Partners HealthCare System
Research Consent Form

Subject Identification

General Template - Drug Clinical Trial
Version Date: October 2014

Protocol Title: Maintenance of ANCA vasculitis remission by intermittent rituximab dosing based on B-cell reconstitution vs a serologic ANCA flare. (MAINTAINCAVAS)

Principal Investigator: John L. Niles, MD

Site Principal Investigator:

Description of Subject Population: Adults who have been diagnosed with GPA (granulomatosis with polyangiitis) (GPA was formerly known as Wegener's Granulomatosis) or microscopic polyangiitis (MPA) and have been receiving Rituxan (rituximab) for treatment for a minimum of two years.

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Why is this research study being done?

This research study is being done to figure out the best way to maintain remission in ANCA vasculitis with rituximab induced B cell depletion. The fixed rituximab dosing schedule appears to be safe and effective; however, patients with ANCA vasculitis likely cannot remain on continuous rituximab forever.

Rituximab along with glucocorticoids (steroids) are approved by the U.S. Food and Drug Administration (FDA) to treat **ANCA Vasculitis.**

We are asking you to take part in this study because you have granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) and have been on Rituximab for at least two years as part of your treatment.

GPA and MPA are autoimmune diseases (the body reacting against its own tissues) that cause injury in different organs in your body. Sinuses, lungs and kidneys are the most common sites of injury. Injury can also occur in other sites, including: nerves, skin, joints, muscles and eyes.

The immune system defends against bacteria, viruses, tumors and other foreign substances in the body. However, in GPA and MPA, the immune system attacks some of your own tissue. The treatment for GPA and MPA is immunosuppression with medications to decrease the immune system response. Without treatment, people with GPA and MPA are at risk of permanent damage to the tissues and organs affected by these diseases. Rituximab has been used successfully to treat these diseases and keep them from coming back. Rituximab every 6 months is safe and effective; however, it is important to know if patients with ANCA vasculitis should remain on continuous rituximab forever or should we be watching and waiting for B cell return or a rise in the ANCA level.

About **200** subjects will take part in this research study at Massachusetts General Hospital (MGH).

There are no additional costs to subjects for participation in this study.

How long will I take part in this research study?

If you decide to take part in the study, you will be followed for about 3 years after the last study participant is enrolled and may continue for a longer period of time if Dr. Niles (the principal investigator) decides to extend the study. During this time, we will ask you to make about 12-14 visits over 3 years; these will be part of your regular scheduled visit with Dr. Niles.

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.

Study Visits will take place during your regularly scheduled clinic visits and will take approximately 30 minutes for each visit.

If you are unable to attend a scheduled visit, an investigator may call you to check-in and complete study forms to assess disease activity and damage.

Screening:
Before you begin the study, a member of the study team will review your length of time on rituximab and the history of your GPA or MPA to find out if you can be in the study. This information will be from your medical record. The study staff will determine if you are eligible to participate in the study during one of your regularly scheduled office visits.

Enrollment/Randomization Visit (Study Visit 1)

This will either be at your planned rituximab infusion or up to 6 months after your last dose of rituximab.

You will be randomly assigned to one treatment or the other. Which treatment you receive will be determined by chance (like flipping a coin). You will know which group you are assigned to; however, neither you nor the study doctor will be able to choose which treatment you receive. You will not know which group you are in before you agree to participate.

Study Group 1: Intermittent B-cell depletion

1. You will not receive rituximab infusions at regular intervals
2. You will have a study visit every 3 months
3. We will monitor routine urine and blood work including monitoring your B-cells and ANCA titer level
    a. If your B-cells have returned, you will be scheduled for 1 dose of rituximab.
    b. After the infusion, you will continue to have study visits every three months
    c. Rituximab will not be given again until your B-cells have returned.

Study Group 2: Re-Dosing with rituximab upon significant ANCA titer increase

1. You will not receive rituximab infusions at regular intervals
2. You will have a study visit every 3 months
3. We will monitor routine urine and blood work including monitoring your B-cells and ANCA titer level
    a. If your ANCA titer level has increased at or above a specified level, you will be scheduled for 2 doses of rituximab approximately 2 weeks apart
    b. After the second infusion, you will continue to have study visits every three months.

c. If your ANCA titer level remains at or above the specified level, you will continue to receive rituximab once every 6 months for a maximum of 2 additional doses, at which time a new baseline ANCA titer level will be determined.

At this visit, we will:

- Ask you about your medical history
- Collect information from your medical record
- Do a physical exam, including height, weight and vital signs
- Collect routine blood work
- Ask you for a urine sample
- Test your **urine** for pregnancy, if you are a female able to become pregnant. Pregnant women cannot take part in this research study.
- Do an ECG (electrocardiogram)
- Ask you to fill out some questionnaires about **your general health and well-being, quality of life, mental health, emotional health and mood.**

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ECG (electrocardiogram)

This test checks the electrical activity of your heart. We will place several small, sticky pads on your chest, arms, and legs. Each pad has a wire attached. The wires connect to a machine that makes a recording of your heart rhythm. This painless test takes about 15 minutes.

Study Visits 2-16: Study visit 2 will occur at the 6 month time point from your last rituximab infusion. This may be the same day as Study Visit 1. We will only collect one set of blood work and information on this visit date. All other visits will be every 3 months until 3 years after the last subject is enrolled.

Each Visit

At each visit during this part of the study, we will assess your GPA or MPA as part of your regular care. We will:

1. Collect routine urine and blood work (about 4 teaspoons of blood per visit, for a total of about 2 cups over the course of the study) including monitoring for your B-cells and ANCA titer level
2. Check a urine pregnancy test for women of child bearing potential.
3. Perform a physical exam including vital signs
4. Assess for any adverse events since your last visit

At each 6 month interval we will ask you to complete the questionnaires about your health, well-being, quality of life, mental health, emotional health and mood.

Once a year we will repeat the ECG.

After You Complete the Study
After you complete the study, we will continue to treat you for your condition as determined appropriate by Dr. Niles and Dr. Cortazar.

Stopping the Study Early

If you decide to stop taking part in the study for any reason, we will ask you to make a final study visit. If you cannot make it to an office visit, one of the study staff will call you on the phone.

- You will be asked about any changes to your GPA or MPA treatment since the last visit or phone call.
- You will be asked questions about any side effects because of a medical condition and medication use.
- You will be asked why you are no longer participating in the study.
- The study doctor will determine the best care for you
    - Do a physical exam
    - Ask you about any side effects or health problems since your last visit
    - Draw a blood sample
    - Ask you for a urine sample
    - Ask you to fill out some questionnaires

Any of your information gathered up until that point in time may still be used for study purposes. We may also ask that we follow you observationally with a phone call.

Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study doctor thinks it is best for you to stop taking the study drug
- You can't make the required study visits
- We stop doing the study for other reasons

If this happens, the study doctor will explain why you need to stop taking part in the study. We will ask you to come in for a final study visit as described above.

Review of Medical Records from Hospital Admissions or Emergency Department Visits

Partners has an electronic system that lets your study doctors know if you are admitted to a Partners Hospital, or if you visit a Partners Hospital Emergency Department. We want to make sure the study doctors know about any possible problems or side effects you experience while you are taking part in the study.

Storing Samples and Health Information at [BWH/MGH] for Future Use

We would like to store some of your health information for future research related to ANCA Vasculitis. We will label your health information with a code instead of your name. The key to the code connects your name to your samples and health information. The study doctor will keep the key to the code in a password protected computer/locked file.

Do you agree to let us store your health information for future research related to ANCA vasculitis?

☐ Yes ☐ No Initials_____

Study Information Included in Your Electronic Medical Record

A notation that you are taking part in this research study may be made in your electronic medical record. Information from the research that relates to your general medical care may be included in the record (for example: list of allergies, results of standard blood tests done at the hospital labs).

Please ask your study doctor if you have any questions about what information will be included in your electronic medical record.

What are the risks and possible discomforts from being in this research study?

Risks of Taking Rituximab

Taking **rituximab** may cause you to have one or more of the side effects listed below.

You may experience side effects while receiving rituximab, which is given to you by your doctors as part of your regular medical care for your GPA or MPA. Your doctor will explain the possible side effects of Rituximab and other regular medical treatment and drugs.

Common side effects of Rituximab:

- Within 24 hours of the 1st infusion
    - Chills, itching, hives, sneezing, throat irritation
    - "flu like" symptoms: headache, nausea, joint pain

- Possible serious side effects or reactions
    - Infusion reactions may be fatal. Serious infusion reaction with hives, low blood pressure, breathing difficulties, irregular heartbeat and chest pain are very rare. Medications given with the infusion can prevent these reactions. We can stop the infusion immediately if a reaction occurs.
    - Infections are a concern with all drugs that affect the immune system. If you develop a severe infection, we will check your labs including a complete blood count. This is always something that needs attention and treatment
    - Reactivation (getting symptoms again) of Hepatitis B and other viral infections. We check hepatitis status at baseline visit to prevent reactivation.
    - Worsening of asthma symptoms
    - A rare brain infection, progressive multifocal leukoencephalopathy (PML), has been reported in people taking this medication. This infection is rare, associated with weakened immune systems, and can lead to death or severe disability.
    - Skin reactions, painful sores, ulcers, blisters and peeling skin (rare)

There may be other risks of rituximab that are currently unknown.

As with any drug, the major possible side effect of rituximab can be an allergic reaction. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.

You **CANNOT** receive a live vaccine such as zostavax while you are taking rituximab. Talk with the study doctor before you receive any vaccine.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant

The effects of rituximab on a fetus (developing baby still in the womb), or on a breastfeeding infant, are unknown and may be harmful. Individual of childbearing potential should use

effective birth control during treatment and for 12 months after rituximab therapy. If at any time during the study you suspect that you have become pregnant, please notify the study doctor immediately. Prior to any infusion of Rituximab to a woman of childbearing age, a urine pregnancy test is done and recorded, this must be negative.

Acceptable birth control methods for use in this study are:

- hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- intrauterine device (IUD)
- abstinence (no sex)

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking the study drug and stop taking part in the study. The study doctor may ask for your permission to collect information about the outcome of your pregnancy and the condition of your newborn.

No pregnancy test is needed if:

- You are a menopausal woman and have not had a period for the past 12 months or more
- There is a documented method of surgical sterilization
    - hysterectomy (removal of the uterus with or without the removal of the ovaries)
    - tubal ligation
    - transvaginal occlusion (plugging the opening of the tubes with a coil

If you are sexually active and able to father a child, you must agree to use one of the birth control methods listed below. You must use birth control **12 months after your last dose of rituximab.** Acceptable birth control methods that you can use in this study are:

- condoms with spermicide (a foam, cream, or gel that kills sperm)
- abstinence (no sex)

Acceptable birth control methods that your partner(s) should use are:

- hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- intrauterine device (IUD)

If your female partner becomes pregnant, we would like to follow the outcome of the pregnancy. You should notify us immediately if your partner becomes pregnant. She may be asked to sign a

release of medical information form that gives her doctors permission to provide information to us. You will not have to stop taking part in the study if your partner becomes pregnant.

Risks of Taking Rituximab with Other Medications

Do not take cisplatin while you are receiving the rituximab infusions. Taking this medication and rituximab together may cause serious side effects. In addition, on the day of your rituximab infusion, do not take your blood pressure medications in the morning. In some patients, blood pressure decreases temporarily during a rituximab infusion. Waiting to take your blood pressure medications will help avoid a dangerously low blood pressure.

For your safety during this study, call your study doctor BEFORE you take any:

- New medications prescribed by your own doctor.
- Other medications sold over-the-counter without a prescription
- Dietary or herbal supplements

Risk of Relapse of Disease

Discontinuing routinely scheduled rituximab will possibly lead to an increase in disease relapse. Relapses have the potential to cause irreversible organ damage especially in subjects with disease affecting their kidneys. However, the risk of relapse must be weighed against the harms of ongoing treatment with immunosuppression. To decrease the risk of worsening organ damage, we have restricted entry to those subjects who have acceptable prespecified kidney function. Subjects will be assessed at regular intervals and as needed to assess for worsening disease activity. If the investigator feels that your disease is coming back (relapsing) then he will treat you with the appropriate medical care and may be removed from the study if necessary.

Risks of Blood Draws

You may have a bruise (a black and blue mark) or pain where we take the blood samples. There is also a small risk of infection, lightheadedness, and/or fainting

What are the possible benefits from being in this research study?

You may not directly benefit from taking part in this research study. Currently, specialists do not know the ideal long term treatment plan for patients in remission with ANCA Vasculitis. We hope that this study provides some answers to that question**.**
Others with **ANCA Vasculitis** may benefit in the future from what we learn in this study**.**

What other treatments or procedures are available for my condition?

You do not have to take part in this research study to be treated for **ANCA Vasculitis**. Your doctor will continue to treat you as deemed appropriate which may or may not include continuing on regularly scheduled rituximab infusions.

Can I still get medical care within Partners if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

You will not be paid to participate in this study.

We may use your information to develop a new product or medical test to be sold. The hospital and researchers may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

What will I have to pay for if I take part in this research study?

Study funds will pay for **study-related procedures, study visits** that are done **ONLY** for research. The study visit schedule is part of your usual care even if you were not participating in the study. Lab tests and infusions are also part of your usual care and will be billed to insurance.

Study funds will pay for certain study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs.

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Dr. John L. Niles is the person in charge of this research study, he or is designee will try to answer all your questions. If you have questions or concerns at any time, or if you need to report any infection or injury related to the research, you may speak with a member of the research staff:

John L Niles, M.D.	Nephrologist	617-726-4132
Reza Zonozi M.D.	Nephrologist	617-726-4132
Anushya Jeyabalan M.D.	Nephrologist	617-726-4132
Karen A. Laliberte RN	Nurse Manager	617-724-6594
Pravarut Nithagon	Coordinator	617-726-4132

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 617-424-4100.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

During this research, identifiable information about your health will be collected. In the rest of this section, we refer to this information simply as "health information." In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so.

In this study, we may collect health information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable health information and why they may need to do so:

- Partners research staff involved in this study

- The sponsor(s) of this study, and the people or groups it hires to help perform this research
- Other researchers and medical centers that are part of this study and their ethics boards
- A group that oversees the data (study information) and safety of this research
- Non-research staff within Partners who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- The Partners ethics board that oversees the research and the Partners research quality improvement programs.
- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- Other:

Some people or groups who get your health information might not have to follow the same privacy rules that we follow and might use or share your health information without your permission in ways that are not described in this form. For example, we understand that the sponsor of this study may use your health information to perform additional research on various products or conditions, to obtain regulatory approval of its products, to propose new products, and to oversee and improve its products' performance. We share your health information only when we must, and we ask anyone who receives it from us to take measures to protect your privacy. The sponsor has agreed that it will not contact you without your permission and will not use or share your information for any mailing or marketing list. However, once your information is shared outside Partners, we cannot control all the ways that others use or share it and cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information.

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifying information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others.

You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

_____	_____	_____
Subject	Date	Time (optional)

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent	Date	Time (optional)

Consent of Non-English Speaking Subjects Using the "Short Form" in the Subject's Spoken Language

Statement of Hospital Medical Interpreter

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Hospital Medical Interpreter	Date	Time (optional)

OR
Statement of Other Individual (Non-Interpreter)

As someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

Name	Date	Time (optional)

Witness to Consent of Subjects Who Cannot Read or Write or are Physically Unable to Talk or Write

Statement of Witness

I represent that the consent form was presented orally to the subject in the subject's own language, that the subject was given the opportunity to ask questions, and that the subject has indicated his/her consent and authorization for participation by (check one box as applicable):

☐ Making his/her mark above

☐ Other means _____
(fill in above)

_____ _____ _____
Witness Date Time (optional)

Consent Form Version:

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