Consent to Participate in a Research Study
Intravitreous Anti-VEGF vs. Prompt Vitrectomy for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy (Protocol AB)

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3 Date 6-24-16

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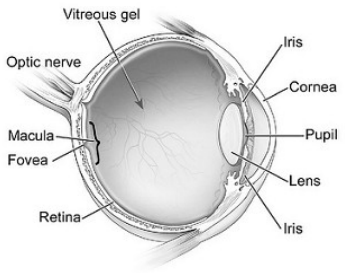
Today, you are being asked to take part in this **research** study because you have bleeding in a part of the eye called the "vitreous". The vitreous is the jelly-like fluid that fills the large space between the lens in front of the eye and the retina, which lines the back of the eye (see Figure). The bleeding is caused by a condition called diabetic retinopathy, which causes abnormal blood vessel growth on the surface of your retina.



https://nei.nih.gov/health/diabetic/retinopathy

Research is done to obtain new knowledge that may help other people in the future. Participation in this study is on a voluntary basis. You can decide not to take part in this study at any time. Your study doctor will be talking with you regarding this document. However, any study-certified doctor from the practice may take care of you during the study if you decide to participate. If you do not clearly understand information in this document, please ask your study doctor to explain.

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.

Before you decide to take part in this research study, we encourage you to speak with friends and family members. Take your time making a decision. Carefully read this document. Your decision will not affect your regular medical care. If you are taking part in another research study, please tell your study doctor.

Important information about this study is found in this consent form. This form is part of the process to inform you about the research study.

Your doctor(s) and/or clinic staff will carry out this study; see their names on the last page. Funding for the study is being provided by 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. Additional support is being provided Regeneron Pharmaceuticals, Inc, which is the company providing drug for this study. This funding will be used by the Jaeb Center for Health Research

to organize the research study and will be paid to your doctor's office for conducting the study. The Jaeb Center for Health Research is the Coordinating Center for this study.

WHY ARE WE DOING THIS STUDY?

The purpose of this study is to compare two available treatment approaches for the bleeding in your eye:

1) Initial surgical treatment (called "vitrectomy") OR
2) Injections into the eye to start and surgery only if the blood does not go away

1) Initial Surgical Treatment

When blood in the eye is affecting vision and is not going away on its own, surgery is often done to remove the blood. This is called a vitrectomy. The surgery involves making a few small incisions in the white of your eye. Then an instrument is put into the eye to remove the blood with the vitreous. As the blood and vitreous are removed, the eye is usually filled with a saline solution that is gradually replaced after surgery by the eye's natural fluids. Laser treatment also is done at the time of surgery to treat the diabetic retinopathy that caused the bleeding.

2) Injections into the Eye

Another recently available treatment is an injection of a drug through the white part of the eye directly into the middle cavity of the eye. The injection of drug may stop or reduce the amount of bleeding in your eye enough to avoid surgery, while also treating the diabetic retinopathy that caused it. The type of drug that is injected blocks or decreases a substance in the retina called Vascular Endothelial Growth Factor ("VEGF"). VEGF plays a role in the development of the diabetic retinopathy that has caused the bleeding in your eye. Drugs that block VEGF are called "anti-VEGF" drugs. There are several anti-VEGF drugs that are used to treat diabetic eye diseases; however Eylea® is the anti-VEGF drug being used in this study. Eylea injections into the eye have been approved by the U.S. Food and Drug Administration for treatment of DME and also for treatment of diabetic retinopathy in eyes with DME. Injections of Eylea have not been approved for treatment of vitreous hemorrhage. Therefore, injections in this study are considered experimental.

The information collected from this study will be used to weigh the costs and benefits of the two treatment approaches described above.

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

We expect about 200 people will take part in this study at about 60 different medical locations.

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

To take part in the study, you will need to carefully read and sign this document. Your participation is VOLUNTARY. You can decide not to take part in this study. You can decide to stop your participation in this study at any time. You may continue to receive medical care not related to this study. No penalty or loss of medical care will result from your decision.

The study will last 2 years. During that time, your visit schedule and treatment will vary. All of this will be explained in more detail below.

First, testing will be done to find out if you are eligible for the study. If both of your eyes have bleeding and are eligible for the study, you and the eye doctor will select one eye to be included in the study. We will refer to an eligible eye as a ***study eye.***

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

- Vitreous hemorrhage (bleeding in the eye) from diabetic retinopathy
- Decreased vision (about 20/32 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. Some conditions that would exclude you include:

- The eye being considered for the study has already had vitrectomy surgery.
- 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).
- You are pregnant or intending to become pregnant in the next 2 years or are nursing an infant. *If you are a woman who has the potential to become pregnant, a pregnancy test may be done to be sure you are not pregnant before you enter the study. BE CERTAIN TO TELL US IF THERE IS ANY POSSIBILITY YOU COULD BE PREGNANT, AND WE WILL OBTAIN A PREGNANCY TEST.*

- You have taken part in a study in which you received investigational 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.

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. Vision Testing

- This will include measurement of your visual acuity (the ability to read letters on the vision chart) using an electronic tester. This measurement will be done of each eye separately.

2. Eye Exam

- An eye exam will be performed as is done typically for anyone with diabetic retinopathy. The structures inside the eye will be examined through a special microscope after drops have been placed in your eyes to dilate your pupil. The pressure in your eye will be measured. The eye exam will be completed on both eyes, even if only one eye is being evaluated for the study.

3. Ultrasound

- As part of standard care, an ultrasound might be performed in the eye being evaluated for the study to determine if the retina is attached to the back wall of the eye. The ultrasound uses sound waves and measures the echo of those waves to determine the status of the retina structures behind the blood.

4. Optical Coherence Tomography

- Optical coherence tomography (referred to as OCT) uses a dim beam of light to measure the thickness of the retina. You will look into a machine at a pattern of flashing and rotating red lights. This test is done to make sure you do not have swelling of the center of the retina to start. During the study, OCT will be used to find out if retinal swelling has developed and requires treatment. OCT will only be done on the eye being evaluated for the study.

5. Measurement of Blood Pressure

- Your blood pressure will be checked with a cuff that is placed on one of your arms.

6. Laboratory Tests

- A blood test called HbA1c will be done to see how well your diabetes is controlled. In most cases, a fingerstick will be done for HbA1c testing. If needed, a blood sample less than 3 teaspoons (15 mL) may be taken instead.
- If there is any chance that you might be pregnant, a pregnancy test will also be done.

7. Questionnaire

- You will also be asked to complete a questionnaire about how your vision affects your daily life.

If any of the screening tests above 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 the bleeding in your eye. Whatever treatment is chosen, the results will not be part of the study.

B. Study Treatments

If you are eligible and agree to take part, we will then determine whether your study eye will receive:

1) Initial surgical treatment (***"Surgical Group"***) OR

2) Injections into the eye to start and surgery only if the blood does not go away (***"Injection Group"***)

A computer program will be used to select whether or not you will be receive initial surgical treatment or injections in the eye to start. This is similar to flipping a coin to decide which treatment approach you will receive. There is an equal chance of getting each treatment approach.

Surgical Group

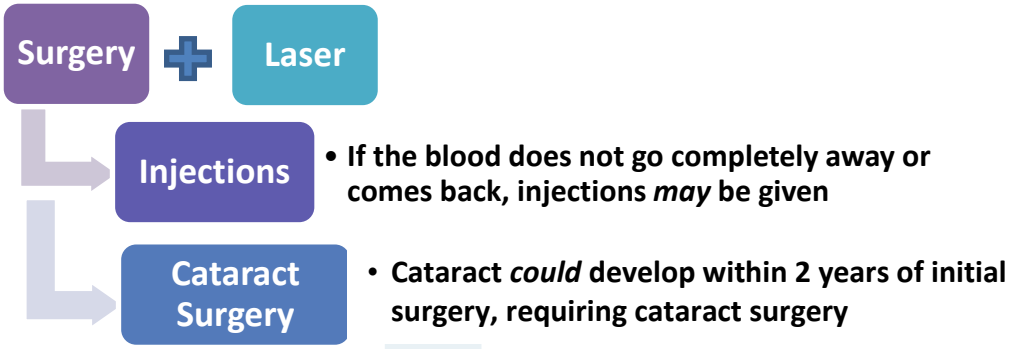
If you are in the Surgical Group, surgery must be scheduled within 2 weeks. The surgery will be done however your eye doctor would perform the surgery in usual practice. In general, a vitrectomy involves the surgeon removing the vitreous gel and replacing it with saline. Occasionally, the surgeon will add silicone oil or a gas to restore normal pressure in the eye or help to attach the retina to the back wall of the eye. The surgery usually lasts about 1 to 3 hours.

During surgery, you likely will have laser treatment to the retina. The laser is done to make the blood vessels that caused the bleeding go away.

After surgery, you will be monitored to make sure the blood has gone away. If the blood does not completely go away or comes back, injections into the eye may be given, similar to the Injection Group described below. If the injections do not work, it is possible another surgery may be needed to remove the blood, although this is not expected to be very common.

It is possible that a cataract could develop as a result of the surgery. "Cataract" is haziness in the lens of the eye. The lens is involved in focusing so that the eye can see clearly. The haziness causes vision to be blurred. If a cataract develops, cataract surgery may be needed. The cataract surgery itself is not part of the study. The cataract surgery will be done however your surgeon would do it if you were not in the study. In most cases, this surgery is successful in improving vision.

The figure below summarizes the Vitrectomy Group treatment for the bleeding and PDR:



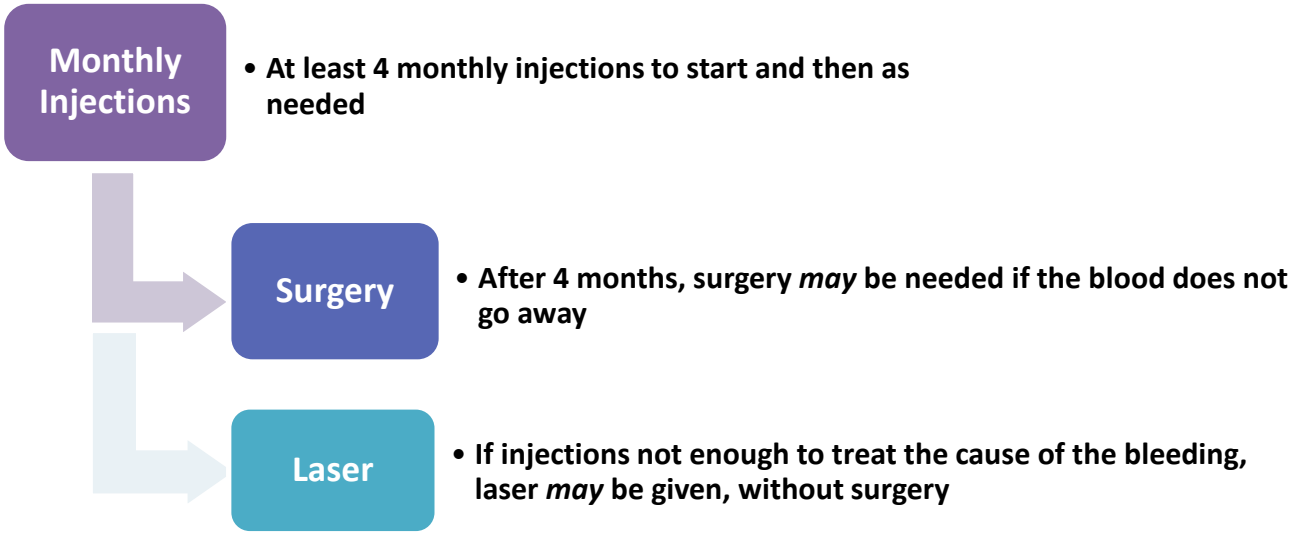
Injection Group

If you are in the Injection Group, you will receive at least 4 monthly injections to start. 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 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.

After the first 4 monthly injections, your study doctor will decide whether injections should continue based on how your eye is doing. If the blood is not going away after 4 months, you may need to have a vitrectomy. If your eye doctor decides you need a vitrectomy, it will be done as described for the Surgical Group above.

Even if a vitrectomy is not needed but injections are not enough to also treat the abnormal blood vessels that caused the bleeding in the first place, laser treatment may be given if your eye doctor thinks it is needed. Laser treatment is a method that has been commonly used for many years as part of standard care.

The figure below summarizes the Injection Group treatment for the bleeding and PDR:



Treatment for DME in Both Groups

During the study, you may have or develop swelling of the center of your retina. This is called diabetic macular edema or "DME". Anti-VEGF injections have already been shown to be beneficial for DME and are an FDA approved treatment. For both groups, injections of Eylea will be given to treat DME if your eye doctor thinks it is needed.

Treatment of the Non-Study Eye

If you and your doctor decide that the eye that is not in the study also needs anti-VEGF treatment during the study, then the non-study eye will receive the same anti-VEGF drug as the study eye (Eylea). The study will provide this treatment. If you and your doctor decide that a different anti-VEGF drug should be used, this will not be provided by the study. All other treatment in your non-study eye will not be provided by the study.

C. Follow-Up Visits

The study will last two years for each participant. All participants will have visits at the following time points:

Year 1: 1 month, 3 months, 6 months, 9 months, 12 months
Year 2: 16 months, 20 months, 24 months

Eyes receiving injections will also be seen as often as every 4 weeks to receive treatment. If you no longer need injections, you will still have follow-up visits every four to sixteen weeks depending on how your eye is doing.

At the end of each visit, you doctor's office will inform you of the timing of your next appointment.

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

	0	1 week after surgery[a]	Treatment Assessment Visits[b]	Non-Annual Study Visits[c]	6-Month and Annual visits
Vision testing	X		X	X	X
OCT	X		X	X	X
Ultrasound (if needed)	X	X	X	X	X
Eye exam	X	X	X	X	X
Blood pressure	X				X
HbA1c	X				X
Questionnaire	X			X	X
Vitreous/aqueous sampling[*]	X[*]				

a = Surgical Group at baseline and Injection Group if vitrectomy is performed during follow-up.

b = Every 4 to 16 weeks if receiving injections.

c = 1 month, 3 months, 9 months, 16 months, 20 months

*At the time of surgery (optional procedure)

If you decide not to take part in this study and do not sign this document, you may continue receiving medical care not related to this study. You can decide to stop your participation in this study at any time. No penalty or loss of medical care will result from your decision not to take part in this study.

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.

A. Risks of Vitrectomy Surgery

The risks of vitrectomy surgery listed here are general risks. Your eye doctor may discuss more specific risks with you depending on the exact procedure that is planned.

1. Risks Related to Anesthesia

Surgery may be done under general anesthesia or under sedation with numbing of the eye. Numbing of the eye is done with an injection. Your eye doctor will inform you of the approach that will be used.

- Very rare risks of sedation and general anesthesia include cardiac arrhythmia and death (less than 1 in 10,000).

- Risks of the injection to numb the eye include: less common side effects such as double vision lasting up to 24 hours or more, drooping of the eye lid lasting up to 24 hours or more, bleeding behind your eyeball or around the eyelids, and rare side effects including damage to your eyeball by the needle, damage to the optic nerve; difficulty speaking or breathing, lightheadedness or fainting, allergy to any components of the injection, or a life threatening response due to the spread of anesthesia to the brain stem, resulting in seizures, drowsiness, confusion, loss of ability to talk, convulsions, stoppage of breathing, or stoppage of heartbeat.

2. Risks Related to the Procedure Itself

Common risks:

- For eyes that have not already had cataract surgery, there is a risk of development of a cataract. A cataract causes haziness in the lens of the eye, which blurs vision. The lens is involved in focusing so that the eye can see clearly. The haziness causes vision to be blurred. There is a considerable possibility that a cataract will develop. A previous study found that almost half of eyes that had vitrectomy developed cataract within the first two years after vitrectomy. If a cataract develops, cataract surgery may be needed. In most cases, this surgery is successful in improving vision.

Less common risks include:

- Vitrectomy can affect the surface of the cornea in patients with diabetes. Some mild irregularity can commonly affect vision short term. Corneal edema is the temporary swelling of the cornea following ocular surgery and occurs in about 1 in 4 patients. When the cornea swells, it can effect vision. Topical drops or ointments can be used to relieve the swelling. Corneal erosion, a more severe problem of the corneal surface can also happen (approximately 2 in 100 chance). Symptoms include pain, tearing and foreign

body sensation which are commonly helped by the use of eye drops. Usually cornea problems heal on their own or with drops but sometimes the problem can be long lasting.

- A tear in the retina (approximately 10 in 100 chance). If a retinal tear occurs, it can be usually be treated with laser treatment or cryotherapy (freezing treatment). If properly treated, a retinal tear may not affect your vision, but should be addressed as quickly as possible by your doctor to prevent loss of vision.

- Separation of the retina from the back of the eye (1 in 100 chance). This is called a retinal detachment and can lead to loss of vision. If this occurs, surgery may be needed to repair the retina.

Rare (uncommon) risks include:

- An infection can develop in the eye after the surgery. 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.

- More serious hemorrhage (1 in 5,000) that can lead to decreased vision if the hemorrhage does not clear.

- Very rare risks include a defect in your peripheral (non-central) vision, vision loss due to excessive bright light, trauma to the retina or retinal dyes used during surgery, and damage to the optic nerve

B. Risks of Laser Treatment

The laser burns are part of routine care for your diabetic retinopathy. Laser treatment can cause loss of areas of retinal function that may lead to noticeable loss of peripheral (side), color vision or night vision and some worsening of macular edema (swelling of the central retina) that can affect central vision. One or more of these side effects can occur in up to 50% of persons treated

with laser. After several years, the scars caused by the laser may also enlarge and cause vision to decrease further.

Other serious, but rare (less than 1 in 1000) side effects which may reduce vision include, but are not limited to:

- Laser burn too close to the center of vision. This could cause a permanent black spot in your vision.
- Damage to the membrane underneath the retina, sometimes resulting in growth of abnormal blood vessels under the retina.
- Increase in pressure inside the eye, which can occur right after the laser or at a later time
- Damage to the optic nerve, iris, or lens
- A tear or small break in the retina called a retinal hole. Treatments for retinal holes include surrounding the hole with laser or freezing. These treatments are usually successful in sealing the hole so it does not get bigger. However, there is a small risk that a retinal hole could grow and lead to a retinal detachment.
- Blindness

C. Risks of Eylea 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.

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.

2. Risks in the Eye Related to Eylea

Eylea is well tolerated in people. Possible side effects to the eye from the drug itself 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 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.

3. Risks to the Rest of the Body Specific to Eylea:

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.

4. Risks if You Become Pregnant

The effects of Eylea 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.

D. 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 raise. 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.

3. **OCT:** There are no known risks associated with OCT.

4. **Risks of Ultrasound (if performed):**
   - These sound waves are of no risk to your retina, although the probe used to produce the sound waves rarely can cause some slight irritation to the surface of the eye; this irritation almost always resolves within a short time without treatment.

5. **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.

WHAT ARE THE BENEFITS OF TAKING PART IN THIS STUDY?

The study treatment may help clear the bleeding in your eye and help preserve your vision, 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.

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 could receive the alternative procedures or treatment listed below:

- Observation outside of the study to see if the blood clears on its own
- An anti-VEGF drug outside of the study
- Vitrectomy surgery outside of the study

Any of the above alternatives may be done with or without laser treatment.

We encourage you to discuss these alternative procedures and/or treatment with your study doctor, your primary care physician, or another health care professional.

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. No penalty or loss of medical care will result from your decision. However, we encourage you to talk to a member of the research group so that they know why you are leaving the study. If there are any new findings during the study that may affect whether you want to continue participating, you will be told about them.

The investigator may decide to stop your participation without your permission, if he or she thinks that being in the study may cause you harm.

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.

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 it.

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 go with your study results instead of your name, address, telephone number, or social security number. Your study results will be given to the Jaeb Center for Health Research. The Jaeb Center is the coordinating center for the study. It is located in Tampa, Florida.

This 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 your protected information may appear in medical journals and be shared at scientific meetings. Your records will be kept confidential. No one will disclose your identity in a medical journal or at a scientific meeting.

C. Authorized Recipients and Users

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 for HbA1c to a central laboratory for this study.
8. The OCTs of your eye may be sent to a central reading center.
9. The industry partner, Regeneron Pharmaceuticals, Inc., their agents, collaborators, and representatives.

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 with it. 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. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be disclosed.

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.

After the results are made public, all of the study data collected may also be made public. However, there will be no identifying information included. You will be informed of the study results when they are made public.

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 the information you have given us to try to locate you through the use of 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 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 it is on an adverse (unfavorable) event that is related or potentially related to the study. If one happens, your entire medical record may need to be reviewed.

The Jaeb Center will receive all the information that has already been collected for the study up to the time of cancellation or withdrawal. Any new information about any adverse (unfavorable) event that is related or potentially related to the study will also be sent to the Jaeb Center.

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*

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 at 1 month, 9 months, 16 months, and 20 months in both groups, and treatment assessment visits required in the Injection Group
- The OCT at baseline, 6 months, and annual visits.
- All study injections, including Eylea injections in the non-study eye if needed.

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

- The eye exam at 1 week post-vitrectomy, 3 months, 6 months, 12 months, 24 months
- OCT as needed for DME assessment.
- Vitrectomy surgery
- Laser treatment
- Cataract surgery (if needed)

Depending on your insurance plan, it is possible that your insurance will not pay for some of the procedures and testing listed above; if they do not pay, the study may become responsible for these costs if you have a financial hardship. For surgical costs (vitrectomy and cataract), for cases of financial hardship, the study is able to reimburse up to a certain amount. It is possible that costs above that amount will not be covered. Costs for other tests and procedures not listed above that are done as part of your usual eye care, including testing and other treatment in an eye not in the study, will not be covered by the study.

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.

WHO SHOULD I CONTACT, IF I SHOULD EXPERIENCE ANY PROBLEMS OR HAVE ANY QUESTIONS?

If you have questions about this study, a research-related injury, have concerns, suggestions or questions about the study, please see the contact information on the last page.

If you have 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

WITHDRAWAL BY INVESTIGATOR, PHYSICIAN, OR FUNDING SOURCE

The investigators, physicians or funding source may stop the study or take you out of the study at any time should they judge that it is in your best interest to do so, if you experience a study-related injury, if you need additional or different medication, or if you do not comply with the study plan. They may remove you from the study for various other administrative and medical reasons. They can do this without your consent.

Consent to Participate in a Research Study
Intravitreous Anti-VEGF vs. Prompt Vitrectomy for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy (Protocol AB)

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: ***Intravitreous Anti-VEGF vs. Prompt Vitrectomy for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy (Protocol AB)***

_____ _____
Participant 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.

Consent to Participate in a Research Study
Intravitreous Anti-VEGF vs. Prompt Vitrectomy for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy (Protocol AB)

****Optional Sample Collection During Surgery****

Your eye doctor's office may be part of an ancillary study to collect fluid samples at the time of surgery that will be studied to look at different factors related to diabetic retinopathy or other conditions. If so, you will be asked to complete this section.

☐ **This box will be checked if your eye doctor is NOT participating (leave next page blank); otherwise continue reading and complete next page.**

If you have vitrectomy surgery during the study and agree to take part in this sample collection study, one sample can be taken from the vitreous that is already being removed, without any additional procedures or risk. A second sample may be taken, which will likely require an additional needle stick through the cornea, the clear surface on the front of the eye. A common risk of this second needle stick is the formation of a small corneal scar which is unlikely to be visible or to affect the vision. Less common risks include substantial leakage of fluid from the eye or damage to the lens. An eye infection may rarely develop and may be treated with antibiotics or surgery if it develops.

If you agree to take part in this additional sample collection, you will have the option to provide one or both samples.

The samples will be stored at a facility located in the United States until the researchers are ready to analyze them. All identifiable information about you will be removed from the research specimen. Your sample and study data will be linked only by a code. The results from these samples will be used for research purposes only and you will not be told the results of the tests.

Consent to Participate in a Research Study
Intravitreous Anti-VEGF vs. Prompt Vitrectomy for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy (Protocol AB)

Sample Collection Study Enrollment

I have read the explanation above about the optional sample collection during surgery. I have been given the opportunity to discuss the study and to ask questions. I understand if I consent to provide additional samples, they will be used by investigators within the DRCR.net for research purposes only.

I authorize the use and disclosure of my protected health information collected as part of this study. I acknowledge that I will not be contacted or asked for my consent again at the time when my sample is used.

Please choose only one of the options below:

1. ____ I hereby give my consent to have **both samples** drawn during surgery. I acknowledge that there is additional risk to the second sample, which will likely require an additional needle stick.

2. ____ I hereby give my consent to have **only the vitreous sample** drawn during surgery (no additional needle stick).

3. ____ I **do not** want to provide any additional samples for this ancillary study.

If you consent, you have the right to request at any time that your samples be destroyed. Your sample can be destroyed (when possible) on your written request. However, if the sample has already been tested, the information obtained from the sample will not be destroyed.

Participant Signature: _____ Date: _____

I certify that to the best of my knowledge the subject understands the nature, demands, risks and benefits involved in participating in this ancillary study.

Investigator's Signature: _____ Date: _____

Appendix – Glossary of Terms

Anti-VEGF – the type of drug being used in this study, which blocks a substance called Vascular Endothelial Growth Factor (VEGF). Anti-VEGF drugs decrease the growth of new blood vessels and prevent leakage of fluid.

Diabetic Retinopathy – a condition that causes abnormal blood vessel growth on the surface of the retina.

DME –diabetic macular edema (DME) is the term used for swelling in the small central part of the retina.

DRCR.net – the Diabetic Retinopathy Clinical Research Network (DRCR.net) is conducting the study under a grant from the National Eye Institute, one of the National Institutes of Health of the U.S. Public Health Service, a part of the federal government

HbA1c - A blood test to see how well your diabetes is controlled

Jaeb Center - the coordinating center for the study located in Tampa, Florida.

OCT - optical coherence tomography (referred to as OCT) uses a dim beam of light to measure the thickness of the retina

PHI – protected health information, which may be collected as part of the study

Retina - the light-sensitive tissue which lines the back of the eye.

Study eye - the eye to be included in the study

Visual Acuity Testing - the ability to read letters on the vision chart

Vitreous Hemorrhage – bleeding in a part of the jelly-like fluid that fills the large space in front of the retina.

Vitrectomy – surgery in which an instrument is put into the eye to remove the blood with the vitreous.

INVESTIGATOR CONTACT INFORMATION

Name of Investigators: _*<list all investigators at site>*_____
_____
_____
_____
_____

Address: _____
_____

Telephone: _____

After hours telephone: _____