is to assess whether replacing their current TNF-biologic with a non-TNF-biologic is superior to adding a targeted synthetic DMARD (disease-modifying anti-rheumatic) medication with active RA despite current TNF-biologic treatment.
Duration & Visits	You will be in this study for 12 months.
Overview of Procedures	Your rheumatologist will talk with you during a regularly scheduled visit and ask you whether you would be willing to participate in this research study. If you are interested in learning more about this research study, you will meet with a member of the study staff who will tell you more about the study and the consent process. An experienced healthcare provider will draw a small amount of your blood (about 2 teaspoons), which will then be tested by the research lab. We will test these samples for certain genetic markers and store them for use later.

Risks	There may be a minimal risk and discomfort involved in drawing your blood sample. The most common side effects can include dizziness or nausea. There is also a possibility that a small bruise may appear at the entry site to your vein when a needle is used for the collection of blood. This side effect is infrequent in participants with normal veins and usually disappears within a few days. There is a risk of the loss of confidentiality as part of participating in this study. However, we will take great care to safeguard your information.
Benefits	You may not benefit directly from taking part in this study. However, this study may help us to better understand whether addition of one type of treatment (non-TNFi-biologic medication) for your rheumatoid arthritis is better than adding another type of treatment (targeted synthetic DMARD medication) in improving your sleep, fatigue, and ability to do daily activities.
Alternatives	If you do not want to take part in the study you can decline to participate. This decision will not affect your healthcare provided by your doctor.

Purpose of the Research Study

We are asking you to take part in a research study. The purpose of this research study is to see if replacing your current TNFi-biologic with a targeted synthetic disease-modifying anti-rheumatic drug (tsDMARD) is better than replacing it with a non-tumor necrosis factor inhibitor (non-TNFi)-biologic medication for Rheumatoid Arthritis (RA) treatment in patients who have taken a TNFi-biologic and it may not be working well enough. This study will answer the question: Which of these two medication groups is better for RA patient to be used first? We currently do not know the answer to this question. RA patients care about if their treatments will help their symptoms get better (daily function, sleep, fatigue, pain). Results from this study will help both patients and physicians in the future pick a treatment option that may work better for specific symptoms of RA that bother them the most.

Both groups of medications (targeted synthetic DMARDs (tsDMARD) and non-tumor necrosis factor inhibitor (TNFi)-biologics) are currently prescribed and used for people with RA when patients continue to have active disease after having tried a TNFi-biologic and other medications first. Both these groups of drugs are widely used for RA treatment. Even outside of the study, these are the most common medications offered to patients for the treatment of RA to improve joint pain, joint swelling, and other RA symptoms. The study plans to enroll about 924 people.

The University receives compensation from the sponsor of this study for the conduct of this study. If you have any questions, please discuss this with your study doctor.

Study Participation & Procedures

Participants with active RA despite having taken a TNFi-biologic will be recruited at 36 geographically diverse RA/rheumatology clinics in the U.S. If you agree to participate, your participation in this study will be 12 months, and will include 6 study-related visits. At each of these visits blood collections and/or urine samples will be collected. All other study visits will last approximately 1 hour. The things you will be asked to do are described in detail later in this consent form.

At the initial screening visit, you will undergo a blood draw, and physical examination where a member of the study staff will ask you questions about your medical history. If you continue to qualify to participate in this study by meeting all study requirements, you will be randomized to receive either the non-TNFi-biologic strategy which includes the following four medications given by injections that participants and their providers can chose from: abatacept, tocilizumab, sarilumab, and rituximab; or randomized to the tsDMARD which includes three tsDMARDs (Xeljanz™, Olumiant™, Rinvoq™), which are taken as pills by mouth. No investigational product will be dispensed as part of participation in this study.

At 4 months or later, if your RA does not get better with the medication you were randomized to, you can either continue with the current medication to give it a little more time, or switch to another medication, in discussion with your doctor. Regardless of whether you continue your first medication or switch to another medication, we will complete all the remaining visits for the 12 month study period.

All medication received by participants will be in original packaging, labeling, and manufacturer formulation. All medications will be prescribed and dispensed as part of your usual clinical care.

Blood Tests: Blood will be drawn 3 times during this study. Blood is typically drawn at these time points for standard clinic care. Needle sticks are painful for a short period of time and sometimes will cause bruising at the site for a couple of days. You might feel dizzy or faint during a blood draw but this generally passes within a few minutes. Each time we draw blood, we will take about 2 teaspoons of blood. We will do several tests to make sure it is safe to use the standard of care medicine, and to look for any side effects of the standard of care medicine. This will include tests to check for infection, proteins in your blood, certain cell counts. If you are pregnant or planning to become pregnant, you will not be able to participate in the study.

Taking the standard of care medications may involve risks to a pregnant woman, an embryo, fetus (unborn baby) or nursing infant. Therefore, if you are pregnant, planning to become pregnant, or are breastfeeding a child, you cannot participate in this study.

All women of childbearing potential must use an effective form of birth control during this study and for 30 days after completion of the study. Subjects taking abatacept, tocilizumab, or sarilumab must use an effective form of birth control during the study and for 70 days after completion of the study. Subjects taking rituximab must use an effective form of birth control during the study and for 12 months after the last dose of study drug. Acceptable methods of birth control include:

- Hormonal birth control methods
- Intra-uterine device (IUD)
- A double-barrier method (diaphragm with spermicide, condom with spermicide)
- Abstinence

All male participants will be cautioned to use proper birth control methods with their partners during the course of the study.

Participants should discuss contraception with their study doctor.

If you become pregnant, the study staff may collect information about the pregnancy, its outcome, and the health of the child after birth.

Your blood samples will be labeled with a numerical code for analysis for this study in laboratories located at the study site. Any remaining samples may be used for further analysis of other related or unrelated research studies. However, you will have the option at the end of this consent form to not agree to the storage of your blood or urine samples for research purposes other than those specifically involved with this study.

Screening Visit

Before the study starts, you will be asked to sign and date this consent form and give your health history. The study doctor will ask you questions and perform procedures and tests to find out if you can be in the study. These include:

- Review inclusion and exclusion criteria to assess your eligibility for the study.
- Recording of your personal information, such as your name, age, race, etc.
- Recording of your medical and surgical history.
- Collection of participant-reported measures such as physical function and levels of pain you may be experiencing.
- Recording of all prior and current prescription medications, over the counter medications, vitamins and herbs.
- Collection of blood samples (about 2 teaspoons of blood) for clinical laboratory analysis and pregnancy screening for women of childbearing potential. The study doctor or study staff will tell you if the pregnancy test results are positive. The results of the pregnancy test must be negative and you must be free of infection to be in the study.

VISITS 1-6 (Month 2-12)
Following your screening visit you will be followed as part of your usual care for the next 12 months (1 year).
While participating in this study you will be asked to provide updates about your health and how you are feeling, as well as complete some exams with your study doctor. This includes:

- Recording any updates of your medical and surgical history.
- Recording any updates to prescription medications, over the counter medications, vitamins and herbs.
- Obtain and record current vital signs including pulse rate, sitting blood pressure, and body temperature.
- A targeted physical exam. You should ask the study doctor about what will happen during this exam.
- An assessment of your status and how your rheumatoid arthritis is affecting your daily activities.
- Answer questions about your rheumatoid arthritis and any flares you may have experienced.
- Blood draw collection only at visits 0, 4, 12.
- Assess compliance/adherence to prescribed medication.
- Recording any adverse events you may have experienced.

Blood samples (about 2 teaspoons) are collected at study visits 0, 4, and 12; some of the blood samples collected may be used to help the study staff determine effects of standard of care drug treatments. These samples may be stored for up to 7 years.

If you stop getting treatment before 12 months pass, you will be asked to stay in the study for follow-up. Follow-up will consist of answering questions about your health, and changes in your medical conditions and medications during your routine care visits.

Risks and Discomforts
There may be a minimal risk and discomfort involved in drawing your blood sample. The most common side effects can include dizziness or nausea. There is also a possibility that a small bruise may appear at the entry site into your vein when a needle is used for collection of the blood. This side effect is infrequent in donors with normal veins and usually disappears within a few days. There is a risk of loss of confidentiality as part of participating in this study; however, we take great care to safeguard your information.

Both targeted synthetic DMARDs and non-TNFi biologics are Food and Drug Administration approved medications for the treatment of RA. Targeted synthetic DMARDs have been used for treatment of RA for up to 9 years and non-TNFi biologics for up to 23 years. Uncommon or rare side effects may occur.

For targeted synthetic DMARDs which include the following medications Tofacitinib (Xeljanz™), Baricitinib (Olumiant™), and Upadacitinib (Rinvoq™), the following life-threatening side effects have been reported:

Serious Infections
Cancer: RINVOQ may increase your risk of certain cancers by changing the way your immune system works. Lymphoma and other cancers, including skin cancers can happen in people taking RINVOQ.
Thrombosis/clotting: Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) and arteries (arterial thrombosis) can happen in some people taking RINVOQ. This may be life-threatening and cause death.
Gastrointestinal Perforations: Some people taking RINVOQ can get tears in their stomach or intestines. This happens most often in people who take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
Changes in laboratory values: low red blood cell count (anemia), low white blood cells, increased liver enzymes, and increased cholesterol levels
Embryo-Fetal Toxicity: Based on animal studies, RINVOQ may harm your unborn baby.

The most common side effects for Upadacitinib/RINVOQ™ are upper respiratory tract infection, nausea, cough, and fever.

The most common side effects for Tofacitinib/XELJANZ™ are upper respiratory tract infection, runny nose, common cold, diarrhea, and headache.

The most common side effects for Baricitinib/OLUMIANT™are upper respiratory tract infection nausea, herpes simplex infection and herpes zoster infection.

For non-TNFi-biologics, which include the following medications: -abatacept (Orencia), tocilizumab (Actemra), sarilumab (Kevzara), rituximab (Rituxan) respectively, the following possible side effects have been reported:
Serious infections, including fungal infections
Lymphoma and other cancers, Serious allergic reactions
Hepatitis B virus reactivation: If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you use TNFs.
Demyelinating neurological disease: Signs and symptoms of a nervous system problem include: numbness or tingling, problems with your vision, weakness in your arms or legs, and dizziness.
Decreased red blood cell count (anemia), white cells or platelets
Lupus-like disease: Symptoms include chest discomfort or pain that does not go away, shortness of breath, joint pain, or a rash on your cheeks or arms that gets worse in the sun.
Liver toxicity: Liver problems can happen in people who use TNF-blocker medicines. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms: ◦ feel very tired ◦ poor appetite or vomiting ◦ skin or eyes look yellow ◦ pain on the right side of your stomach (abdomen)

Stroke or heart attack

Specific risks for each individual medication also include but are not limited to the following. There may be risks which are currently unknown.

The most common side effects for tocilizumab/ACTEMRA™ are upper respiratory tract infection, (common cold, sinus infections), headache, increased blood pressure (hypertension), injection site reactions. The most common side effects for abatacept/ORENCIA™ are headache, sore throat, upper respiratory tract infection, and nausea.

The most common side effects for sarilumab/KEVZARA™ are injection site redness, upper respiratory tract infection, urinary tract infection, and nasal congestion, sore throat, and runny nose.
The most common side effects for rituximab/RITUXAN™ are infusion reactions (which could include itching, rash or hives, swelling of the tongue, lips, or eyelids, redness on the face and neck area, also called flushing, cough, nausea, muscle or joint pain, swelling of any part of your body, feeling short of breath), chills, infections, body aches, tiredness, and low white blood cells (which can lead to an increased risk of infection).

The FDA recently issued a warning related to the targeted synthetic DMARDs which include the following medications Tofacitinib(Xeljanz™), Baricitinib (Olumiant™), and Upadacitinib (Rinvoq™), based on a study that compared Tofacitinib(Xeljanz™) to TNFi-biologics.

(1) Risk of heart attacks: This risk is 4 out of 1000 people taking Tofacitinib (Xeljanz™) compared to 2 out of 1000 people taking TNFi-biologics.
(2) Risk of stroke: This risk is 3 out of 1000 people taking Tofacitinib(Xeljanz™) compared to 4 out of 1000 people taking TNFi-biologics.
(3) Risk of cancer: This risk is 12 out of 1000 people taking Tofacitinib(Xeljanz™) compared to 8 out of 1000 people taking TNFi-biologics.
(4) Risk of venous clots in legs or the lung (also called deep venous thrombosis [DVT, blood clots in the vein, which can cause pain, swelling and/or redness] and pulmonary embolism [PE, blood clots in the lung (possible failure to breathe)] respectively): This risk is 9 out of 1000 people taking Tofacitinib (Xeljanz™) compared to 3 out of 1000 people taking TNFi-biologics.

Whether or not there is an actual difference between these medications in these risks is unclear, since the range of risk varies, and these events are not common. Rheumatoid arthritis is known to increase the risk of heart attacks, stroke, cancer and clots.
The exact amount of risk of these conditions that is due to rheumatoid arthritis versus due to one of these medications is unknown.

There may be risks with each class of medication which are currently unknown.

You will be assigned to a group by chance, which may prove to be less effective or to have more side effects than the other study group or alternatives.

Injury Compensation

This research study does not involve an intervention, nor does it involve more than minimal risk. Therefore, it is not expected that you will be injured as a result of taking part in the study.

The sponsor of this study, the University of Arizona and Banner-University Medical Center have no funds set aside for the payment of treatment expenses for this study.

Benefits

You will not benefit directly from taking part in this study. However, this study may help us to better understand how to better provide treatment and care for participants like you with rheumatoid arthritis.

Alternatives

If you do not want to take part in the study you can decline to participate. This decision will not affect your healthcare provided by your doctor.

Will my study-related information be shared, disclosed, and kept confidential?

It is anticipated that there will be circumstances where your study related information and Protected Health Information (PHI) will be released to persons and organizations described in this form. If you sign this form, you give permission to the research team to use and/or disclose your PHI for this study. Your information may be shared or disclosed with others to conduct the study, for regulatory purposes, and to help ensure that the study has been done correctly. These other groups include:

- Office for Human Research Protections or other federal, state, or international regulatory agencies
- Food and Drug Administration
- *Banner University Medical Group and Banner Health*
- Advarra IRB
- The University of Arizona (UA) and the UA Institutional Review Board
- The sponsor supporting the study, their agents or study monitors
- Your primary care physician or a specialist taking care of your health.

If you agree to take part in this study a copy of this signed informed consent form will be saved into your electronic medical record (EMR) at Banner Health. As a result, healthcare providers and staff who are not working on this study, but who may provide you medical treatment in the future, will know that you are taking part or took part in this study.

Your PHI may no longer be protected under the HIPAA privacy rule once it is disclosed by the research team.

What study-related information and PHI will be obtained, used or disclosed from my medical record at Banner?

Information related to this research study that identifies you and your PHI will be collected from your past, present, and future hospital and/or other health care provider medical records.

The PHI you are authorizing to be used and/or disclosed in connection with this research study is:

- Your name.
- Address.
- Phone number.
- Date of birth.
- Medical history.
- Information from your study visits, including all test results.

Demographic information to be disclosed may include, but is not limited to, your name, address, phone number, or social security number. If you receive compensation for participating in this research study, information identifying you may be used or disclosed as necessary to provide that compensation.

Your existing health records may include information related to the diagnosis or treatment of sexually transmitted disease (STD), acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), other communicable diseases, genetic information (e.g., genetic testing), and/or alcohol and/or drug abuse. The study staff and study sponsor's monitor may see this information while reviewing your regular health records for this study, but they WILL NOT create, collect, or disclose this type of information for the purposes of this research study.

When will my authorization expire?

There is no expiration date or event for your authorization. Therefore, unless you cancel this authorization (as instructed below) this authorization will continue to be effective.

Do I have to sign this authorization form?
You do not have to sign this authorization. However, if you decide not to sign, you will not be able to participate in this research study; and it will not affect any non-study Banner Health medical treatment or health care, payment, enrollment in any health plans, or benefits.

What do I need to know if I decide to cancel my authorization?
After signing the authorization, you may decide to cancel your previous authorization for the research team to use your PHI. If you cancel the authorization, you will no longer be able to stay in the research study. Please note that any PHI collected before you cancel the authorization may still be used. You may revoke the authorization by contacting the Principal Investigator in writing. The Principal Investigators address and telephone numbers is listed on the first page of this form.

Will access be limited to your research study record during this study?
You may not have access to the research information developed as part of this study until it is completed.

STATEMENT OF AUTHORIZATION
I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

<u>Voluntary Participation and Withdrawal</u>
Whether or not you take part in this study is your choice. Choosing not to participate in the study, or leaving the study after you join will not result in any penalty or loss of benefits to which you are otherwise entitled.

You are free to withdraw from this study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the standard of care drug and referred for follow-up care. You can contact the study doctor or the study staff at the telephone number listed on page one of this form if you want to withdraw from the study. The study doctor can end your participation in the study at any time without your consent.

Cost of Participation

There are no anticipated additional costs for you to be in this study, except for your time. Regular medical care performed while participating in study (including physical exams, lab work, medications, etc.) will be billed to you and / or your insurance company as usual. Not all insurance companies are willing to pay for services performed in a clinical trial. Please speak with your insurance company to find out what you may be financially liable for.

Payment for Participation

You will receive $25 for each study visit you complete, up to total payment of $150 if you complete all visits for the study. You will not receive payment for the screening visit.

You will be paid following each completed visit.

If you do not finish the entire study, you will be paid at the time you decide to stop taking part in the study. Ask the study staff about the method of payment that will be used for this study (for example, check, cash, gift card, direct deposit).

Compensation for participation in a research study is considered taxable income for you. If your compensation for this research study or a combination of research studies is $600 or more in a calendar year (January to December), you will receive an IRS Form 1099 to report on your taxes.

For any compensation or reimbursement you receive, we are required to obtain identifiable information such as your name, address, and Social Security number for financial compliance purposes.

New Findings

You will be told by the study doctor or the study staff if new information becomes available that might affect your choice to stay in the study.

Optional

Will my data or specimens be stored for future research?

We would like your permission to keep your private information (data containing personal information) and bio specimens (RA) collected in this study for future research. The future research may be similar to this study or may be completely different. Your private information and bio specimens will be stored indefinitely or until used.

Your private information and bio specimens will be identifiable. Results of any future research will not be given to you or your doctor.

You can take part in this study even if you decide not to let us keep your identifiable private information and identifiable bio specimens for future research.

If you give us permission now to keep your identifiable private information and identifiable bio specimens, you can change your mind later and ask us to destroy it. However, once we have analyzed your private information and bio specimens, we may not be able to take it out of our future research.

We may share your identifiable private information and identifiable bio specimens, so that others can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your identifiable private information and identifiable bio specimens with other researchers, we will not be able to get it back.

Future research use of your identifiable private information and identifiable bio specimens will be conducted in compliance with applicable regulatory requirements. You will not find out the results of the future research. Allowing us to do future research on your identifiable private information and identifiable bio specimens will not benefit you directly.

The identifiable private information and identifiable bio specimens used for future research may be used for commercial profit. There are no plans to provide financial compensation to you should this occur.

Future Use of PHI

Future research activity is part of this project. If you choose to participate in the future research activity your PHI will be included in this future research activity.

> By initialing the line below, you agree to allow your information to be used and/or disclosed for the optional future research referenced above.
>
> _____ Initials

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 participants. If you have any questions about your rights as a research participant, 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: Pro00055380.

If you have questions, concerns, or complaints about the use or sharing of your health information or would like a copy of the Banner Notice of Privacy Practices, you may contact the Banner Research HIPAA Liaison at 602-839-4583 or BHResearchCompliance@bannerhealth.com.

To cancel your authorization for access to PHI you must notify the study doctor listed on page one of this document.

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.

Legal Rights

You are not waiving any of your legal rights by signing and dating this consent form.

Signatures

Your signature and date below indicates that you have read the information provided above and agree to participate in this study. You will receive a copy of this signed and dated consent form.

_____

Participant's Printed Name

_____ _____

Participant's Signature Date

_____

Printed Name of the Person Conducting the Consent Discussion

_____ _____

Signature of the Person Conducting the Consent Discussion Date