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Cell Therapy for Early Osteoarthritis: Autologous Stem Cells, Chondrocytes, or the Two? ASCOT Trial - Patient Information Sheet

Introduction

You are being invited to take part in a research study because you have damage to the cartilage in a knee joint. Before you decide whether to take part, it is important for you 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 your relatives or family doctor if you wish.

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

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

If there is anything that is not clear or you would like more information, please do not hesitate to ask us. Take time to decide whether or not you wish to take part.

PART 1

What is the purpose of the study?

The purpose of this study is to compare three different cell therapy treatments for cartilage defects in the knee. We aim to enrol 114 participants into this study, which will take place at the Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust. The cells used in the treatment will be your own cells (autologous), grown in a laboratory from a small sample taken from you. About three weeks later, these cells will then be implanted into your knee.

The three different treatments are as follows:

A. Stem cell implantation – a sample of bone marrow is taken from the hip and a mixed population of cells (including stem cells) are grown from this in the laboratory

B. Cartilage cell implantation- a sample of healthy cartilage is taken from your knee joint and cartilage cells (chondrocytes) are grown from this in the laboratory

C. A combination of stem cell and chondrocyte implantation

By comparing these treatments it will enable us to decide which option is best to use in the future.

Why have I been invited?

You have been chosen because you have early arthritis in your knee joint.

Do I have to take part?

No. It is up to you to decide whether or not to take part. We will describe the study and go through this information sheet which you may keep and discuss with others. We will then ask you to sign a consent form to show that you have agreed to take part. You are free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you will receive.

What will happen to me if I take part?

The research study will last about 20 years. You will be involved in the research study for as long as it continues, which may involve some extra visits to the hospital or your own GP. This is explained below.

The type of research you are being invited to take part in is a randomised trial. Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To make sure the groups are the same to start with, each patient is put into a group randomly (by chance) using a computer programme, which will allocate you to one of the treatment groups described on the previous page (A, B or C). You will not be told which treatment group you have been allocated to. You have an equal chance of being allocated to any one of the three groups. Please note that once you have entered the trial and your treatment option has been randomised, you are not able to move to another treatment group within the trial protocol.

Before your surgery

All patients who have cell treatments in the UK must have a blood test for HIV, Hepatitis B, Hepatitis C, syphilis and human T-lymphotrophic virus (HTLV I & II). This will require you to donate 10ml of blood (about 2 teaspoons). This is routine clinical practice and, if your surgeon feels you may be suitable for cell therapy, will be done as part of your first consultation. If you have a positive result you will not be able to have cell therapy or take part in this clinical trial and your surgeon will discuss this with you. Counselling will be available to you before and after the test if you wish.

If you have not already had an MRI and/or CT scan as part of your diagnosis, we will ask you to have one. This will help to identify where the damaged cartilage is in your knee and how severe it is. Again, this is routine clinical practice.

A research nurse will discuss the trial with you and answer any questions you may have. You will have the opportunity to discuss the clinical trial with your surgeon, your GP and your family. Once you have made a decision to take part, you will be asked to sign a consent form.

You will be asked to complete questionnaires to assess your joint function, pain and general health. You will then be allocated to one of the three treatment groups A, B or C and placed on a waiting list until it is time for your first procedure. You may be asked to provide a sample of blood at this point (approximately 100mls or half a cup full) to use in the laboratory to help your cells to grow (known as feeding the cells).

We will also ask you to have an extra MRI and CT scan close to the time of your surgery. This will provide us with more detailed information about the condition of your knee cartilage.

If you are a female of childbearing potential you will be required to have a urine pregnancy test prior to the first stage of surgery. If you are found to be pregnant you will not be able to take part in the trial at this time.

The 1st operation (cell harvest procedure)

Your first procedure will be a keyhole (arthroscopic) examination of your knee performed under general anaesthetic. It is usually done as a day case, however you will be required to attend the hospital the day before this to provide some blood (approximately 100mls or half a cup full) to use in the laboratory to help your cells to grow (known as feeding the cells).

At the same time, depending on which treatment group you have been allocated to, you will also have **one or both** of the following cell harvesting procedures:

(a) A bone marrow biopsy where a fine needle will be inserted into your pelvis to extract tissue containing stem cells.

(b) A biopsy of healthy cartilage containing cartilage cells taken from your knee during the arthroscopy.

If you are allocated to the group receiving cartilage cells (chondrocytes) only, you will also be given 1 or 2 small skin incisions, approximately 5mm in length, above the pelvic bone so that you remain unaware of which type of cells have been harvested.

Soft tissue found beneath the knee cap (infrapatella fat pad) and attached synovium tissues that are routinely removed for some patients as part of the preparation of the joint for cell implantation, along with any other waste surgical tissue, will also be collected during the surgical procedure

These are a valuable resource for research. If you agree, we would like to collect and store these together with a sample of your blood and synovial fluid to use for histology and biochemical tests and possibly for genetic analysis.

Between the 1st and 2nd operations

The extracted cells will then be grown in the laboratory for around three weeks. Everyone's cells grow at different rates. If your cells grow more quickly than expected we may need you to provide an extra sample of blood to feed your cells with. If your cells grow very quickly we may need to bring the date of your stage 2 surgery forward in order to use the cells at their optimum condition. Driving cars and using machines may be restricted during the rehabilitation period after the harvest procedure.

We will give you a diary to record any symptoms you may experience and medications you are taking.

The 2nd operation

Your second operation will be to implant the cells into your knee, and takes place around three weeks after the cell harvesting procedure. This is an open-knee procedure and you will remain in hospital for a few days afterwards. During this procedure we will collect synovial fluid, waste joint tissue and a blood sample again with your permission. We would also like to retain a small number of your grown cells for examination. This may require that your samples will be sent in an anonymised form to collaborators in other research institutes, for example, Aberdeen.

During the harvesting or implantation of your cells, pictures and/or videos may be taken of the procedure for your medical records. These may also be used for teaching purposes for other orthopaedic surgeons and by the research team, but they will be anonymised.

After the 2nd operation (cell implantation procedure)

You may not be able to drive a car for 6 weeks after this procedure and you will also need to use crutches during this time or limit the range of motion of your knee, depending on the location of your cartilage defect. You will need to follow the rehabilitation guidance given to you by your physiotherapist. Cartilage

repair using this procedure is a slow process and the tissue continues to mature for typically between twelve and eighteen months but may be longer.

We will give you a diary to record your progress through the rehabilitation program, and also to record any symptoms you may experience and medications you are taking. The research nurse will contact you a week after you are discharged from hospital following the cell implantation to see how you are feeling and to take a note of any symptoms you may have had since the surgery.

At Approximately 2, 12 and 15 months after your operation, you will have an appointment to come to the clinic for your routine follow-up. To track your progress you will be asked at each of these appointments to complete the same questionnaires as you did before your operation; you will also be given a new rehabilitation diary to complete.

Approximately 12-15 months after your procedure, you will be invited to come into hospital again for another arthroscopy. This will allow us to check how successful the treatment has been and how well the cartilage harvest site has healed. To enable us to do this, 1.8mm diameter cores of cartilage and bone (about the size of half a matchstick) will be taken at the time of your arthroscopy. We will also ask you to have another MRI and CT scan as it provides more information on the quality of repair of the cartilage and the underlying bone.

Every year for 20 years after your initial treatment, you will be sent further questionnaires. Information held by the NHS Joint Replacement and Cancer Registries may also be used to follow up your health status. If you return for further surgery on the same knee joint at a later date we would like to collect a further sample of synovial fluid and blood.

Pregnancy/breastfeeding

If you take part in the study and think you or your partner want to become pregnant in the study duration please talk to your doctor or research nurse. This is still possible but it would be advisable not to get pregnant and/or breastfeed within the first 6 months after cell implantation. We will do a pregnancy test prior to your surgery.

Expenses and Payments

You will be able to claim back travel expenses for any visits to the hospital which are not part of your routine clinical care.

What will I have to do?

The study does not require much more from you than standard cartilage cell therapy. We will ask you to complete additional questionnaires, provide us with some of your blood, and undertake additional scans and arthroscopy (see above).

What are the alternative treatments?

Losing weight, taking pain killing medicine, or using dietary supplements such as Glucosamine or Cod Liver Oil have all been reported to have some benefit in early arthritis. Other surgical procedures may be used (like microfracture, debridement or washout). Eventually, you may need a joint replacement.

What are the possible disadvantages and risks of taking part?

One of the main risks is that the treatment you are allocated may fail to improve your symptoms and the pain and stiffness of early arthritis may continue to worsen. After surgery, you will have to follow a rehabilitation program for approximately one year, allowing your knee to heal well. Your doctor and

physiotherapist will give you more details on your rehabilitation. If you do not follow your rehabilitation schedule, the risk of treatment failure may increase.

We do not anticipate that your arthritis will be made worse by any of the treatment options in this study.

Most side effects of cell implantation are those related to open-knee surgery such as joint pain and swelling. In general, these side effects are quite mild and disappear in the weeks following surgery.

Infection can follow any surgical procedure to a joint. This is very rare and has occurred in only 1 in 300 similar cases at our hospital. Infection may result in pain and swelling and the need for repeated arthroscopy. It may also limit future options for the treatment of arthritis.

Stiffness of the joint may result if the injected cells form scar tissue. The injection of cartilage cells has not been problematic but there is a theoretical risk of joint stiffness with large numbers of stem cells. Previous experience has shown that small numbers of stem cells released into the joint as a result of surgical treatments do not cause stiffness.

You may experience some pain at the cartilage and/or bone marrow harvest sites after the procedure. Your doctor will give you advice regarding suitable pain relief medication.

An excess of repair tissue or, more rarely, overgrowth of the patch used to secure the cells in place may cause pain in the knee. An arthroscopy may be necessary to trim this tissue.
There may be a risk of an allergic reaction to some of the products used in the cell culture procedure, so please let us know if you have any allergies.

Concerns have been raised in the past that stem cells may cause cancers. Our previous experience and knowledge has not found an increased risk of cancer from cell therapy treatment, however, we will be collecting information on any diagnoses of cancer for 20 years following your treatment.

The rates of cell growth varies between individuals and it is possible that your cells will fail to grow sufficiently to produce enough for implantation. Cell numbers are monitored throughout the culture period and we will let you know, as soon as possible, if we think there may be too few cells for your procedure to take place. Your surgeon will discuss the alternative options available with you.

What is an MRI and CT scan?

MRI stands for Magnetic Resonance Imaging and will give us detailed pictures of the cartilage and other soft tissue in your knee. An MRI scan uses a strong magnetic field and radio waves to create these pictures; it does not use ionising radiation (X-rays). There is very little risk associated with an MRI scan.

CT stands for Computed Tomography and uses special X-ray equipment and sophisticated computers to create more detailed pictures of your knee than other imaging procedures. The amount of radiation you would receive in this study, if a CT scan was performed, is equivalent to approximately one seventh of the annual natural background radiation in the UK.

Both procedures are non-invasive and painless, although women should inform the radiographer if there is any possibility that she may be pregnant before having the scan.

What are the possible benefits of my taking part?

Although we cannot promise that the study will help you, the information we get might help improve the treatment of other people with arthritis. You will receive information and feedback about the procedure you have been allocated.

What if there is a problem?

If you have a problem, this can be discussed with your surgeon (Professor J. Richardson, 01691 404386; Mr T. Smith 01691 664849; Mr S Roberts 01691 404094, Mr P Gallacher 01691 404849).

Will my taking part in the study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

<u>If the information in Part 1 has interested you and you are considering taking part, then please read the additional information in Part 2 before making any decision.</u>

PART 2

What if relevant new information becomes available?

Sometimes we get new information about the treatments being studied. If this happens, your research doctor will tell you and discuss whether or not you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study, you may be asked to sign an updated consent form.

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

You are free to withdraw from the study without giving a reason. A decision to withdraw at any time will in no way affect the standard of care you receive. If you withdraw from the study, we will keep the samples already collected with your consent and the data generated from them, but no further data or tissue would be collected and no further research procedures would be carried out.

What if there is a problem?

Complaints

If you have a concern about any aspects of this study please contact the researchers who will do their best to answer your questions directly or they will liaise with your clinician. Please phone 01691 404664 or 01691 404660.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the Trust.

Harm

In the event that something does go wrong and you are harmed during the research study, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS Trust but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you if appropriate.

Will my taking part in this study be kept confidential?

All personal information which is collected about you during the course of the research will be kept strictly confidential. Data collected will be stored on a secure database according to the Data Protection Act 1998. Samples may be sent to another centre, for example to a laboratory in Philadelphia and/or Aberdeen but would be anonymised before doing so. Authorised personnel, for example, research staff, representatives from the regulatory agencies (MHRA) and research and development audit personnel (who monitor the quality of the research) will have access to the data to ensure the study protocol is being followed correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

We also have duty to 'share' the data we collect with other researchers, in order to maximise its value for the public good. This could mean answering new questions with existing data, or combining the results of several similar studies. Only anonymous data would be shared, and your identity would not be revealed. We would like your permission to share the data we collect during this study in this way.

Involvement of the General Practitioner/Family Doctor (GP)

Your GP will be interested to know about this study so please take this information sheet with you when you next see them. As per standard hospital policy a copy of your operation and clinic notes will be sent to your GP following each attendance.

What will happen to any samples I give?

Some samples may be completely used up in this research project but, if not, we will store them appropriately (dried, frozen or in fixative) for up to 20 years.

The samples may be used in ongoing research into osteoarthritis. The samples will not be used in any future research without Research Ethics Committee approval.

What about other research?

Early arthritis has no proven current treatment. Researchers in the field of Orthopaedics at this hospital are very keen to search for a solution and to understand the process of arthritis. You may therefore have the opportunity to help with other studies. However, you do not have to take part in these studies. A decision not to take part will not affect the standard of care you receive.

Will any genetic tests be done?

No genetic tests are required for the study itself, but we may like to perform some genetic analysis in the future. This will involve searching for genes that are associated with arthritis. If you do not wish this aspect of the research to be carried out, then please mark the consent form appropriately.

What will happen to the results of the research study?

The results generated from the study will be presented in scientific meetings and published in peer reviewed medical journals. At the end of the study you will receive a summary of the results.

Who is organising this research study?

The research is organised by Professor James Richardson of the Robert Jones & Agnes Hunt Othopaedic Hospital NHS Foundation Trust.

Your doctors will not be paid for including you in the study.

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 safety, rights, well-being and dignity. This study has received a positive opinion from the NRES committee West Midlands – Coventry and Warwickshire. The study has also received authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Thank you for taking time to read this sheet and if you have any other questions which are perhaps not covered then please do not hesitate to ask.

Further information and contact details

For further information please contact your surgeon (Professor J. Richardson, 01691 404386; Mr T. Smith 01691 664849; Mr S Roberts 01691 404094, Mr P Gallacher 01691 404849) or the research team on 01691 404664.

Independent advice may be sought from the Patient Advice and Liaison Service (PALS) on 01691 404606 or e-mail PALS.office@rjah.nhs.uk.

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