Appendix 5 – Patient information sheet and consent form.

Version 4 dated 17th September 2015 is shown below.

Patient Information Sheet

Clinical Efficacy and Mechanistic Evaluation of Aflibercept for Proliferative Diabetic Retinopathy (acronym CLARITY)

Invitation

You are being invited to take part in a research study. Before you decide whether to take part, you need to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

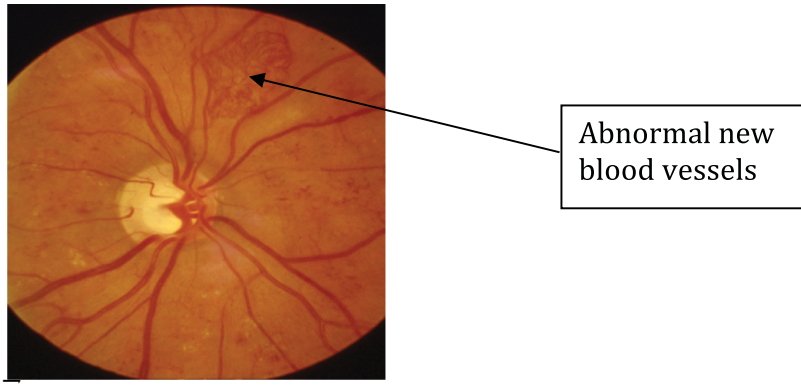
Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

What is proliferative diabetic retinopathy?

Diabetes causes blood vessels to die and areas of retina become starved of blood supply. This process triggers the retina to produce a small molecule called vascular endothelial growth factor (VEGF) that stimulates the existing blood vessels to grow new blood vessels in an attempt to repair the damage ones. However, these blood vessels may bleed and pull on the retina causing visual impairment. This over production of new vessels and the damage it causes in diabetics is known as proliferative diabetic retinopathy

The standard treatment for this condition is to apply laser therapy to the outer part of the retina so there is less retina available to produce VEGF. Laser therapy (otherwise called panretinal photocoagulation) is a good treatment in that it causes a decrease in blood vessels in most cases. However, repeated treatment is sometimes required and this can lead to a decrease in the peripheral vision (visual fields). Below shows a diagram of the retina and abnormal growth of blood vessels.



What is the purpose of the study?

We are conducting an investigational study using aflibercept injections into the eye. Aflibercept works by blocking VEGF and therefore may prevent new blood vessels from developing. This drug is used routinely for other eye conditions such as wet age related macular degeneration (AMD) which is a condition that affect a tiny part of the retina at the back of the eye. This study is designed to compare how well aflibercept works versus the standard laser treatment for proliferative diabetic retinopathy.

Why have I been invited?

You are being asked to take part in this research study because you have proliferative diabetic retinopathy. 220 patients will be taking part. Only one eye will be treated in the trial. The other eye will receive standard care of laser treatment if necessary.

Do I have to take part?

It is up to you to decide to join the study. We will go through the patient information sheet and describe the study in detail with you. If there is anything you do not understand or want to clarify something you have read, the study doctor and his team will be able to answer your questions. At any point of the study, you will be free to withdraw without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

If you take part, we will ask you to sign an informed consent form before any study-specific procedures are performed. You will attend regular study visits over a period of 52 weeks.

The **first visit** may last approximately 4 hours. We will do the following to see if you are suitable for the study

1. Take a medical and eyesight history and ask about any medications you are taking.
2. You will then complete questionnaires about your vision, quality of life and how satisfied you are about your treatment.
3. Perform tests on your visual function in different lighting conditions using different sized letters on a chart with one eye and both eyes. This will also include your driving vision test. These tests will take about 20 minutes.
4. Check your blood pressure.
5. Take a sample of blood. This will be used to see what your average blood sugar levels have been over the last three months.
6. Take a urine sample to perform a pregnancy test. This will only be done if you are a woman of child-bearing age.
7. You will be given eye drops to dilate your pupils (make your pupils bigger) to do the rest of the tests. The pupils usually become bigger in about 15 minutes. You may find bright lights hurt your eyes for 4-6 hours after this test but sunglasses will help. You must not drive until the effects of the eye drops have worn off.
8. We will then perform a routine eye examination which will involve looking closely at your retina for anything unusual and testing the pressure inside each eye.
9. Perform a test similar to an ultrasound on your eye. The test is quick and painless. For the test, you will sit in front of a machine and a light beam will scan the retina in each eye. This test lasts about 10 minutes.
10. Take colour photographs of the retina in each eye. You will notice a bright flash after each photo is taken, but this will not have any long-term effect on your eye. This test takes about 10 minutes.
11. Perform a test, which is done very often in clinic, to check the status of your retinal blood vessels. The test involves a fluorescent dye being injected in to your hand or arm with a needle before further photographs of the eyes are taken. This test lasts about 20 minutes.
12. Towards the end of the visit we will check that you are feeling ok after having all the assessments completed.

If after the initial tests above, your ophthalmologist (eye doctor) decides that you are suitable for the study, we will ask you to return for the **second appointment** which can be up to 15 days after your first visit. This appointment will take approximately 1 hour. Your study doctor may be able to perform the second visit on the same day as your first visit, but this will depend on whether he/she has all of your results.

We will perform the following tests and assessments which will be similar to those performed in your first visit.

1. An eye examination
2. Visual acuity tests. Only routine vision charts will be used in this visit.
3. Medication review to see whether medication you were on at your fist visit has changed.
4. We will ask whether you are feeling ok since the first visit
5. If you consent to participate in the sub- study, you will have an additional photograph taken of your retina taken to look at the oxygen carrying capacity of your retinal blood vessels. You will only be asked to take part in this sub-study if you are taking part in the main study at the Moorfields Eye Hospital.

At this point you will be randomised (similar to flipping a coin) to receive either aflibercept injections or laser therapy. You should also be informed which eye will be classed as the study eye (the eye that will receive either aflibercept or laser therapy for the study). Shortly after randomisation you will receive your first treatment. If you are in the laser group, you will be required to attend the clinic in between the study visits to complete your treatment as each delivery of the laser is usually completed over several appointments. This is how the therapy is delivered in routine practice. If you are receiving the aflibercept injections, you will not require further appointments in between study visits unless your eye doctor wants you to attend for safety reasons

Only you, your study doctor and nurse will know which treatment group you are in. The assessors who will be performing vision tests and taking images of your eyes will not know what treatment you are on. We ask that you do not discuss this information with the assessors. It may affect the way they deliver the assessment and this could affect the data we collect on you as part of the study.

Your **next appointment** will be approximately 4 weeks after the second study visit. The following will be performed:

1. An eye examination
2. Visual acuity tests. Only routine vision charts will be used in these visits.
3. If you are in the aflibercept arm, an additional photograph will also be taken
4. Medication review to see whether medication you were on at your fist visit has changed.
5. We will ask whether you are feeling ok since your last visit
6. If you are in the **laser therapy group**, your study doctor will check your eye to see whether it needs further laser. If he is satisfied that it has been sufficiently treated, he may decide not to deliver any more therapy at this visit. If you are in **the aflibercept group**, you will receive your second injection into the study eye.

The schedule that you will follow after week four will depend on what treatment group you are in. If you are in the **laser group,** you will attend study visits approximately **every 8 weeks**. **Your next appointment will be week 12 of the study**. If you are in the **aflibercept group,** you will attend study visits approximately **every 4 weeks**. **Your next appointment will be week 8 of the study**.

Patients in the aflibercept group only

Approximately 8 weeks after your second appointment, you will have similar tests that were performed at your second appointment and will also receive your second aflibercept injection.

Patients in both treatment groups

Approximately 12 weeks after your second visit, you will have the following tests:

1. An eye examination
2. Visual acuity tests. Only routine vision charts will be used in these visits.
3. Medication review to see whether medication you were on at your fist visit has changed.
4. We will ask whether you are feeling ok since your last visit
5. Take colour photographs of the retina in each eye. Similar to that in your first visit

6. Perform the test that is similar to an ultrasound on your eye. Similar to that in your first visit

During this and subsequent appointments, until approximately week 48, your study doctor will check the level of growth of abnormal vessels in the study eye. You will receive further treatment based on how well the treatment has worked so far. In addition, to whether your study doctor treats your eye, you will have tests performed, similar to those completed at your second appointment. However, you will not have the additional photograph taken of your eye at any of these visits, if you consented to taking part in the sub-study.

Treatment in the non- study eye

If you develop macular oedema in your non-study eye during the study, you doctor may recommend you to have laser treatment to this eye. If macula oedema is too severe, your doctor/nurse may treat it with either intravitreal anti-VEGF therapy or steroid therapy as appropriate.

Your doctor may also treat your non-study eye with laser treatment during any visit, if abnormal blood vessels start to grow in your retina.

In both scenarios, you will continue to attend all study visits until end of study.

For your **final visit,** which will be approximately 52 weeks after your second visit, we will perform similar tests and assessments to that in your first appointment, so this visit may last approximately 4 hours. You will not receive any treatment relating to the study at this visit. If you have consented to take part in the sub-study, you will have the additional photograph taken of your retina.

What will the aflibercept injection involve?

Before the injection of aflibercept, your eye will be prepared with antibiotic and antiseptic eye drops. Then the eyelids will be thoroughly cleaned with a cotton-tip applicator soaked in iodine cleaning solution. The eye is then held open and anaesthetic eye drops (numbing medication) are dropped onto the lower part of your eye.

After a few minutes you will receive your aflibercept injection. Your doctor may decide to prescribe some antibiotic drops to put in your eye after the injection to prevent you from getting an infection. This decision will be based on whether your doctor feels it is necessary.

What will the laser therapy involve?

If you are in the laser arm, we will numb your eye with eye drops and then place a contact lens on your eyes while you sit in front of the laser machine. Whilst having the treatment, you may see this as tiny spots of bright light entering the eye at quick succession. The procedure lasts about 10 minutes.

Expenses and payments

If any of your study visits last more than 4 hours we can offer you a snack. Reasonable travel expenses above and beyond any routine clinic appointments will also be covered up to a maximum amount of £20 pounds. We will need you to retain your receipts so that you can give them to the study team.

What will I have to do?

- We ask that you attend and complete all tests and treatment at each study appointments as described above under *What will happen to me if I take part?*.
- We ask that you complete the questionnaires about your health, vision and treatment satisfaction as fully as possible, at the study visits that require you to.
- You, your study doctor and nurse will know what treatment you are having in the study. Those that will be performing the visual assessments will not know what treatment you are on. We therefore ask that you do not discuss this with them.
- Let your study doctor know if you experience any pain or discomfort during the study or have any side effects.
- Let your study doctor know if you plan to fall pregnant or are pregnant.
- Inform your study doctor about any changes in medication
- Inform the study doctor if you are or plan to take part in any medicinal study other than this one.

What are the alternatives for diagnosis or treatment?

The standard treatment for this condition within the NHS is to apply laser treatment to retina. Whilst laser treatment is good in that it causes a decrease in blood vessels in most cases,

repeated treatment is sometimes required and this can lead to a decrease in the peripheral vision (visual fields).

We are comparing the laser treatment to aflibercept injections in this study.

What are the possible disadvantages and risks of taking part?

There will be a pricking sensation during the procedure but your eye will be prepared with numbing medication before the procedure to make you more comfortable.

There is a slight increased risk that your eyesight in the study eye will deteriorate despite treatment with aflibercept or laser therapy. It is very rare that this will be caused by the study drug or the laser and is usually down to natural progression of the condition.

What are the side effects of any treatment received when taking part?

Aflibercept

Some patients may develop a serious eye infection called endophthalmitis. To try and stop this happening, your eye is treated with antibacterial iodine before the injection. The injection is also done in very clean sterile conditions. Your study doctor may also give you antibiotics to take after the eye injection to prevent any infection. The risk of infection occurring is 1:3000.

The other rare but serious side effects are retinal detachment (which is when the retina comes away from the back of the eye), bleeding at the back of the eye or damage to the lens from the needle. All together there is about a 1 in 3000 risk of a serious complication with each injection. This risk is minimised as the procedures will be performed by trained ophthalmologists.

Less serious but more common side effects are a slightly bloodshot eye, temporary visual floaters (small specks like flies flying around in front of your eyes), temporary visual flashes and inflammation of the eye. You may temporarily experience reduced vision after the injection and you must not drive or operate machinery until it is resolved.

There may also be a mild temporary increase in the pressure inside the eye (often as a result of the injection).

It is extremely important that you are aware of any symptoms that might mean you are having one of these problems described above, and that you tell your study doctor immediately about any new symptoms you are having.

The symptoms to be aware of include:

- Eye pain or increased discomfort
- Worsening eye redness
- Blurred or decreased vision
- Increased sensitivity to light
- Increased number of floaters

IF YOUR DOCTOR IS NOT ACCESSIBLE FOR ANY REASON AN

ALTERNATE DOCTOR SHOULD BE CONTACTED IMMEDIATELY.

CONTACT DETAILS FOR YOUR STUDY DOCTOR IS AT THE END OF PART 2 OF THIS INFORMATION SHEET

The fluorescent dye

This dye is widely used in routine practice within clinics and helps the eye doctor see how your retinopathy is doing. However, like with any drug or procedure, it is important that we let you know what the side effects are for the dye.

Sometimes you may get some bruising or swelling where the dye is injected. The fluorescent dye may affect the colour of your skin for a few hours after it is injected and your urine may be orange for up to 24 hours. You may also feel sick.

On rare occasions, the dye may leak out of a weakened vein and your skin at the site of the injection might turn yellow for a few days. You might also feel some burning at the site of injection, which usually lasts a few minutes. On rare occasions, there have been reports of an allergic reaction to the dye. The risk of fatality to the procedure is less than 1 in 200,000 cases.

Laser therapy

Immediately after the laser treatment, you may experience increased discomfort, blurred or decreased vision and increased sensitivity to light. These symptoms may last a few days but should subside. Some patients experience a dull ache around the eye which some people describe as a headache. With repeated treatment, you may find it difficult to adjust to change in lighting in an environment, especially when you go from a bright to a dark area. The visual fields may become affected with the increased number of laser sessions and this may affect your ability to drive.

Harm to the unborn child: therapeutic studies

For women

It is not known whether the study medicine aflibercept can cause harm to an unborn child or through breast feeding. As a result, if you are pregnant, you will not be able to take part in the study. If you are of child bearing potential, you should refrain from falling pregnant during the study and for at least 3 months after study participation has ended. If you are a breastfeeding mother, you will not be eligible to take part in the study either. We ask that you use a suitable form of contraception throughout the duration of the study until at least 3 months after you have finished the study. Types of suitable contraception include barrier method (e.g. condoms with spermicides), true abstinence, sterilisation and use of established oral, injected or implanted hormonal methods of contraception.

All women of child bearing potential will have a pregnancy test at the start of the study. A negative pregnancy before randomisation days before starting the study drug is required in women who are able to get pregnant. We will repeat the pregnancy test if your doctor thinks it is necessary.

If you become pregnant during the study, you must tell the study doctor immediately. Because of the possible risks to your unborn child, the study drug will be stopped immediately, but you will remain under regular follow-up within the study and for the duration of your pregnancy.

For men

Animal studies where they have been exposed to high systemic levels of aflibercept have been shown to impair male and female fertility but such side effects are not expected when

used as an eye injection. This is because the level of aflibercept that goes into your system is low. However, we still recommend that male participants use a suitable method of contraception for the course of the study and for three months after the study.

What are the possible benefits of taking part?

We believe that the chances of improvement in vision, contrast sensitivity and retaining visual fields are higher with aflibercept. That is why we want to test the medication and the dosing frequency. However this cannot be guaranteed.

The information we get from this study may also help us develop new treatments for this condition, which may benefit other patients or yourself in the future.

What happens when the research study stops?

When the research ends, you will return to standard of care follow up. Aflibercept will not be provided beyond the study period, even if it shows benefit. Should any further treatment be required for your condition you will be offered the best available standard care which is laser treatment.

We may wish to monitor whether the study drug has any long lasting therapeutic effects after the trial has ended. If we do, we will need your permission to look at your medical notes to check if there have been any changes to your eye condition. Once again, any information we use will be treated in the same confidence and manner as we have done for the CLARITY trial.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This completes part 1.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2 of the information sheet

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your study doctor will tell you and discuss whether you should continue in the study. If you decide to continue in the study he may ask you to sign another consent form outlining the discussion.

What will happen if I don't want to carry on with the study?

If you or your doctor decide it is in your best interest not to carry on, your study doctor will make arrangements for your care to continue in routine practice. We will ask you to complete a withdrawal visit at that point. The assessments within that appointment will be similar to those performed at your first appointment

If you are happy to, we will ask you to continue attending your study visits for data collection as scheduled by your study team, up to the last visit at week 52 or at a minimum to attend your final visit at week 52. The information that we collect from these visits will still be very helpful to the study.

What if there is a problem?

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. Please contact the hospital's Patient Advice & Liaison Service (PALS) department. Their contact details are: <insert details>.

Complaints

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints procedures are available to you. Please discuss this with your study doctor.

Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study may be looked at by authorised people from the hospital sponsoring the research and authorised people supporting the Chief Investigator to conduct the study. Authorised people from the bodies that have approved this study may also want to look at your medical records and the study data collected from you. This will be to make sure that the study is being run correctly. However, everyone will have a duty of confidentiality to you as a study participant and we will do our best to meet this duty.

The results of your treatment may be published for scientific purposes; however, your identity will not be revealed.

The data collected as part of the study will be kept in a secured location for at least five years from when the study has finished.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will be informed that you are participating in the study. If your blood pressure or your HbA1C is high, we may also send them a letter to follow up the results. We may also exchange information regarding your general medical health with your GP.

What will happen to any samples I give?

At the start and end of the study we will take a blood sample from you to check how well controlled your diabetes is. The local laboratory at your hospital will perform this test.

Once we have the result of the test, the sample will be processed according to your hospital's policies. We will not hold onto this sample for future research.

Will any genetic tests be done?

This study does not involve any genetic testing. We will however ask some participants to take part in a sub-study to look at how well the treatment has reduced the level of abnormal vessels in the eye. It will involve an additional image of your retina that will be taken at the start and end of the study. This will involve 40 participants at the Moorfields Eye Hospital only. If you agree to take part, there is an optional box on the consent form to initial to reflect your decision.

What will happen to the results of the research study?

Results from this study are likely to be published in a medical journal and presented at national and possibly international conferences. If you would like to know what the study results showed, you will be able to obtain a copy of published results from your study doctor but only after the project has finished, after all participants have completed their treatment and the study has been analysed. You will not personally be identified in any report/publication.

Who is organising and funding the research?

The study is being sponsored by Moorfields Eye Hospital and is funded by National Institute of Health Research, Medical Research Council and Bayer Plc Pharmaceutical Company.

The doctors conducting the research are not being paid for including and looking after the patients in the study and have no conflicts of interests.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by NRES Committee London – South East.

Further information and contact details

For further general information on the study, please contact your study doctor (during office hours)

Principal Investigator (study doctor): <add name>

Tel:<add suitable number>

After normal working hours you may contact (insert contact) on (insert number).

In an emergency please contact (insert emergency contact).

For general information about research or If you have any questions about your rights as a research subject, please contact the hospital's Patient Advice & Liaison Service (PALS) department. Their contact details are: <insert details>.

If you choose to participate, you will be given a consent form to sign. By signing the consent form, you have not waived any of your legal rights. You will receive a copy of this patient information and the signed consent form that will show all signatures and dates.

Thank you for reading this information and considering taking part in the study.

Centre No:

Name of Principal Investigator:

Patient ID:

CONSENT FORM

Clinical Efficacy and Mechanistic Evaluation of Aflibercept for Proliferative Diabetic Retinopathy (acronym CLARITY)

Please initial box

1. I confirm that I have read and understand the information sheet dated 17/09/2015 (Version 4.0) for the above study and understand the risks of aflibercept and laser treatment. I understand that my blood will be taken for an HbA1c test at the start and the end of the study and that if I am a woman of child bearing potential I will be asked to undertake a pregnancy test prior to enrolment and will be followed up should I fall pregnant during my participation in the study. I have had the opportunity to ask questions. A

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rightsbeing affected. ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study maybe looked at byresponsible individuals from Moorfields Eye Hospital (the sponsor), King's Clinical Trials Unit, individuals from regulatory authorities, the ethics committee or the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I understand that confidentiality will be maintained. ☐

4. I understand that my GP will be informed of my participation in this research project and of any findings significant to my general health ☐

5. I understand that I will not benefit financially if this research leads to the development of anew treatment or medical test. ☐

6. I agree to take part in the above study.

7. I agree to collection of data from my medical records after the end of the study. ☐

For patients from Moorfields Eye Hospital only (optional)

8. I agree to take part in the mechanistic sub- study. ☐

_____	_____	_____
Name of Patient	Date	Signature

_____	_____	_____
Name of person taking consent	Date	Signature

When completed: Original for researcher site file; a copy for the participant; a copy for the medical notes.