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Research Participant Information Sheet

INFORMATION FOR PATIENTS – RETINA IMPLANT TRIAL (RI-MC-CT-2009)

The safety and effectiveness of subretinal implants for the partial restoration of the eyesight of blind patients: A prospective mono- & multicentric clinical trial on the basis of a comparison of the function between an activated and a deactivated implant for patients with degenerative retinal diseases.

You are being invited to participate in a research study of a new electronic device which will be inserted into your eye. Before you decide whether to participate, it is important for you to understand why the research is being conducted and what it will involve for you. Please take time to read the following information carefully. We are happy to answer any further questions you may have. You may find that talking to your friends, family or your GP is helpful in deciding whether to participate in the study.

You may also wish to contact INVOLVE, which is a national advisory group funded by the National Institute for Health Research (NIHR). The role of INVOLVE is to support and promote active public involvement in NHS research and it provides more information about what is involved in clinical trials on their website: www.invo.org.uk. Alternatively INVOLVE can be contacted for further advice at the following address: INVOLVE, Wessex House, Upper Market Street, Eastleigh, Hampshire, SO50 9FD, Telephone: 02380 651088, Textphone: 02380 626239, Fax: 02380 652 885, Email: admin@invo.org.uk.

Preliminary comments on the Clinical Trial with Implant Alpha

Following informal discussions in the run-up to the trial, we should now like to discuss exactly what is involved with you. We are grateful to have had your help and interest in the study so far. As you know, in this trial an implant (chip) will be inserted below the retina, i.e. “sub-retinally”. The retina is the lining of the back of the eye that is light-sensitive in normally sighted people. This research participant’s information sheet aims to inform you about the purpose and stages of the trial, the commitment it requires from you and the risks involved. We have included a great deal of

information - please do not hesitate to ask if anything at all is not clear to you. We should like to begin by giving a short summary of the course of the entire trial. After that, we will go into more detail on the individual stages of the examinations.

About one week before the start of the trial, the necessary baseline examinations will be performed at the Oxford Eye Hospital where the chip will subsequently be implanted. A preliminary version of the chip has already been tested extensively in patients undergoing surgery and tests in Tübingen in Germany. This trial represents the next stage with a more sophisticated implant. The aim is to improve or partially restore your eyesight with the aid of this device.

Your stay as an inpatient here in the John Radcliffe Hospital is expected to be three days but may last up to five days. You will receive examinations by the ophthalmic (eye) and otological (ear) surgeons and daily follow-up checks on your progress after surgery every day and as an outpatient for a week. In the course of the subsequent 2-3 weeks the function and stability of the implant will be assessed through specific examinations. These examinations will be carried out as an outpatient at some point between weeks 2 and 12 after the implantation procedure. You will be given accommodation near the hospital, for yourself and a companion, should you require it. In rare circumstances you may also be admitted for some of these tests as an inpatient. After this (2-6 months after your operation), you will need to travel to Tuebingnen in Germany to have some specific tests with the scientists at Retina Implant AG (the company that makes the implant). These tests will provide valuable information about the function of the implant. All travel and accommodation expenses will be paid for you and a companion. On these test days, predefined specialised examinations (e.g. mobility test) and the training of fixation and eye movements will be carried out. The dates for these will be agreed with you by those responsible for the coordination of your trial. On return to the UK, 3 to 6 further single test days will be scheduled up to 12 months. In addition, you would receive the normal checks and follow-ups with your optician and general practitioner (GP) as required.

Chart: Timetable

Preliminary examinations	Surgery at John Radcliffe	Daily follow up and post-op checks	Photographic and visual tests	Visit to Retina Implant in Germany	Follow-up safety checks on 3 to 6 scheduled days
2 days before	0	days 1-7	weeks 2-12	months 2-6	up to month 12

Background to and purpose of this clinical trial

The sponsor of this trial is the Retina Implant AG in Reutlingen (for contact details see below). Research into implants that are inserted under the retina has been carried out since 1995 in Germany by a major research organisation which includes ophthalmic opticians from Tübingen and

Regensburg, as well as biologists, physicists and engineers from Tübingen, Reutlingen, Ulm and Stuttgart. The project was initiated by Prof. Zrenner in Tübingen, who is an ophthalmologist known to the specialists at the Oxford Eye Hospital. The project is sponsored and funded by the German Federal Ministry of Research and Education (BMBF) in Berlin.

The results of the first pilot trial showed that these implants do indeed make it possible for blind people to experience some visual sensations. They also confirmed the suitability of the surgical procedure and the compatibility of the implant inside the retina. The experiences gained from comprehensive tests and examinations in the first pilot trial make the further development of the implant possible, which is now available in a new, improved version known as Alpha.

The purpose of this new trial is so that we can test the new implant. Above all, we wish to establish how well the implant is tolerated and the extent to which it can improve the eyesight of completely blind patients suffering from retinitis pigmentosa (or similar illnesses). The new thing about this trial is that the implant does not have to be removed after a few months, but can remain in the eye for as long as it is tolerated and is of benefit. Also, for the first time, you as a patient should be able to activate the implant at home or your place of work, and thus gain experiences in the context of daily routines. The implants being used in the context of this second trial are specially labelled medical devices that have been specifically made for this clinical trial. From this trial we hope to gain further essential information regarding function and safety of the implant within the human eye. To this end we need to test the implant under controlled experimental conditions. We are thereby dependent upon the cooperation of you as a volunteer. The statements that we obtain from you are of great significance for the application of the implant as well as for the further development of future implants that, it is intended, should be available to many patients in a few years' time.

Testing of the implant may, at the instruction of your ophthalmic optician, also take place in your own home. By participating in this trial you can make a contribution towards the further development of the implant. The possibility that you yourself might, at a later date, receive a more developed implant is by no means ruled out. A further implant could be used if the retina is not scarred by the surgery and assuming that blood flow is maintained. This appears to be the case with the implants used so far, which appear to be quite stable. Nevertheless it is important that you understand that this is a trial not a treatment and there is no guarantee of the device working in your case. Furthermore we have no indication yet of how long the implant will last.

Results of the Pilot Trial

In the pilot study eleven patients were operated on without any serious complications. In the course of the pilot trial the patients were provided with an implant having two different functions.

There was a direct stimulation unit for the active stimulation of the retina with 16 electrodes and also a chip with 1500 electrodes that react according to the incoming light (like a digital camera). The direct stimulation function of the implant helped to determine many fundamental properties of the previously blind retina and thus identified the optimal electronic settings for the chip. With direct stimulation the patients were able to perceive light in prescribed shapes and patterns. Visual shapes seen via the chip made the recognition and localisation of sources of light possible (windows, lamps), something which is of great importance for the ability to orient oneself independently. It was in part possible to perceive and locate bright objects (e.g. crockery) against a dark background and in some cases it even proved possible to recognise letters (4-6 cm in height at a distance of 60 cm) and to put them together to form words.

All patients tolerated the implant well. There were no cases of retinal detachment, inflammation, rejection, serious bleeding or disfigurements to the face. There were no reported problems with the electronic lead inserted under the skin of the face and head. Swollen retinas were easily treatable, minor cases of bleeding rapidly reabsorbed. Swellings of the retina and tiny concentrations of liquids under the retina were observed. These could be treated with a course of eye drops or at least kept stable without treatment. The surgical procedure, carried out through the choroid membrane of the eye, was considered safe.

In the cases of 8 patients the chip could be activated successfully, 7 patients were at least able to perceive light as a result, 5 patients were able to localise objects, 5 patients could successfully perceive the outlines of objects and 3 patients were able to recognise smaller objects. The very first patient, when subjected to direct stimulation from horizontally or vertically arranged electrodes, was able to differentiate with certainty between horizontal and vertical beams the size of a matchstick and correctly identify the direction in which moving points were going. The other patients, by whom light impressions were triggered, reported similar effects in the shape of blocks consisting of 4 activated electrodes in each individual case. In the cases of two patients, however, the retina above the active implant proved to have been insufficiently supplied with blood, so that no stimulation of the nerve cells was possible. Circulatory disturbances to the retina are frequently a consequence of the underlying disease retinitis pigmentosa (RP). In the first two patients, the covering of the chip itself was not completely watertight and allowed fluid in, causing the amplifiers to cease function after a while. Aside from these leaks, other technical problems with the implant could be fixed later on in the trial. The most frequent problem was posed by the cable cord due to its high number of wires. The new implant requires one-third fewer wires, as the direct stimulation is no longer required. The cable now consists of one continuous tube of especially biologically compatible silicon and has been successfully tested in the laboratory for its long-term stability.

The three patients to be operated on last were able, with the 1500 electrode sight-chip, to perceive light stimuli, localise larger objects (plates on a table, areas of light such as windows) and/or correctly reproduce the number of flashes of light in a sequence and the direction of striped patterns with the aid of the direct stimulation unit. It was revealed that the chip could restore to blind people the benefit of recognising visual objects up to the reading of individual letters and of identifying till now unknown objects of everyday life. Problems and the need for further research was established with regard to the perception of several smaller objects presented at the same time as well as the long-term stability of the wiring, which have been significantly improved in the shape of the implant now to be used, the Model Alpha.

The first pilot trial has so far provided exceptionally useful data for the further clinical development of the chip: for the strength of the stimulation currents, their optimal duration and polarity, the temporal sequence of light stimuli, spatial resolution, homogeneity and stability of perception and the tolerance of the retina. Although it was not possible to give any guarantees of success, and it will not be possible to give such guarantees in the future, all patients described their participation in the trial as an all-round positive and exciting experience, despite the inconvenience of the surgery and the often tiresome test procedures. At the end of the trial all patients declared that they would, should they ever have to decide on their participation again, always take the same decision. In conclusion, the results of the first pilot trial encouraged the continuation of the clinical trial with this new implant.

What is a retinal implant and how is it constructed?

The core of the retinal implant is a chip that consists of many small photocells. A photocell is an element from the world of electronics that converts light to electricity, in exactly the same way that a solar cell on the roof a house produces electricity from sunlight. In the eye, the individual photocells are a good deal smaller, the entire chip measures approximately three by three millimetres. The implant is about 100 microns (one tenth of a millimetre) thick and thus about as thin as a human hair. On it, between 1500 and 1600 photocells together with the switches for brightness adjustment and safety circuits are accommodated. Each individual photocell reacts to light and conducts external electricity to the nerve cells above it via tiny little electrodes. In principle, therefore, it functions as a photo-receiver or digital film in the retina.

The implant as a whole consists largely of silicon. Other ingredients used in its construction are silicon-dioxide (=glass), silicon-nitride, Titan-nitride, gold, and Teflon. The chip is coated with especial biologically compatible silicon in order that neither the retinal tissue nor the chip can suffer biodegradation. All these materials and the composition thereof have proven themselves in numerous experiments on animals and in the first pilot trial with patients to be harmless for both the eye and the individual. The retinal chip itself sits on a foil tape with hairline wires that continue

on in a thin spiral cable that travels outside into the orbit through a small hole at the back of the eye. This ends in a small coil in a ceramic housing behind the ear that provides the energy supply and also allows adjustment of the chip.

Energy supply to the retinal implant

The energy supply is very similar to that to an internal ear-implant and is done via a small coil (about 3 x 2 x 0.5 cm) that is implanted under the skin behind the ear. A small magnetic counterpart is attached externally to this coil and connected to a power pack. There is no break in the skin as the electrical energy is passed between the power pack and coil by induction (like recharging an electric toothbrush). At night, the implant is deactivated by removing the power pack. The adjustment of the electronics in the chip by technicians at the beginning of the trial is also done through the power pack. The power pack is activated and deactivated during the examinations in order to register the functioning of the implant. Control tests of eye sight are also performed with the implant switched off.

Number of participants in the trial: There are 6 participants in the first stage of the trial in Tübingen (Module-1) and a total of 35 patients will be able to take part in the second stage of the trial (Module-2, multi-centre). The site here in Oxford is part of Module-2.

Who may participate in this trial?

In principle patients participating should allow their GP to be informed that they are in the trial. Patients may participate in the trial who are blind in at least one eye, defined by an ability only to be able to localise light to an extent that is no longer of any use to them in orientation or mobility. Participants must be adults and be suffering from Retinitis Pigmentosa (RP), choroideraemia or extensive cone-rod dystrophy. They should have been able to see for at least 12 years of their lives and previously been able at some point to have read small print without a magnifying glass.

Cataract surgery with insertion of an intraocular lens is necessary as it is known that RP patients often suffer from cataract which could cause blurring of vision once an implant is inserted. The cataract operation is one of the most frequent operations in ophthalmology. If cataract surgery has not been done before, it could be included at the same time as insertion of the implant and generally would take about an extra 10 to 15 minutes. In some cases, the cataract surgery may be performed several weeks prior to insertion of the electronic device (for instance, if the cataract is too dense for accurate pre-operative assessment).

CONTRACEPTION: If you are a woman of child-bearing age, then you should be prepared to use a medically accepted form of contraception during your participation in the trial. It is recommended that women should, before the beginning of the trial, use two of the following contraceptive

methods for a period of at least one month or a period that the prescribing doctor considers necessary in order that these methods should become fully effective. Among the approved contraceptive methods are: oral contraceptive pill, diaphragm, progesterone implants, medroxy-progesterone acetate, or condoms. Your trial doctor must document the methods of contraception used by yourself and your partner.

You should be prepared to subject yourself to a pregnancy test at the beginning and the end of the trial. A repetition of the pregnancy test is necessary if you miss a period or your menstrual cycle should become irregular. Should you become pregnant during the trial, or believe yourself to be pregnant, then we ask that you should inform your examining doctor accordingly. The risks for your unborn child are not known, and the examining doctor will inform you as to the options available to you.

Who may not participate in this trial?

Patients suffering from other eye diseases such as age-related macular degeneration, inflammation of the eyes, retinal vascular diseases, vitreous blurring or uncontrolled eye movements may not, unfortunately, participate in this trial. The same applies to patients suffering from serious metabolic disorders such as thyroid over-activity, neurological illnesses such as Parkinson's disease or psychiatric illnesses such as depression as well as from diseases that would mean a high risk for the operation (such as severe circulatory disturbances to the coronary vessels). Anticoagulant medicines should be discontinued if possible before surgery and this would be coordinated though your GP, where indicated. Patients with a previous history of allergy to components of the implant or to medicines (e.g. ointments containing iodine) would be excluded. Patients with specific eye signs may also be excluded, for instance, those with excessive pigment or scar tissue at the back of the eye, a very thin retina or a previous 'lazy' eye.

Planned examinations before the implantation

In order to review the above-mentioned criteria a basic ophthalmic examination is carried out in the course of which the visual acuity, spectacle prescription and front and back of the eye are examined. An electrical test of the retina known as a full-field electroretinogram (ERG) is carried out, which is a test you may have had earlier on in the disease process. The electroretinogram is a way of testing whether the remaining retina has any ability to send signals to the brain by measuring electrical activity of the eye. To this end fine thread electrodes are attached to the lower lid or the eyeball and skin electrodes to the forehead. In order to test whether your optic nerve is still able to conduct light signals to the brain, an electro-stimulation is carried out by attaching a fine thread electrode to the cornea. This determines whether you perceive light and if so, at what threshold. The exact calculation of the dimensions of your individual implant is then determined

though routine imaging tests, which include optical coherence tomography (OCT), fluorescein angiography a magnetic resonance imaging (MRI) scan of the eye.

Where there is any doubt about possible eligibility on medical grounds, further medical examinations may be carried out by specialists in general medicine, neurology/psychiatry and anaesthetics. The following examinations will be arranged in the ophthalmology clinic:

- Documentation of your previous medical history, current treatments, laboratory examinations and medicines (duration about 1 hour).
- Dilation of the pupils followed by a detailed examination of your eye on the slit lamp ophthalmoscope (the microscope normally used for your examinations) and photographic tests (duration about 1 hour).
- We may need to check your blood parameters at various times during the study if there are concerns about infections or inflammatory reactions and so a pre-operative blood sample will be taken at this stage to establish a baseline. This is a general safety test and there is otherwise no use of the blood for the study (duration about 10 minutes).

Before the implantation all the functional tests planned for later will be carried out in order to establish baseline values. These tests and their duration are described in more details below.

How will the operation be performed?

The implantation surgery for the chip is similar in many ways to the standard operation that would be performed on your retina in cases of complicated retinal detachment, diabetes-induced retinal illnesses or injuries. For documentation purposes the operation is usually recorded in video.

The steps of the implantation surgery are as follows:

- **Anaesthetic:** You will receive a general anaesthetic (you will not be awake for the operation).
- **Positioning of the power supply:** Small incisions (each about 1 cm long) will be made into the skin behind your ear and next to your eyebrow at the edge of the eye-socket. Using a special drinking straw-shaped surgical instrument, a tunnel will be made through the skin to link the cut above the eyebrow to the cut behind the ear. The implant will then be pulled through this channel. The electrical coil for the energy supply will be attached under the skin on the bone behind the ear. The earth cable will also be placed under the skin close to the temple.
- **Preparation of the eye:** An incision will be made into the conjunctiva (white of the eye), which will then be folded back and three smaller incisions will be made into the eye through the sclera for the instruments. These include a light stick and a tube-like instrument to suck up the vitreous jelly that normally fills the back of the eye. It is a known fact that the eye is able to function well without vitreous. Then a small trap-door window is made in the sclera

(white of the eye) and folded back. The choroid membrane underneath it is identified and cauterised in order to reduce the risk of bleeding.

- **Insertion of the implant into the eye:** A solution is then injected from the inside of the eye at this point to lift the retina away from the underlying choroid and thereby prevent it from being touched and the implant is slid through this trapdoor window and into the subretinal space. Once the implant and attached ribbon is in the correct plane (lying between the retina and choroid layers) it can be gently slid backwards towards the back of the eye. In cases where the choroid cannot be entered successfully using this method, the retina may be detached and the implant positioned directly from the inside of the eye, however, this has not been necessary in the operations performed so far.
- **Closure of the eye:** After implantation the retina is reattached and may require securing with a laser beam as is standard practice in retinal detachment surgery. The eye will also be filled with standard clear silicone oil which also keeps the retina attached. The openings in the sclera and overlying conjunctiva will be closed using fine suture material. Finally the anaesthetic, antibiotics and cortisone are injected into the area around the eye-ball and a dressing is applied prior to waking up from the anaesthetic.

If there are unexpected problems during the surgery then it may be necessary to change the methods described above and this decision would be taken by the operating team during the course of the operation. The operation would take several hours and may, under exceptional circumstances, last up to 8 hours. You may need to lie with your head in a certain position during the first few days after the operation, in order that the silicone oil can support the retina as it heals. You will be given medications for any pain (e.g. paracetamol) and you should alert the doctors looking after you if you are uncomfortable at any stage during the trial.

What are the complications that may arise during or after the operation?

- General risks of surgery: anaesthesia, allergy, shock, pulmonary or cardiac arrest (less than 1%). For this reason those with significant medical problems would not be eligible to enter the trial.
- Due to the relatively long duration of the anaesthetic, cardiovascular problems, drowsiness, dizziness or nausea may arise afterwards. Such complaints are mostly restricted to the hours after the operation or the following day. Elderly persons may suffer from states of confusion and concentration problems as a consequence of a general anaesthetic.
- Minor bleeding over the implant (this has occurred in some cases temporarily during the postoperative recovery process) or swellings of the retina and the formation of small retinal fluid cysts (so far 5 of 11 patients have suffered temporarily from this in connection with the postoperative recovery process, one patient remained in a stable condition after cyst

removal). You would not be aware of these complications but they could affect the ability for the implant to function correctly.

- Retinal detachment (which affected one patient in the first trial) and increases in intraocular pressure, which again you may not be aware of, but could require further surgery or treatments to preserve any sight you gain in the eye.
- Inflammation in the eye requiring treatment (no cases as yet).
- Over-sensitivity of the temporal nerve (the nerve sensing the skin around the forehead and ear) as a result of the electronic device lying under the skin (no cases as yet).
- Feeling of numbness around the skin wounds (temple/ear in the context of the postoperative recovery process).
- Collapse of the eye or subsequent need to remove the eye due to intolerable pain or other problems (very unlikely: no cases as yet).
- Removal of the implant shortly after insertion on medical grounds (no cases as yet)
- Damage to the remainder of the retina due to the removal of the implant (no cases as yet).
- Scarring of the retina and subsequent detachment (no cases as yet).
- A complication that may make further implantations in the same eye more difficult (2 cases so far), or even render this impossible due to scarring.

Most of these complications can also occur with standard operations on the eye, such as retinal detachment surgery and can be dealt with using standard clinical approaches. Complications beyond this are unlikely and so far the specific complications mentioned above (in relation to the retina) have been found to be temporary and easy to control during the postoperative recovery period. In one patient, retinal swelling remained after implant removal and a partial retinal detachment persisted in another. All patients would continue to be supervised at regular intervals in the ophthalmic clinic in order to continue to monitor individual progress and treat any problems accordingly. This would be similar to the visits you already have as part of your normal care for your retinal degeneration. It is not possible to rule out with total certainty effects upon the whole body. However, the animal experiments and tissue tests carried out during the past years have not provided any pointers to such effects, and neither have any such pointers been received from any of the patients who have received implants till now. Cochlear implants used to treat congenital deafness have a similar power supply and are used routinely in children without any known systemic side effects of having electronics under the skin.

For which examinations should I prepare myself?

a) Check-ups in the first week after surgery:

You will be an inpatient or making daily visits to the hospital for about a week after your surgery, when you will be examined by the eye and ear surgery teams who performed the operation.

b) Examinations in Oxford:

In addition to the usual ophthalmic examinations, inspection of wounds and a safety check-up you will be subjected to specific functional examinations during the period up to three months (2-12 weeks) after your operation. These tests of retinal integrity and visual function form part of the trial and will help determine the effectiveness of the electronic implant. They are therefore very important and will be carried out in the Eye Hospital. The tests include the usual retinal examinations, but also repeat fluorescence angiography and imaging/photographic tests (up to three times each during this period). There will also be tests to check the mobility of the eye and a spectacle refraction test to check your ability to see shapes and figures (see details below). All functional tests of vision will be carried out with the implant switched on and then off as a control. In order to rule out any experimental bias, when carrying out the vision tests the energy supply to the chip will be activated and deactivated by an independent third party without either you or the person examining you being aware of this. In this way the true improvement to your eyesight as a result of the implant will be investigated. The vision with the implant switched off gives an indication of any residual visual function in your retina.

The following tests of vision will be carried out:

- Tests of practical living activity using objects such as cup and saucer on the table. This is referred to as the 'LPF' test and takes about 1 hour.
- Examination with individual light stimuli and with two light stimuli closely following one another to test the ability to localise sources of light and perceive movements. Also the grid test will be used with these lights to determine the minimal size of shapes that can be recognised. These are known as 'BALM/BaGA' tests and take about one hour.

If positive results are achieved in the BALM/BaGA examinations, then the following two sight tests will also be carried out:

- Freiburg Vision Test, which is a computerised test of vision otherwise known as the 'FrACT' test and lasts about 30 minutes.
- A test using a normal eye chart lasting about 30 minutes. This is similar to the type of chart test at the opticians except it has more evenly spaced numbers. Ophthalmology specialists often refer to this as the 'ETDRS' test and it is a standard used for many studies.

Other examinations required are:

- Simple photography of the back of the eye (about 15 minutes).
- Optical coherence tomography or OCT (about 15 minutes) which is a non-contact, virtually risk free scan of the back of the eye. You almost certainly would have had one before. With the aid of light the health and thickness of your retina can be measured. You would need to keep your eye still to get the best images from this test.

- Examination of the integrity of the blood vessels of the retina by a technique known as fluorescence angiography. A fluorescent dye solution is injected into a vein in your arm and photographs are taken of the back of the eye to see the blood vessels and whether they leak. This is a very safe procedure performed in tens of thousands of people in the UK every year – it is the main test for age-related macular degeneration (AMD). Nevertheless there are occasional side effects. Your urine may be coloured bright yellow for a day or more. Very rarely (less than 5% of cases) a feeling of nausea been observed shortly after the injection, but this usually passes away completely after 1-2 minutes. In a very low percentage of cases allergic reactions may result. An allergic reaction usually sets in directly after the injection of the dye and takes the form of eczemas, itching, in extremely rare cases respiratory difficulties and, even more seldom, heart problems or even an allergic shock leading to cardiac arrest. The frequency of these side-effects is quoted in the relevant literature as less than 1 %. It goes without saying that, in the examination room of the ophthalmic clinic all necessary medicines for the treatment of an allergic reaction are available. There will also be a doctor or nurse in the room to perform the injection and an anaesthetist in the building who can be on the spot in a few minutes if required. Fluorescence angiography is a standard clinical examination which is performed in the Oxford Eye Hospital up to 10 times every day (each lasts about 30 minutes).
- Electroretinography (ERG) may be performed up to twice during this period. This is to determine any electrical changes in your retina and may last up to one hour for each test. It will be similar to the one you would have had on enrolment into the trial.
- A questionnaire about your subjective feeling of well-being (duration about. 15 minutes).
- Taking of blood samples several times over the course of the study (up to 100 ml total). There is a minimal risk with blood taking, such as puncturing a nerve or artery, but this is rare and usually self-limiting.
- Counselling is also available if required (optional), at least once a week with the senior nurse co-ordinating the study (up to 60 minutes) or with a clinical psychologist if necessary.

c) Examinations in Tuebingen in Germany:

Whilst we will be able to achieve a great deal of information about the implant through your visits to Oxford, it will still be necessary for you to make one visit to see the scientists and engineers at the company 'Retina Implant AG' in Germany. There will be between 15 and 30 electronic chips being inserted into blind patients around Europe and it is essential that certain visual results from all patients can be standardised and in one centre. You may also find it interesting to meet some of the scientists involved in developing the chip. The trip to Germany will last no more than a week and will occur at a pre-arranged time between 2 and 6 months after the surgery, but most likely around month 4.

Some of the tests will be similar to those performed in Oxford, but they will be done under standard conditions. There will also be a maze to test your ability to navigate using the implant in a large room. This is specially designed with foam obstacles to reduce the chances of injury and will be led by an experienced mobility trainer. There will also be training in Tübingen to help improve your eye stability and movements. All visual examinations (BaLM, BaGA, LPF) will be repeated but recorded on video for documentation purposes and in order to clarify any questions arising later. These video recordings are therefore part of the trial.

The mobility trainer in our trial is an experienced specialist who takes into account the specific needs of completely blind people with regard to their individual mobility requirements and is also able to give them valuable tips beyond the scope of the participation in the trial. The designation mobility trainer is one that will be familiar to you if you have taken part in a so-called long stick training course: otherwise such a course of training can easily be arranged for you. If it is not possible to get visual sensations from the chip when stimulated by light, then the electrically triggered signals from the electroretinogram (ERG) will be recorded. This serves the purpose of testing whether the retinal chip is actually functional.

Duration and end of the trial

The concluding examination after 12 months will form the end of the clinical trial (Module-2). We request that you should attend the ophthalmic clinic for follow-up checks annually thereafter. Should you experience any complications we would request you to report to the doctors in charge of your tests or the leaders of the trial on the spot so that an additional follow-up check or treatment can be carried out at no extra cost. Although it is designed to be left in, the chip can be removed if it is no longer functional or causes problems, or indeed if you wish it to be removed for any reason. The long term stability of the chip is unknown but the coil and power supply are known to be stable for at least a decade or more in patients receiving cochlear implants for congenital deafness. One patient in the first trial elected to have his retinal chip left in place even though it was no longer functional, so that it could be exchanged for a newer model, should one arise in future. If your chip is still functional at one year then we will continue to service the power supply as part of your normal NHS care, but we would not be a position to replace the chip itself if it failed. This would need to be part of another trial and we can make no guarantees about this until studies such as the current one with the Alpha implant are completed.

What are the advantages of your participation in the trial?

The aim of the trial is, by using the implant, to restore some degree of vision to an otherwise blind and visually useless eye. Participants in the trial will be able to describe what they see with the new Alpha implant. These visual sensations may be of great interest and enrichment to you, as previous patients with implants have confirmed to us. As this particular retinal chip can also be

used in your everyday environment, it may also provide vision that has some degree of practical benefit, particularly with regard to your orientation and mobility. We expect that there will be clear learning effects over the course of time, which would enable you to make increasingly good use of the new electronic vision in your daily life. If you participate in the trial then the results of your treatment will be analysed medically and documented. In every case you would personally make a significant contribution to the further technical development of future implants. However it must be remembered that you are participating in a clinical trial for one year only and although the chip may last longer than that, this is not designed as a lifelong treatment.

Removal of the implant if it is not working

Removal of the implant during or after the trial is not planned as long as as you tolerate it well. It can be left in as long as there are no significant complications and we would certainly not wish to remove the implant if you benefit in any way from the visual improvement. If there is a significant problem, or the chip is non-functional and you wish it to be removed, then the ophthalmologist leading the trial will discuss this with you and, if necessary, recommend a suitable date for the removal of the implant. This removal requires your consent and subsequently a similar operation to the one by which the implant was inserted. It requires a lot less time, however, namely 1 to 3 hours. The experiences of the pilot trial showed that the implant could easily be removed from its sub-retinal position, even months after its implantation, by simply sliding it out from the other surrounding tissue. In the course of removing the implant, excess tissue may be taken away and subjected to a histological examination, in case there is any unexpected inflammatory or other reaction to the implant. The pilot trial has proven that the implant cable and other components are tolerated well by the tissues around the eye and orbit. The coil under the skin above the ear and the cable running under the muscle in the temple to attach it to the implant in the eye could also be removed if requested. This might lead to a more prominent scar above the ear at the implant site.

Can an implant of the next generation be inserted at a later point in time?

The current state of research leaves open the possibility that a second implantation in the same eye is possible at a later date. In suitable cases, replacement of the implant could take place during the same procedure, i.e. directly after the removal of the first implant. This decision would be taken by your retinal surgeon at the appropriate time. As is the case with all repeat operations on the same organ, the risk of complications arising may be higher. A second implant could be inserted if there is no significant scarring and assuming the retina and its blood supply remain intact. This appears to be the case with the implants inserted to date. A 'next generation' implant could in any case be implanted into the other eye which has not yet been operated on.

What are the possible risks of participating in the trial?

Each one of the procedures that we have described here can produce variable side effects areas as described above. If you participate in the trial, your eye will be operated on at least once to insert the implant and possibly a second time to remove the implant again. According to our experiences in the first clinical trial, the implantation method used does not pose a significant infection risk when the implant is inserted (e.g. by allowing bacteria access into the eye), but we are obliged to inform you as to this possibility. Such infections as a rule first draw attention to themselves in the form of pain, restrictions to movement, a feeling of sickness and fever. In such cases please inform your doctor immediately so that a suitable antibiotic therapy can be started. It may be that further operations become necessary. Spread of the infection (sepsis) is also possible and could in theory lead to a life-threatening situation. In the event of a severe infection, irreversible damage leading to removal and loss of the eye) could result. In such cases a glass eye could be provided at a later date. To reduce the chances of infection, precautionary measures are taken, such as thorough disinfection and daily dressing of the wounds. Antibiotics are also infused into the eye and surrounding tissues during the operation.

In order to carry out this trial, blood samples need to be taken. The risks involved with the puncturing of a vein are minimal, but there is a small risk of infection, the formation of haematoma (i.e. bruises) and possible allergic reactions to the needles. The total amount of blood required in the course of the trial is about 100 ml. None of the patients who have so far received an implant showed an allergic reaction to the materials of which the implant is made. The following should, however, be mentioned as possible allergic reactions to substances foreign to the body: rashes, wheals, itching, fever, nausea, headaches, dizziness, shivering, muscle cramps, tingling sensations, numbness, peripheral accumulation of liquids, exhaustion, respiratory problems, hot flushes and general swellings or very rarely, shock.

It may also be that you do not experience any improvement in your ability to see as a result of the implant, but the risks of the implantation as described above would still exist in the same way. We will inform you of any new discoveries that could influence the benefit or the safety of the course of the trial and thus could affect your declaration of consent.

Your insurance protection during your participation in the trial

By participating in this UK-based clinical trial you remain eligible for any NHS treatments require. NHS indemnity operates in respect of the clinical treatment with which you are provided. The trial is sponsored by a German company (Retina Implant AG) which has provided additional insurance relevant to any medicolegal issues that may arise from the study. This is in accordance with European Legislation to the benefit of anyone adversely affected by a clinical trial (Medical Products Act § 20 (3)). In the event of damages, this clinical trial insurance covers the costs of possible damages to your health that may arise in the context of the trial, in the event that no other

person shall be liable for said damages. Representatives from the NHS will instigate the necessary steps in the event of liability of an NHS-employed individual. You will receive from the sponsor of the clinical trial (Retina Implant AG) a copy of the clinical trials insurance policy for your own records:

Gothaer Insurance No. 38.980.549691 info@gothaer.de

Address: Arnoldiplatz 1, 50598 Cologne, Germany

Tel. 0221130832502 Fax. 0221308954816

Whilst the clinical trial is in progress you should only subject yourself to a new medical treatment after consulting one of the ophthalmologists conducting the clinical trial. This does not apply in the case of an emergency: however, in the event of emergency treatment, one of the doctors running the clinical trial should be informed without delay.

With regards to your clinical trials insurance we explicitly refer you to the exclusions, the scope of the benefits and your own obligations. Please contact in the event of damages or an emergency the examining doctor without delay in order that the insurance benefit(s) to which you are entitled might be preserved. The trials sponsor, the "Retina Implant AG", will assist you in this and has also arranged travel accident insurance policy on your behalf, as you will be travelling in connection with the trial. This accident insurance is restricted to the direct route between your place of residence or your accommodation and your ophthalmic clinic. The insurance number and the name and address of the insurer will be provided in your copy of the travel accident insurance policy.

You should also be aware that for a period of 30 days before the beginning of this trial as well as during your participation up to one year, you should not participate in any other such clinical trials. If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Professor MacLaren or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 743005, or the head of CTRG, email: heather.house@admin.ox.ac.uk.

Rights and Duties of the participating patients

We ask you to participate actively in this important trial for the development of an implant for the blind. You should be prepared to allow yourself to undergo follow-up examinations during your stay as an inpatient conducted by the surgeons who will be performing the implantation surgery. You should also be prepared to participate in the subsequent check-ups and visual tests. If and when the silicone oil is to be removed is a question that the retinal surgeon treating you will discuss and decide with you. If you should suffer unexpected or unusual symptoms we request you to inform one of the doctors in charge of your trial without delay. We also request you to inform the doctors in charge of your trial of all medicines that you are taking or should you intend to start taking any

new medicines during the trial. Your participation in this trial is completely voluntary. You may, of course, revoke your consent to participate therein at any time without giving any reasons and without suffering any disadvantages with regards to any further medical care. In particular, this shall not have any consequences whatsoever regarding medical care at your ophthalmic clinic.

Will my participation in the trial be treated with confidence?

During this clinical trial medical details and personal information about you will be recorded in writing (patient's file) and kept in confidence, as is normal for medical records. Any data of importance for the clinical trial will be used without mentioning your name or by use of a pseudonym, such as 'P1' (patient number one, etc.). Protection by pseudonym is the replacement of the real name by a code for the purpose of excluding the identification of the person concerned, or to make this identification significantly more difficult (§ 3 clause 6 BDSG (Data Protection Act)). By means of an allocation system your data and your name can subsequently be linked again. Your name will only be passed on together with your data for public relations purposes if you have given your express permission.

In accordance with the legal stipulations, the implementation of a clinical trial is only possible if you agree to the recording of your health data and agree to these being passed on under a pseudonym to the responsible health authorities (local health authority, foreign health authorities) and to the Sponsor Retina Implant AG as the manufacturer of the medical device. At regular intervals the original data from your patient's file will be compared with those data that have been recorded on the documentation sheets by so-called monitors. These are persons who have been specially trained and sworn to secrecy. These entries in the pseudonym-protected documentation sheets can also be inspected by the staff of state authorities (e.g. the Medicines and Healthcare products Regulatory Authority – MHRA). In this context you release the examining doctor from his obligation to secrecy towards monitors, as well as towards representatives of either the responsible authorities or of the manufacturer of the medical device. We would expect you to give consent for your GP to be informed of your participation in this trial. In the event of your revoking your consent to this trial, it will not be possible to delete any data that has already been gathered owing to the duty to preserve all records for a period of 30 years.

What restrictions will I have to put up with when the implant is in my eye?

In order to minimise the risk of negative consequences for yourself as far as possible, the following examinations may only be undertaken during the trial with the implant (with or without external energy supply) in emergencies and if the doctors in charge of the trial are informed accordingly:

- Examinations of the head incl. the area around the eyes using X-ray apparatus
- Examinations with magnetic resonance imaging (MRI, nuclear spin)

Please to take care to avoid the following activities during the trial with the implant:

- Using mobile telephones on the side of the implantation without hands-free facilities
- Security checks at airports with electromagnetic fields (manual checks permitted)
- The practice of sports where there is a danger of injury in the head area

On the day of the operation you will be handed an implant pass which is a card to be kept with important information – also for emergencies. You should carry this with you at all times.

Will participation in the trial be compensated?

For your participation in the trial you will receive an expenses allowance amounting up to £ 900 per month (a max. of 4 months during the active phase of the trial). All reasonable travel and accommodation costs you incur in connection with the examination visits at the Oxford Eye Hospital during the period of the trial will be refunded upon the presentation of receipts. The invoice address should be that of the Retina Implant AG. All invoices must be approved by the local medical coordinator in Oxford (address below), who will then sign and forward the receipts to the sponsor of the trial for refunding. You will also receive travel expenses for your trip to Germany and this will be organised at the time by representatives from Retina Implant AG.

Ethical aspects of the clinical trial

This trial was reviewed from a medical-ethical point of view on November 9th 2009 by the Ethics Committee of the Medical Faculty of the University of Tübingen (Chair: Prof. Dr. D. Luft) and received approval. In the UK it was reviewed by the King's College Hospital Research Ethics Committee on 17 March 2010.

Should you still have any further questions, please contact the head of this clinical study or the patients' contact in Tübingen:

Head of the Clinical Trial (Principal & Coordinating Investigator)

Prof. Dr. med. Eberhart Zrenner

Department of Ophthalmology, Schleichstr. 12-16, D-72076 Tübingen

Tel.: +49 (0) 70 71-29 8 4786

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