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Randomized trial of intravitreous aflibercept versus intravitreous bevacizumab +deferred aflibercept for treatment of central-involved diabetic macular edema (Protocol AC)

20 September 2018

Consent to Participate in a Research Study
Randomized Trial of Intravitreous Aflibercept versus Intravitreous Bevacizumab +Deferred Aflibercept for Treatment of Central-Involved Diabetic Macular Edema (Protocol AC)

Today, you are being asked to take part in this **research** study because you have swelling in the center of your retina (the light-sensitive lining inside of the back of the eye) from diabetes. This condition is called diabetic macular edema or "DME". The goal of this research is to get new knowledge that may help other people, but it is not the same as treatment of DME. We want to find what works best for treating your and others with this condtion.

Your study doctor will be talking with you about this research and this document. Please take your time deciding whether you want to participate in this research and please carefully read this document.

Before you decide to take part in this research study, we encourage you to speak with friends and family members about it. If you do not understand all the information, please ask your study doctor or nurse to explain. If you are taking part in another study, please tell us right away.

NON-PARTICIPATION STATEMENT

Participation in this study is voluntary and you must agree to take part. If you decide to stop participation in this research, that will happen immediately. No penalty or loss of medical care will result from your decision. While the study is occurring you may continue to receive medical care not related to this study.

WHO IS DOING THE STUDY

This study is being conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net), which is a group of clinical sites dedicated to research of diabetic retinopathy and its associated conditions.

Your study doctor(s) and/or clinic staff will carry out this study. Their names are listed on the Cover Page of this form. The National Eye Institute (NEI), one of the National Institutes of Health of the U.S. Public Health Service, a part of the federal government is paying for this research. This funding will be used by the Jaeb Center for Health Research to organize the study and pay your study doctor(s). The Jaeb Center for Health Research is the Coordinating Center for this study.

WHY ARE WE DOING THIS STUDY?

Diabetic macular edema (DME) is the term used for swelling in the small central part of the retina. The retina is the light-sensitive tissue which lines the back of the eye. The macula or center part of the retina is used for sharp, straight-ahead vision. It is nourished by blood vessels that may become affected by diabetes. The blood vessels are weakened by diabetes and may become leaky. This causes the retina to become thickened or swollen. Swelling of the central part of the retina can lead to decreased vision.

HOW IS DME TREATED?

DME can be treated with repeated injections of drug into the eye to try to make the swelling of the retina go away. The drug is used to block or decrease a substance called vascular endothelial growth factor (it is an "anti-VEGF drug"). There are currently three different anti-VEGF drugs that are used as injections in eyes. However, only the following two, Avastin® and Eylea®, are being used in this study.

Avastin is approved by the Food and Drug Administration (FDA) for the treatment of cancer. It is not approved for treating DME. It needs to be specially prepared for injecting into the eye. However, studies have shown that Avastin injections can be beneficial for DME. Therefore, many doctors have been injecting it into the eye to treat DME.

Eylea is the other type of anti-VEGF drug being used in this study and was made for injection into the eye. It has been approved by the FDA for treatment of DME.

A recent survey of eye doctors estimated that about 60% of the injections in the U.S. for DME are given with Avastin, about 25% of the injections are given with Eylea, and about 15% with a third anti-VEGF drug called Lucentis®.

DOES ONE OF THE TREATMENTS WORK BETTER?

Recently, a study was done by the DRCR.net comparing Avastin and Eylea for eyes with DME. The study showed that both drugs work very well to reduce DME and improve visual acuity. However, when the starting vision was moderately or severely reduced (20/50 or worse), Eylea was better on average than Avastin at improving vision.

Even though Eylea was better on average, most people who received Avastin still had very good results. After 2 years, about half (50%) of eyes receiving Avastin injections improved at least 3 lines on the vision chart, compared with slightly more than half (58%) with Eylea. An example of improving by 3 lines on a vision chart would be if vision started at 20/50 and improved to 20/25 or better.

SO WHY IS AVASTIN BEING USED TO TREAT DME MORE OFTEN THAN EYLEA?

Avastin is much less expensive than Eylea. Avastin costs about $60 per injection compared with about $1,800 per injection for Eylea. Most patients will receive about 9 injections within the first year of treatment and 4 injections in the second year. The out-of-pocket cost to each patient may be different depending on his/her insurance. In some cases the patient may be responsible for the entire cost of the drug, or insurance may require the patient to pay some portion of the drug cost. For example, if insurance requires the patient to pay 20% coinsurance, the cost of the more expensive drug would be $360 per injection ($3,240 for the first year if 9

injections are needed). Even if the patient was responsible for the full cost of Avastin, it would only cost about $540 for the first year if 9 injections are needed.

Because of the large difference in cost between the two drugs, many patients and clinicians are choosing to start treatment with Avastin and then switch to Eylea if vision stops improving and is still decreased. In some cases insurance companies are requesting that clinicians start treatment with Avastin because of the large cost difference.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to find out if starting with Eylea has better results than starting with the less expensive drug, Avastin, and only switching to Eylea if needed. If starting with Eylea is not better than starting with Avastin and switching to Eylea if needed, the potential cost savings to future patients and the health care system would be substantial. However, if starting with Eylea is better, then patients, clinicians, and health care providers can make informed decisions for how to best treat patients with DME and at least moderate vision loss.

If you agree to take part in the study, you will have a 50:50 chance of receiving Eylea from the start or receiving Avastin to start and switching to Eylea only if needed. If you start with Avastin, you initially will get an injection once a month for 3 months. At 3 months or anytime thereafter, if there has not been enough improvement in your vision and DME, you will be switched to Eylea. We expect about half of the eyes to switch to Eylea during the study. The entire study will last 2 years.

To summarize, both Eylea and Avastin have been shown to work for DME treatment. However, in patients with vision and DME like yours, Eylea has been shown to work better on average. It is possible that starting with Eylea will have similar results to starting with Avastin and switching to Eylea only if needed. By doing this study, we hope to be able to provide additional information for people with DME on how these two approaches compare.

HOW MANY PEOPLE ARE WE EXPECTING TAKE PART IN THIS STUDY?

We expect about 260 people will take part in this study at 80 different medical locations.

WHO CAN PARTICIPATE IN THIS STUDY?

To take part in this study, you must be or have the following:

- Diabetic macular edema in at least one eye that meets certain criteria
- Visual acuity of 20/50 or worse

There are some exclusion criteria that may prevent you from being part of the study. Your study doctor will check if you have these or not.

- You are on dialysis or have had a kidney transplant.

- Your blood pressure is greater than 180/110 (systolic above 180 OR diastolic above 110).
- Pregnant or breastfeeding women cannot participate. If you are a woman who has the potential to get pregnant we may do a urine test to be sure you are not pregnant before you enter the study.
- You have taken part in a study in which you received treatment within the last 30 days.

To be eligible to be in this study, you must be willing to comply with all study procedures and tests. You must also agree to be present at the clinic for all scheduled visits. If you are planning to move out of this area within the next two years and want to be in this study, please let us know. We will see if we can arrange for you to still be in the study.

WHAT HAPPENS IF I AGREE TO TAKE PART IN THIS STUDY?

First, testing will be done to find out if you are eligible for the study. If you are eligible, we will explain the study to you and you will watch a short video (about 5 minutes). Then you will answer a few questions to show you understand the study. You will need to sign this form if you want to take part in the study.

At least one eye must be eligible for you to enter the study. However, both eyes can be entered into the study if both are eligible at the time of enrollment. We call any eye that enters the study a "study eye".

Then we will determine what treatment you will receive. You will receive either Eylea from the start or Avastin to start and switch to Eylea if needed. A computer program will randomly pick the treatment approach that will be used, with each treatment equally likely to be picked. If you have two study eyes, one eye will randomly be picked to receive Eylea from the start and the other eye will receive Avastin from the start. You will not be told which drug was selected for your eye.

The study will last two years. During that time, your visit schedule and treatment will vary. All of this will be explained in more detail below.

A. Screening for the Study

We will ask you questions about your medical history and previous eye problems and treatment. Then, some tests will need to be completed, if they have not already been done, to find out if you are eligible for the study. The tests include:

1. **Eye Exam**
   - The eye exam will include measurement of your visual acuity (the ability to read letters on the vision chart). The pressure in your eye will be measured. After drops have been placed in your eye to dilate your pupil the doctor will study your retina

with an ophthalmoscope (an instrument with a strong light and a magnifying lens). The eye exam will be completed on both eyes.

2. **Optical Coherence Tomography**
   - Optical coherence tomography (referred to as OCT) uses a dim beam of light to measure the thickness of the retina. During the study, OCT will be used to find out if the retinal swelling is getting worse, better, or staying the same. You will look into a machine at a pattern of flashing and rotating red lights.

3. **Photographs of the Retina**
   - A special camera will be used to take photographs of your retina (referred to as fundus photographs) after drops have been placed in your eyes to dilate your pupil.

4. **Measurement of Blood Pressure**
   - Your blood pressure will be checked with a cuff that is placed on one of your arms.

5. **Laboratory Tests**
   - A blood test called HbA1c will be done to see how well your diabetes is controlled. Less than 3 teaspoons (15 mL) will be taken for HbA1c testing. If you have had this test recently, it may not need to be repeated.
   - If there is any chance that you might be pregnant, a pregnancy test will also be done.

If the tests show that you are not eligible for the study or you decide not to take part, the eye doctor will discuss your options for treatment of your DME. Whatever treatment is chosen, the results will not be part of the study.

B. Study Treatments

If at least one of your eyes is eligible for the study and you sign this form, a computer program will determine what treatment will be received. This will be determined by chance similar to flipping a coin. There are two possible treatment groups:

1. Group A: Eylea injections
2. Group B: Avastin injections with deferred Eylea injections if needed

If you have one study eye, there is a 50:50 chance of the eye being in group A or group B. If you have two study eyes, one eye will be selected by chance for group A and the other eye for group B. You will not know which treatment you are getting.

The injection procedure is the same for both of the drugs. To prepare for the injection, anesthetic (numbing) eye drops and eye drops to dilate your pupil will be placed on the surface of your eye.

An antiseptic solution will be used to reduce the chance of infection. The eye doctor may decide that you should also have an anesthetic injection under the surface of your eye. After the preparation is complete, the Eylea or Avastin injection will be given. The amount of drug that will be injected into your eye each time is less than the amount of liquid in 1 drop from a medicine dropper. After the injection, you will stay in the eye clinic until your doctor believes it is safe for you to leave.

C. Follow-Up Visits

During the first year, you will have follow-up visits every 4 weeks. During the second year, you will have follow-up visits every 4 weeks as long as you need monthly injections. The frequency of injections can often be decreased and if that happens you will have follow-up visits either 8 weeks, or 16 weeks apart, depending on how your eye is doing. At the end of each visit, your doctor will inform you of the timing of your next appointment. You will also have a follow-up visit at 2 years.

The testing at each of the visits includes the following:

- Visual acuity testing of both eyes
- Eye exam of the study eye (and both eyes at the one-year and two-year visits)
- OCT of the study eye
- Photographs of the retina of the study eye (at the one-year and two-year visits only)
- Blood pressure (at the one-year and two-year visits only)
- Laboratory test of HbA1c (at the one-year and two-year visits only)

The eye doctor may decide you need to be seen more often or need more testing as part of standard care depending on how you are doing.

D. Treatment During Follow-Up

<u>Injections During Follow-Up</u>

At the enrollment visit and then again at the 4-week visit the study eye will receive an injection of Eylea or Avastin. At and after the 8 week visit, the eye doctor will determine if another injection should be given. This will be based on whether or not your vision and/or DME have changed. After 8 weeks, if your vision and DME are not changing, monthly injections may no longer be necessary.

<u>Switch from Avastin to Eylea</u>

If your study eye is selected to receive Avastin injections from the start, you may switch from Avastin injections to Eylea injections if certain criteria is met. At or after the 12 week visit, if your vision and DME are not improving over the previous two visits, your eye may receive Eylea.

In the table below you will find what will be done at each visit.

Visit	Initial Visit	1 and 2 year visit	All other study visits
E-ETDRS best corrected visual acuity	X	X	X
OCT	X	X	X
Eye Exam	X	X	X
Fundus Photography	X	X	
Blood pressure	X	X	
Hemoglobin A1c	X	X	

ARE THERE RISKS IN THIS STUDY?

If you decide to take part in the study, you will be at risk for the side effects listed below. We encourage you to discuss these with your study doctor, your primary care provider, or another health care professional. If a treatment or procedure has increased risks because it was not done according to study procedures due to error, you will be informed, and the necessary steps will be taken to care for you.

Risks related to your normal medical care are not listed in this form. We encourage you to discuss these with your study doctor, your primary care provider, or another health care professional.

There may be additional risks associated with the drug and/or with the administration method that are not known at this time. If we become aware of any new risks, you will be told about them. You will be able to decide if you want to continue to receive the study drug.

For an eye with DME and decreased vision like yours we know that Eylea on average works better than Avastin. It is possible that by starting with Avastin and switching to Eylea if needed you may not gain as much vision if you are not treated with Eylea initially.

A. Risks of Injections

Injections may cause none, some, or all of the below side-effects.

1. Risks Related to the Injection Procedure

- It is unlikely that the drugs used to numb your eye before the study drug injections (proparacaine, tetracaine, or xylocaine) will cause any problems. However, in rare instances, these drugs can cause an allergic reaction, seizures, and an irregular heartbeat. A serious allergic reaction occurs in less than 1 in 100,000. Your doctor will monitor any effects these drugs may cause and treat them as necessary. In addition to topical numbing drops your doctor may also give you a tiny injection of xylocaine to numb your eye before the study drug injection is given. You may feel a temporary stinging sensation from the xylocaine injection. If an injection is given, in very rare instances the injection can cause damage to your eyeball, damage to the optic nerve, or double vision lasting up to 24 hours or more. Once your eye feels numb, you may still be able to feel touch or pressure within your eye, but you should not be able to feel pain. Sensation usually returns within two hours.

2. Risks Related to the Anti-VEGF Injection Procedure (but not the drug itself)

More common:

- You may have pain, redness, discharge, irritation, increased tearing, itching, or a foreign body sensation in the eye for a few days after the injection.

- After an injection, you may see spots in your vision (floaters). The spots may be more noticeable certain ways you look or with certain lighting. They usually do not affect your vision. The spots usually go away after a few days or weeks.

- You may experience bleeding in the clear layer of tissue covering the white of the eye and inner eyelid or inflammation of the eyelid.

Less common:

- In rare cases, you may experience temporary drooping of the eyelid lasting up to 24 hours. In very rare cases the eyelid may droop indefinitely. In such rare cases, surgery on the eyelid may be the only treatment to correct the drooping. The surgical procedure is typically successful, but in some cases may not work, and the procedure is accompanied by other risks to the eyelid and/or vision.

- The injection or drug could cause an increase in the pressure of the eye right after the injection. The risk of developing an increase in eye pressure is less than 10 in 100. If this happens, eye drops may be given to lower the pressure. Your chance of permanently losing vision is much less than 1 in 100.

- The injection could cause haziness in the lens of the eye. This is called cataract. The lens is involved in focusing so that the eye can see clearly. The haziness causes vision to be blurred. The risk of developing a cataract from the injection is much less than 1 in

1000. If a cataract develops, cataract surgery may be needed. In most cases, this surgery is successful in improving vision.

- An infection can develop in the eye after the injection. This is called endophthalmitis. Endophthalmitis is treated by injecting antibiotics into the eye. This usually gets rid of the infection. However, endophthalmitis can produce permanent loss of vision and even blindness. Your chance of having endophthalmitis is less than 1 in 100.

- The injection could cause the retina to separate from the back of the eye. This is called a retinal detachment. If this occurs, surgery may be needed to repair the retina. The surgery is usually successful at reattaching the retina. However, a retinal detachment can produce permanent loss of vision and even blindness. Your chance of having a retinal detachment is much less than 1 in 100.

- The injection could cause bleeding in the middle cavity of the eye. This is called a vitreous hemorrhage. Usually the blood will go away on its own. If it does not go away, surgery may be needed to remove the blood. This surgery usually removes the blood completely. However, a vitreous hemorrhage can produce permanent loss of vision and even blindness. Your chance of having a vitreous hemorrhage is less than 1 in 100.

3. Risks in the Eye Related to Eylea and Avastin

Eylea and Avastin are well tolerated in people. Possible side effects to the eye from both drugs include:

- Inflammation of the eye. This is called uveitis. Uveitis can be successfully treated with steroid eye drops, injections, or pills. However, uveitis can lead to permanent loss of vision if not treated early. In previous studies, approximately 2 out of 100 patients developed uveitis.

- Traction retinal detachment. It is possible that injection of Eylea or Avastin might increase the chance of developing a traction retinal detachment, but this risk has not been seen in large studies evaluating for this possibility. A traction retinal detachment can lead to additional vision loss or possibly permanent vision loss and often requires surgery to try to re-attach the retina to the back wall of the eye. Your eye doctor for this study will monitor for this complication so that it can be managed appropriately if it develops.

4. Risks to the Rest of the Body Specific to Eylea and Avastin:

Anti-VEGF agents are used to treat certain types of cancer. The dose of these drugs when used to treat cancer is much higher than comparable doses used for injections into the eye. When used to treat cancer, these drugs have caused certain side effects including high blood pressure, blood clots in arteries such as heart attack or stroke, kidney problems, bleeding within the

gastrointestinal (digestive) tract, vaginal bleeding, surgery and wound healing complications, joint pain, skin rash or hives, and breathing difficulties or shock. Since the dose used for the eye injections is so low, we do not expect any of these side effects to occur due to the drug. However, we cannot rule out the possibility of a small risk from the drug. In our prior study comparing different anti-VEGF drugs in people with diabetes, we did not find an increased risk of serious events like heart attack or stroke from Eylea compared with other available anti-VEGF drugs, including Avastin.

5. Risks if You Become Pregnant

The effects of anti-VEGF drugs on a human fetus (unborn baby) or nursing (breast feeding) infant are unknown. It is possible that use of these drugs may be associated with unanticipated risks to a pregnancy or fetus. Therefore, you will not be allowed to participate in this study if you are pregnant, planning to become pregnant within the next 24 months, or if you are nursing an infant. During the study, females who are capable of bearing children must agree to use an effective method of birth control to prevent pregnancy. In the event of pregnancy during the study, injections will be discontinued.

B. Risks of Eye Examination and Tests

1. **Eye Exam:** As part of the eye exam, drops will be put in your eyes to dilate the pupils. The drops may blur your vision and make you sensitive to light. The drops will wear off over several hours. There is a small risk of an allergic reaction to the drops. There is also a small risk that the drops could cause the eye pressure to rise. If this happens, it will be treated, but there is a small risk of losing vision from the pressure rise. Due to the blurring effect on your vision and possible light sensitivity, we recommend that you do not drive until the blurring effects of the drops have worn off. If necessary, have someone come with you who can drive for you after the exam.

2. **Blood Draw Risks:** Possible risks from blood draws include the following: bruising, arm discomfort, clotting, excess bleeding, infection, or fainting. Please note that although these are possible risks they are unlikely.

We encourage you to discuss the risks with your study doctor or any other health care professional who may understand our process.

WHAT ARE THE BENEFITS OF TAKING PART IN THIS STUDY?

There may be a possible medical benefit to you if you decide to take part in the study, but it is not a guarantee. You may receive no direct benefit from being in the study. People who take part in this research study will add to new knowledge that may help other people with the same problem.

If you participate in this study, regardless of your initial treatment, you will have access to Eylea if needed during the study. You may or may not have access to Eylea outside of the study.

WHAT ALTERNATIVE PROCEDURES OR TREATMENT ARE AVAILABLE IF I DO NOT TAKE PART IN THIS STUDY?

If you do not take part in this study, you might be able to receive Avastin or Eylea outside of the study. You also could receive Lucentis, a third anti-VEGF drug which is FDA approved for DME treatment. This treatment is approximately $1,200 per injection. It has shown to work a little better than Avastin but not quite as well as Eylea.

We encourage you to discuss these alternative procedures and treatments with your study doctor, your primary care physician, or another health care professional who has knowledge of DME.

WHAT IF I WANT TO WITHDRAW FROM THE STUDY, OR I AM ASKED TO WITHDRAW FROM THE STUDY?

You can stop participating in this study at any time. You may continue to receive medical care not related to this study. However, we encourage you to talk to a member of the research group so they know why you are stopping the study.

If there are any new findings during the study that may affect whether your participation, you will be told about them so you can decide if you want to continue.

No penalty or loss of medical care will result from your decision. You may continue to receive medical care not related to this study.

The investigators, physicians or funding source may stop the study or take you out of the study at any time. They may remove you from the study for various administrative and/or medical reasons. They can do this without your consent.

Some reasons why you may be removed from include:

- The doctors judge that it is in your best interest
- The doctors think that being in the study may cause you harm
- If you experience a study-related injury
- If you need additional or different medication
- If you do not follow the study plan.

If you are removed from the study or the study is stopped, you may continue to receive medical care not related to this study.

ARE THERE COSTS RELATED TO TAKING PART IN THE STUDY?

Testing that is specifically for this study will be paid for by the study. The costs of treatment,

office visits, and tests that are part of your usual eye care will be your or your insurance company's responsibility. The study will pay for:

- Visual acuity using an electronic tester at each visit.
- The eye exam and OCT at the baseline visit
- Fundus photographs when required for the study.
- The drug and injection procedure for study Avastin
- Any Eylea expense, including the cost of the drug and injection procedure, if not covered by your insurance (see additional details below)

All other tests and procedures, including the following, are your or your insurance company's responsibility:

- The eye exam and OCTs at 4 week-20 week visits, 32, 52 and 104 weeks, and any visit at or after a study injection is considered standard care. Eye exam and OCT at additional visits required when treatment is no longer needed will be paid for by the study.
- Laser or any other treatments (other than study injections), if needed.
- Exams, tests, procedures for the eye not in the study.

Depending on your insurance plan, it is possible that your insurance will not pay for some of the procedures and testing; if they do not pay, the study may become responsible for these costs if you have a financial hardship. In addition, although Eylea injections will initially be billed to your insurance, the study will pay for any portion of the Eylea drug and injection procedure cost that is not paid for by your insurance company. By signing this form, you certify that you understand that not all of the tests and procedures will be paid by the study and that you are aware that you or your insurance company will be charged for standard care procedures.

If you have travel expenses that make it difficult for you to return for study visits, additional funds may be available.

IS THERE COMPENSATION FOR TAKING PART IN THIS STUDY?

If you take part in the study, you will be given a $25 gift or money card for each visit required for the study. This gift or money card is being given to you to help with the additional costs that may result from completing study visits. If you do not complete all of the visits or discontinue the study before it ends, you will only receive a gift card for the visits that you did complete. You will not receive a gift or money card for extra visits your doctor believes are needed for your usual care.

WHAT HAPPENS IF I EXPERIENCE A RESEARCH RELATED INJURY?

Medical care is available if you have a research-related injury. If you have an emergency, you can get emergency care. If possible, you should tell the emergency care medical staff that you are

in a research study. You should also tell your study doctor about the emergency as soon as possible.

The study will not provide costs for medical expenses or any other costs for research-related injuries. The costs of care are your or your insurance company's responsibility. Money for lost wages and/or direct or indirect losses is not available.

If you have questions about the study or research-related injuries, contact DRCR.net staff at 1-866-372-7601 during normal business hours.

CONTACT INFORMATION FOR QUESTIONS OR PROBLEMS

If you have questions about this study, a research-related injury, have concerns, suggestions or questions about the study, contact your study team using the provided contact information on the Cover Page.

If you have unanswered questions about your rights as a research participant, wish to talk about your concerns or suggestions linked to the research study, want additional information about the research, or want to provide comments about the research, contact the Jaeb Center for Health Research Institutional Review (IRB) Office at 813-975-8690 or irb@jaeb.org

HOW WILL MY INFORMATION BE PROTECTED AND KEPT CONFIDENTIAL?

As required by law, study related records with identifying information will be kept confidential. Safeguards for authorized access, security, and privacy of your information have been put in place by the Federal Privacy Regulations. Unless the law requires it, your name, address, social security number, telephone number, or any other direct identifying information will not be used to identify you.

Certificate of Confidentiality

The National Institutes of Health (NIH) has given us a Certificate of Confidentiality for this study. This adds special protection for study information that identifies you and allows us, in some cases, to refuse to give out information that could identify you without your consent. This could be done when the information is requested by a federal, state, local court or public agency. If you need medical help, we may still share your identifiable information. As described in this form or in other cases, we may share identifiable information. For example, if the government inspects us, they may see your identifiable information. The study doctor and research team will follow local laws and will tell the local or state authorities:

- if certain diseases are present;
- if they suspect neglect, abandonment, or abuse of you; and
- if the study doctor or research team learn that you plan to harm yourself or someone else

A. Purpose of Authorization

We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your information. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

You must sign the **Protected Health Information Authorization** at the end of this form if you want to be in the study. When you sign the form, you give permission for the use and disclosure of your Protected Health Information (PHI) for the study. PHI is health information that identifies you. Your authorization is beneficial and important for the study. Without your authorization, you will not be able to be in this research study.

B. Use and Disclosure of the PHI

Your study doctor will collect information about you. This information includes things learned from procedures listed and described in this form as well as your name, address, date of birth, and information from your medical records. Your name, address, telephone number, and social security number are examples of identifiable information.

A code number will replace your name, address, telephone number, or social security number in the results given to the study coordinating center which is the Jaeb Center for Health Research in Tampa, Florida.

The study doctor's office will not disclose study results that have your identifiable information except as explained in Section C. or when required by law. The Jaeb Center and this doctor's office will guard the privacy of your study PHI.

Study results without the protected information may be shared in medical journals and at scientific meetings. Your records will be confidential. No one will disclose your identity in a medical journal or at a scientific meeting.

C. Authorized Recipients and Users

It is possible that people outside of this doctor's office and the Jaeb Center may need to see or receive your information from this study. Some examples include:

1. The people who work for this doctor's office
2. The people who work for the Jaeb Center
3. The scientific investigators who help run the study
4. Any review board that oversees human investigations rules for your doctor's office
5. Any federal agency that oversees clinical trials

6. If you have an adverse (unfavorable) event, the people outside this doctor's office who assist in your care.
7. Your doctor may send your blood sample to the central laboratory for this study at the Advanced Research and Diagnostic Laboratory in Minneapolis, MN.
8. The OCTs and photographs of your eye may be sent to a central reading center and their collaborators.

In most cases the information will have a code number with it instead of your name, address, telephone number, or social security number.

There are some situations where the information will not have a code number but may include your name, address, telephone number or social security number (PHI). If so, people outside this doctor's office who assist in your care may see your study PHI. They may not be covered by the federal Privacy Rule. Everyone who needs to see your information will be told it is confidential – but we cannot guarantee fully confidentiality.

Other Considerations

The data collected in the study may be provided to other researchers to use; however, the data that are provided will not contain any information that could identify you.

When the results are made public, all of the study data collected may also be made public. However, there will be no identifying information included.

Separately from your research data, the Jaeb Center for Health Research in Tampa, Florida will be provided with information on how to contact you.

- About every 6 months, you may receive a phone call from a staff member at the Jaeb Center to check on your condition and to see if you have any questions. You will be called at a time that you indicate is most convenient for you. If you are not available at the time of the call and prefer to call the coordinating center yourself, you can call the coordinating center toll-free at 1-866-372-7601

- If we are not able to locate you when we try to schedule your follow-up visit, the Jaeb Center may try to contact you through the alternative contact information you have given us. If this is not successful, the Jaeb Center may use a third-party search service.

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.

D. Cancellation of HIPAA Authorization

You may cancel your permission for the use and disclosure of your study PHI at any time. You need to contact your study doctor and give him/her a notice of cancellation in writing. When you cancel your permission or when you withdraw from the study directly, you are no longer part of the study. No new information about you will be gathered for the study except when there is an adverse (unfavorable) event that is related or potentially related to the study. If an adverse event happens, your entire medical record may need to be reviewed.

The Jaeb Center will receive all the information that was collected for the study up to the time of cancellation or withdrawal. The Jaeb Center will receive any new information about any adverse (unfavorable) event that is related or potentially related to the study.

E. 50 Year Expiration Date and Indefinite Expiration Date

Some of your study PHI does not have a code number with it. Your permission for the use and disclosure of this PHI lasts 50 years from the date of your signature or until the end of the study, whichever is sooner.

The rest of your study PHI does have a code number with it. When it is collected, it becomes a research report. Your permission for the use and disclosure of these coded data will never end. These coded data do not have your name, address, telephone number, or social security number. *The above supports the HIPAA Privacy Rule – 45 CFR 164.508*

Some of your information from this study (for example, your treatment) may be stored separately from or added to your medical record. You will not be able to see this information until the study ends. If your non-study physician requires it for your care, he/she will be able to view it.

Consent to Participate in a Research Study
Randomized Trial of Intravitreous Aflibercept versus Intravitreous Bevacizumab +Deferred Aflibercept for Treatment of Central-Involved Diabetic Macular Edema (Protocol AC)

Your Full Name (printed) _____

Description of Representative's Authority to Act for the Subject
_____ **(**if applicable)

Protected Health Information Authorization

By signing, you authorize the use and disclosure of your protected health information. This information is collected as part of your participation in this study.

_____ _____
Signature Date

Study Enrollment

By signing, you agree to take part in this study. Your signature means that:
- ***you have read this informed consent form about the study named below;***
- ***you have been given the chance to discuss the study and to ask questions;***
- ***you have verbally summarized your understanding of the study to the person who is explaining it to you; and***
- ***you freely choose to participate.***

Name of Study: Protocol AC

_____ _____
Signature Date

I certify that to the best of my knowledge the participant understands the nature, demands, risks, and benefits involved in his/her participation in this study.

_____ _____ _____
Investigator's Printed Name Investigator's Signature Date

You will be given a signed copy of this document in case you want to read it again.