HOBART EYE SURGEONS

The brolucizumab anti-VEGF Treatment of AMD Switch Study (BRAVAS)
Participant information and consent form

Study doctors*	Clinical Professor Nitin Verma (Principal Investigator) Dr Guy Bylsma Dr Andrew Traill Professor Alex Hewitt	
Study Coordinator	Beverley Curry	
Clinical contact person	Nitin Verma	6210 6000
24-hour medical contact	0417 873 213	nitin.verma@eyesurgeons.com.au

1 Would you like to take part in this clinical study?

We would like to invite you to take part in our clinical study. This is because you have a condition called wet age-related macular degeneration (wetAMD) in which there is new blood vessel formation and leakage of fluid behind your retina and you are being cared for by one of the study doctors listed above.*

This document is a Participant Information and Consent form (PICF). It tells you about the study and describes what will happen if you take part. If there is anything you don't understand or would like to know more about, please ask us. You may also take this PICF home with you so you can discuss the study with a relative, friend, or your GP before you make up your mind.

Study participation is voluntary. If you do not wish to participate you do not have to. Your doctor will provide you with the best possible care regardless of whether you decide to participate or not.

If you do decide to participate you will be asked to sign the consent form on page 11 of this PICF. Your doctor will also sign the form and you will be given a copy of the signed document to keep for your records.

2 Why are we doing this research?

The purpose of this study is to test the effectiveness of a new injection treatment for wetAMD called brolucizumab, or"*Beovu®*".

We understand that you are currently having treatment with either Lucentis, Eylea or Avastin injections every 4 to 8 weeks and that previous attempts to increase the time between your injections has resulted in a worsening of your wetAMD.

Like Lucentis and Eylea, *Beovu®* is a treatment specifically designed for intravitreal injection. It is currently licensed for the treatment of wetAMD but it is not yet listed on the Australian Prescription Benefits Scheme.

The results of clinical trials in patients not previously treated by intravitreal injection have suggested that injections of *Beovu*® every 12 weeks may have the same effect on WetAMD as Eylea every 8 weeks. The aim of this study is to see if *Beovu*® might reduce the number of injections that patients currently on frequent anti-VEGF treatment need to have, by increasing the time between injections, while keeping their Wet AMD stable.

3 Do I have to take part?

If you don't wish to take part in this clinical study, you don't have to. If you decide to take part now, and later change your mind, that is fine too. You are free to withdraw at any stage.

If you choose not to take part, or if you decide to take part then later withdraw, you will still be able to access your usual medical care. Your choice will not affect your relationship with your doctor or Hobart Eye Surgeons. You will receive the best possible care whether you take part or not.

4 What is involved in the study?

If you decide to participate in this study, you are required to complete the on page 11 of this PICF of this Participant Information document once you have read it and had the opportunity to ask questions. Signing the Informed Consent section acknowledges that you have read and understood this information leaflet and agree to all the procedures that are required of participants. So please ask as many questions as you need in order to make your decision whether to participate or not.

The first study visit is a "screening visit" where we check that you have all the other qualifications required for the study. At this visit you will be asked for information on your medical history and your medications; have your height, weight, pulse and blood pressure measured. You will have your vision tested, your eye pressure checked and a thorough eye examination directly by your doctor and indirectly using special cameras that take pictures of the back of your eye (retina and macula).

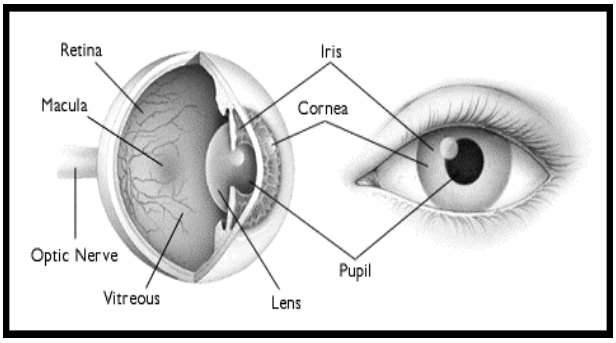
You may already be familiar with most of the study procedures as the majority are considered routine for patients with wetAMD and may already be included in your current care. For all of them you will be seated on a chair and either the examiner, or camera, will come closer to your eyes. For a number of them require your pupils to be dilated.

Pupil dilation

The pupil is like a window to the inside of the eye. Dilating drops open the window (pupil) wider so we can look through it to examine more thoroughly, the retina, optic nerve and other tissues at the back of the eye.

The drops may sting and take 15-20 minutes to work. Once the dilating drops are working, your eyes may be more sensitive to light (because more light is getting in to your eyes) and you may notice difficulty focusing on objects up close. The effect of the eye drops may take a couple of hours to wear off.

The structure of the eye



We do not recommend driving for **at least 4 hours** after any visit where both your eyes have been dilated.

Assessment of your vision:

You will be asked to cover one eye and read the letters on a special eye chart.

Eye examination

Intraocular pressure: The pressure within your eye will be measured using a device with a small, lightweight probe, which make brief contact with the eye and can be used without local anaesthetic

Retinal scans and photographs: Using specialised cameras, we will take photographs and scan of the back of your eyes (this includes the retina and macula). While the technician is taking the pictures, you will see a series of bright flashes. To help you keep your eyes perfectly still for the photographs, you will be asked to stare at a small light.

Fluorescein Angiography: In this test a dye (fluorescein) is injected into your arm and then photographs of the back of your eyes are taken. The pictures show your doctor the blood vessels at the back of your eye and help identify any leaky vessels that may be causing the WetAMD. Angiography may be done at screening, and on any other occasion, if your doctor thinks it is necessary. Your pupils will be dilated for this procedure.

Slit lamp exam: Your doctor will examine the front and back of your eye with an ophthalmoscope (an instrument with a strong light and magnifying lens). Your pupils need to be dilated before this examination.

Your doctor will review the results of your tests and your medical history and to determine whether you meet the requirements of the study.

If you **do not** meet the study requirements, you cannot take part in the study. If you **do** meet all of the requirements, and you wish to continue in the study, your study eye will be treated with Beovu®.

Only one eye per participant can be included in the study. If both of your eyes have wetAMD, and are being treated with ant-VEGF injections, your doctor will decide which eye will be the study eye.

While a participant you will have at least 12 (monthly) clinic visits over the next year. Each visit will take approximately 2 hours of your time. At these visits, you will have your vision tested and your eye examined to check your eye health and your response to treatment.

A summary of the assessments at each visit is presented in the table below. The study treatment will be given by injection every month for 3 doses. After the third injection the interval between treatments may increase depending on how your study eye has responded to treatment. This may result in extra visits to clinic between the scheduled monthly reviews specifically for study treatment. If this is required your doctor will also examine your eyes before injection to make sure it is safe to proceed. . A summary of the assessments at each scheduled visit is presented in Table 1 on the next page.

Table 1 Study assessments over the 12 month study period

	Screening Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	EXIT VISIT
		Day 0*	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
Procedures		0 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Informed consent	X													
Medical History	X													
Current, and recent medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight measurement	X													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test if needed	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Check for any changes to health		X	X	X	X	X	X	X	X	X	X	X	X	X
Eye Pressure measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Best Corrected vision	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Questionnaire on how your vision affects your lifestyle		X												X
Scans and photographs of your eye(s)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fluorescein angiography**	X													X
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X													
Intravitreal Beovu®***		X*	X	X	X	X	X	X	X	X	X	X	X	
Eye Pressure measurement after injection		X*	X	X	X	X	X	X	X	X	X	X	X	
Check for any unwanted effects of injection.		X*	X	X	X	X	X	X	X	X	X	X	X	

The screening visit and Day 0 may be combined in one visit. *If participant meets all the study criteria and agrees to continue; **At the discretion of the investigator; *** From week 12 the time between injections will be increased by two weeks if your eye disease is stable. Extra visits for treatment may be required. The minimum interval between injections is 4 weeks. The maximum is 12 weeks. If study treatment date falls outside the 4 weekly assessment schedule: a thorough eye exam will be performed before injection, to ensure it is safe to continue.

5 Who is conducting and paying for this research?

This study is an "*investigator initiated study*". Dr Nitin Verma is conducting this study to investigate whether switching to Beovu® will benefit patients like you. Novartis Australia Ltd, the manufacturer of Beovu®, will provide the treatment free of charge to study participants. They are also providing some financial assistance to help with the conduct of the study.

The study treatment and all study-related tests will be provided at no cost to you. However some of the tests, medication and or treatments you may require over the course of the study may be part of standard care used to maintain your health, even if you did not take part in the study. You will be responsible for the cost of this standard care in the usual way (health insurance, Medicare and your personal contribution depending on your circumstances).

None of the doctors participating in this study have any conflict of interest: They will not benefit financially from the results of this study.

The study plan (protocol) and this participant information has been presented and approved, as appropriate for use, by the Bellberry Human Ethics Committee. Every year a report will be provided to Bellberry providing information on the study progress, including: the number of participant we recruit; the reasons for any participants withdrawing from the study; any adverse events attributable to *Beovu®* and any serious unexpected events that led to death, hospital admission or disability. The doctors at Hobart Eye Surgeons who are conducting the study will also meet regularly to discuss study progress and review adverse events that they may have observed.

6 What if something new comes up during the study?

If we find out something new about *Beovu®* while the study is under way, your doctor will discuss what it might mean for you and whether you would like to continue in the study. If you decide to continue you may be required to sign an updated consent form.

Should you wish to cease treatment we would like the option to maintain follow-up for the period that you would have been in the study.

7 What will happen to the confidential information about me?

We will keep all personal information confidential and securely stored in locked cabinets. The information collected about you which is stored electronically will have all identifying information removed. The information collected about you will be identified by a code number and will be separated from any personal information e.g. your name or date of birth. No personal information about you, such as your name and address or date of birth will ever leave the clinic.

8 What information will be collected, and how will it be stored?

If you sign the consent form, you agree to the study team accessing your health records that may be relevant to your participation in this study. Information will be collected from you personally, from your record at Hobart Eye Surgeons, from your GP and possibly also from other health services e.g. if you are admitted to hospital while you are a participant. Your medical records relating to this study and any other information received will be kept strictly confidential and all personal information will be used only for the purpose of managing your participation.

Australian and Tasmanian Privacy law gives you the right to request access to your information that researchers have collected and stored. The law also gives you the right to request corrections to any information about you that you disagree with. Please contact the study team (see page 8 of this document) if you would like to access your information.

In addition to the staff involved in your care, members of the Bellberry Human Research Ethics Committee (that approved this study) and the Therapeutic Goods Administration Australia (TGA), the government agency responsible for regulating and monitoring the use and safety of medications used in Australia, may also inspect the study records to ensure that the study has been conducted according to the approved study plan.

We will not disclose your information without your permission, except in compliance with the law.

Your identity will never be revealed in any reviews or reports of this study which may be published and/ or presented at scientific conferences.

All the study documents and any paper copies of the information we collect will be stored securely for 15 years after study completion. After this time it will be destroyed. This is standard for all clinical studies and provides an opportunity for an audit of the study if required the ethics committee or the TGA wish to check that the study was done well. However, the coded information collected during the study may be kept and used for further investigations into the effectiveness and safety of *Beovu*® or for other research studies investigating factors that might be important in improving outcomes for patients with wet AMD.

9 What are my responsibilities during the study?

If you agree to participate in this study, you agree to:

- Keep appointments.
- Follow the study doctor's recommendations
- Let your study doctor know if any of your contact details change
- Tell us about your current medications and medical history and before taking any new medication, even if the medication is prescribed by another doctor for a different medical problem
- Tell us about any adverse events or illnesses you may experience while you are a participant
- Tell your GP about your participation in this study
- Ask questions about anything you do not understand

10 Can I have other medicines or procedures during this clinical study?

Yes. At the screening visit we will ask you about your medical history and any prescription or over-the-counter medications, vitamins, or herbal remedies you are taking. You must also tell us if you are having alternative procedures such as osteopathy, chiropractic, dietetics, acupuncture. Your doctor will review the information you provide along with the results of the screening visit tests. If you are taking any medications that will interfere with the *Beovu*® treatment, or might cause you harm if taken at the same time as *Beovu*®, you will not be able to participate in the study. Your safety is our priority.

If you meet the study criteria and decide to participate in the study it is important that you tell us if you have been unwell, or have had any changes to your medications since your last visit. This is in your interest, as well as important for the study as some medicines may affect the study

treatment and outcomes or may contribute to other adverse events that may occur while you are participating.

If both of your eyes are having injections for wetAMD at screening, your doctor will select only one eye for the study. The other eye will continue with routine care.

11 What possible benefits might I get by taking part?

This study will require you to switch from your current wetAMD treatment to *Beovu*®. There is no guarantee that the *Beovu*® will be more effective than your current treatment.

It is possible that you may have less frequent injections of *Beovu*® than your current treatment but we cannot promise you this or any other personal benefit from the study. However, we hope that the overall study results will provide useful information that may help other doctors decide whether the *Beovu*® might be a useful treatment option for patients with wetAMD currently having treatment at intervals of 8 weeks or less.

12 What risks do I run by taking part?

Your wetAMD is currently being controlled with Lucentis, Eylea or Avastin injections. It is possible that in switching to Beovu® your wetAMD may not change but it also possible that it could get worse. It is also possible that you may experience some side effects of the treatment.

Side effects

Medical procedures, medicines and tests often have side effects. You may get no side effects, some side effects, or all of the side effects listed below. These side effects may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your doctor.

Your doctor will also be looking out for side effects but there may also be side effects that the researchers do not expect or do not know about and that may be serious. If you develop any new or unusual symptoms please tell your doctor immediately. Even if you think that what you are experiencing may not be related to *Beovu*®, it is important to tell us about them.

Risks associated with a routine eye test

• Dilating drops that allow an assessment of the optic nerve and retina may cause blurred vision and light sensitivity. This can last 1-2 hours, rarely more than 3. We encourage you to bring a pair of sunglasses and/or hat to minimise glare sensitivity.

We recommend that you **don't drive** to your appointment. Please get a lift or take public transport. Please contact us if this is a problem.

• The photograph of the eyes may cause slight blurred vision from a bright flash; however, this settles within 1-2 minutes.

Risk associated with Beovu® treatment

Beovu® has undergone many studies to assess its safety and effectiveness for treating wetAMD.

But, as with any medicine, unexpected allergic reactions can occur. These reactions can be mild or more serious.

Common symptoms include: rash, itching, skin problems, swelling of the face and throat or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away or seek medical attention.

Although rare, there are some known risks associated with the use of this medication. These are listed below.

Common side effects that may occur in less than 10 of every hundred patients treated with Beovu include:

- Decreased sharpness of vision (visual acuity reduced)
- Clouding of the lens (cataract)
- Bloodshot eye (conjunctival haemorrhage)
- Small particles or spots drifting across the field of vision (vitreous floaters)
- Eye pain
- Bleeding in the retina (retinal haemorrhage)
- Detachment or tear of one of the layers at the back of the eye (vitreous detachment, retinal tear or retinal pigment epithelial tear)
- Increase in the pressure within the eye (intraocular pressure increased)
- Inflammation or scratching of the surface of the eye (conjunctivitis, punctate keratitis, corneal abrasion)
- Allergic reactions (hypersensitivity)
- Inflammation of tissues lining the inside of the eye (iritis, uveitis)*

Uncommon side effects may occur in less than 1 of every 1000 patients treated with Beovu:

- Redness of the eye (conjunctival hyperaemia)
- Increased tear production (lacrimation increased)
- A feeling of having something in the eye (foreign body sensation in eyes)
- Blindness**
- Blockage of an artery in the eye (retinal artery occlusion)
- Inflammation of the inside of the eye (vitritis, endophthalmitis)
- Detachment of one of the layers in the back of the eye (retinal detachment, and detachment of retinal pigment epithelium)
- Eye inflammation (iridocyclitis, anterior chamber inflammation/flare)
- Swelling in the front of the eye (corneal edema)
- Bleeding in the eye (vitreous haemorrhage)

Inflammation and/or blockage of the blood vessels in the back of the eye have also been reported in patients with wetAMD. In the majority of cases this was associated with eye inflammation. Some of these cases resulted in severe decrease in sharpness of vision.

Risks associated with the injection process

Beovu® is provided as a liquid solution which is injected into the eye with a tiny needle. Your eye will be anaesthetised before the injection but you may still experience some discomfort associated with procedure.

Adverse reactions related to the injection procedure include: raised eye pressure, eye pain, endophthalmitis *(*inflammation inside the eyeball), retinal tear and a temporary increase in eye pressure.

Please tell the staff looking after you, or contact your doctor, **immediately** if you experience any of the following: redness or worsening redness of the eye, eye pain, sensitivity to light, any vision changes, including sudden vision loss; seeing flashes of light with floaters (seeing spots or cobwebs). Your welfare is our priority.

Arterial Thromboembolic Events

There is a potential risk of arterial thromboembolic events (blood clots forming in arteries and causing a stroke or heart attack) after using any anti-VEGF medications. This risk of these events occurring may be increased if you have previously had a heart attack, stroke or mini-stroke (transient ischaemic attack).

If you experience symptoms of a heart attack (chest pain, which may spread to the neck and shoulders) or stroke (weakness or numbness of limbs or face, difficulty speaking or swallowing) please call 000 or present to your nearest hospital emergency department immediately.

Pregnancy

The effects of *Beovu*® on the unborn child and the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant, or father a child, during the course of the study. You must not participate in the research if you are pregnant or trying to become pregnant, or are breast-feeding.

If you are female, and child-bearing is a possibility, you will be required to have a pregnancy test prior to commencing the study and at each visit before *Beovu*® treatment. If you are male, you should not father a child or donate sperm for at least three months after the last dose of study medication.

Both male and female participants are strongly advised to use effective contraception during the course of the research and for at least three months after completion of the study. You should discuss methods of effective contraception with your doctor.

For female participants: If you do become pregnant whilst participating in the study, you should advise your doctor immediately. They will withdraw you from the study and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

For male participants: You should advise your doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

13 How will you use any tissues or samples you take from me?

We will not collect any tissues or blood samples from you in this study unless you are a woman that may be able to bear a child. If you are female, and able to bear a child, a pregnancy test will be required at screening and at each visit before you receive treatment.

14 What happens if I suffer severe side effects as a result of my participation in this study?

You will receive the best medical care available during and after the study

If, as a result of your participation, you become ill or are injured advise your doctor of your condition immediately. They will evaluate your condition and discuss treatment with both you and your GP if required. In case of an emergency, contact 000.

Medical treatment will be provided at no cost to you for any research-related harm. The term “research-related harm” means both physical and mental injury caused by the product and procedures required by the study.

Since you are participating in a non-industry-sponsored study, any question about compensation must initially be directed to your doctor who will advise their insurer of the matter.

15 Will you pay me to participate in this study?

There is no reimbursement or payment for this study.

16 What happens when the study ends?

At the end of the study you will no longer be treated with the study medication. Your doctor will discuss an ongoing treatment regime that is appropriate for your needs. This may include reverting to anti-VEGFs such as Lucentis or Eylea or continuing on Beovu® (if it is available on PBS).

17 Could the researchers stop the study early?

Yes. The study may be stopped for a number of reasons.

If there are signs that the intervention in a study could be unsafe, the study team will stop the study.

If the study is stopped, your doctor will explain the reason behind the decision and what it means for you. Should the study stop early or you decide to withdraw from the study, you will no longer be treated with the study medication.

You can choose to leave a study at any time without giving a reason and without any effects on the care that you will continue to receive. If you do withdraw from a clinical study, the relationship between you and your doctor will not be affected. It is important to discuss your decision to leave a study with the research team before you leave, so that they can advise you about any safety or follow-up requirements and what will happen to information about you that has been collected for the study.

If you withdraw from the study, it will not affect the relationship between you and your doctor but it is important to discuss your decision to leave a study with your doctor beforehand, so that they can advise you about any safety or follow-up requirements of the study and discuss what will happen to information about you that has already been collected for the study and your treatment options after withdrawal.

18 Will the results of the study be published?

The summarised results of the study will be presented at ophthalmology conferences and published in medical journals. No information will be published that could identify you as one of the study participants.

Participants will be informed about the study findings in a study newsletter. They will also be provided with a copy of any study publication on request.

19 Who do I contact if I have a question or complaint?

For all study enquiries, or if you want to talk to the study team at any time during office hours please call: **6210 6000** and advise the receptionist that you would like to speak to someone about the **BRAVAS study**.

If you cannot attend your scheduled appointment or experience any side effects or complications as a result of this clinical study, you should contact the study team as soon as possible:

Study Coordinator:	Beverley Curry	beverley.curry@eyesurgeons.com.au
The Principal Investigator:	Dr Nitin Verma	nitin.verma@eyesurgeons.com.au

Alternative 'phone contact numbers:

Beverley Curry	0409 431 402
Clinical Professor Nitin Verma	0417 873 213

If you are experiencing or are concerned about any symptoms after hours please call the clinic (6210 6000). You will hear a recording that provides the telephone number of doctor on call. They will be able to provide you with any medical assistance you require.

24-hour medical emergency assistance is also available by contacting 000 or going to your nearest hospital.

If you wish to discuss the study with someone not directly involved in the study: Particularly if you have query or complaint about our policies or the conduct of the study, or your rights as a participant, you may contact the Human Research Ethics Committee chair, Bellberry Human Research Ethics Committee on 08 8361 3222

20 What do I do if I need to seek compensation for injury?

This study is not an industry-sponsored study. If you are injured or experience severe side effects, you can discuss your complaints or requests for compensation with Clinical Professor Nitin Verma the Principal Investigator, 6210 6000, nitinverma@eyesurgeons.com.au.

21 Insurance

All doctors participating in this study have Medical Indemnity that covers them for any untoward outcomes associated with their clinical work.

22 The consent form

Sign the consent form attached to this document only after you have made up your mind to take part in this clinical study. You will be provided with a signed and dated copy of the participant information and consent form for your personal records.

HOBART EYE SURGEONS

Consent form

Title	A one-year, unmasked, prospective study to evaluate the effectiveness of brolucizumab in subjects with neovascular age-related macular degeneration resistant to extension of current anti-VEGF treatment beyond 4 to 8 weeks.	
Short title	The brolucizumab anti-VEGF Treatment of AMD Switch Study	
Study doctors	Clinical Professor Nitin Verma (Principal Investigator) Dr Guy Bylsma Dr Andrew Traill Professor Alex Hewitt	
Study Coordinator	Beverley Curry	
Clinical contact person	Nitin Verma	6210 6000
24-hour medical contact	0417 873 213	nitin.verma@eyesurgeons.com.au

Note: All parties signing the consent section must date their own signature.

Declaration by participant

- I have read, or have had read to me, and I understand the participant information and consent form.
- I have had the opportunity to discuss this with an independent person.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I freely agree to participate in this clinical study as described and understand that I am free to withdraw at any time during the study without affecting my future health care.
- I understand the purposes, procedures and risks of the research described in the information sheet.
- I give permission for my doctors, other health professionals, hospitals and laboratories to release information concerning my medical history, disease and treatment to Hobart Eye Surgeons for the purposes of this study. I understand that such information will remain confidential.
- I consent to my GP being notified of my participation in this study and any clinically relevant information noted by the study doctor in the conduct of the study.
- I understand that I will be given a signed copy of this document to keep.

Signature _____ Date_____

Name of participant (please print) _____

Declaration by study doctor/senior researcher[†]

I have given a verbal explanation of the clinical study, its procedures and risks and I believe that the participant has understood that explanation.

Signature _____ Date_____

Name of study doctor/researcher[†] (please print) _____

[†] A senior member of the study team must provide the explanation of, and information concerning, the clinical study.