MONASH University

EXPLANATORY STATEMENT

Project: ***Evaluation of mesenchymal stem cells in the treatment of knee osteoarthritis – prospective case series data collection.***

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Co-investigator : Dr Leesa Huguenin

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Please read this Explanatory Statement in full. If you would like further information regarding any aspect of this project, you are encouraged to contact the researchers via the phone numbers or email addresses listed above.

1. Introduction

Your study doctor will answer questions you may have about the study. The information contained in this Information Sheet will help you to understand the possible risks and benefits involved in the study, what alternatives are available and what would happen. Also your rights and responsibilities will be outlined. Please note you cannot receive any reward for being a part of this study.

This study aims to explore the effectiveness of autologous stem cell injections in treating osteoarthritis. This study involves the use of autologous stem cells, autologous meaning that the cells are taken from and injected back into the same person. Based on previous animal studies and initial human patients, these cells are expected to reduce pain and assist in bone and cartilage tissue repair, supporting their potential in the treatment of osteoarthritis.

The cells will be isolated from fat taken from around your waist, via a liposuction procedure. Under laboratory conditions, the cells will be given nutrients and allowed to grow and multiply. These cells will then be injected into your symptomatic knee. Use of autologous cells is approved by the Therapeutic Goods Administration (TGA) under their Biological Exemption Scheme. Please speak to your study doctor should you seek further information.

This consent form describes the study and your role in participating in this study. Please read this form carefully and ask any questions you have regarding the information it contains. You may like to discuss the information with your family or loved ones and your GP or specialist. Your study doctor will answer any questions concerning the study or this consent form. Once you have read the information and you agree to participate, you will be given a signed copy of this entire document for your records.

Your decision to participate is entirely voluntary. If you do not wish to participate you do not have to. Your decision not to participate will not adversely affect the care you receive from your study doctor, now or at any time in the future. If you decide to participate and later change your mind you can withdraw from the study at any time. You are not required to give a reason but you should discuss this with the study staff as they will be able to advise you if there are any special considerations in regard to stopping this study safely.

2. Purpose of Study

The purpose of this pilot study formally follow up and record the effectiveness of stem cell injections in the treatment of knee joint OA. A secondary objective is to determine whether stem cell therapy offers disease modifying potential and therefore whether it can limit, prevent or possibly reverse progression of osteoarthritis.

3. Why are you suitable?

You have been invited to participate in this research as you have either been referred by a treating practitioner/doctor or have made a direct enquiry. You have also met the required inclusion/exclusion criteria.

4. Duration of Participation

Your participation in this study will be up to approximately 12 months. During this time, up to 10 visits may be required. These may involve web-based or paper questionnaires from home. The study staff will discuss this with you. The visits will vary in length, but are expected to last on average 30mins -2 hours each. During this study you will have up to two MRIs. You will also be required to complete follow-up questionnaires at regular intervals to allow us to determine the results of treatment.

5. Where are procedures/investigations done ?

The lipoharvest procedure and stem cell injections will be performed at Melbourne Stem Cell Centre. MRI imaging needs to be performed on the same machine each time. Imaging will be primarily performed at two possible radiology sites (Box Hill Imaging Associates and VicHouse Imaging) though may be able to be performed at other sites if necessary.

6. Cost of treatment

All treatment and investigations performed are as a private patient and are not funded. Costs are met by each individual patient.

7. Study Procedures

The details of what will happen at each visit are described below.

Visit 1 – Baseline Assessment

Prior to any procedures being performed one of the study doctors will personally explain the study to you. You will be informed of the purpose of the study and of the risks involved and will be given formal written material explaining the study. A routine physical examination will be conducted that includes height, weight and assessment of your knee. Pregnancy testing will be performed on all females of child bearing age. You will also be asked about drug and alcohol use. Should you accept to be part of the study you will be asked to complete a formal written consent and formally enrolled in the study. A baseline scan (MRI) will be required prior to undergoing your scheduled therapy. Visit 1 is estimated to take up 2 hours, plus the time required to undergo the MRI.

Visit 2 – Adipose Tissue Harvest Procedure

You will undergo a mini-liposuction to harvest stem cells. Approximately 100 ml of abdominal fat will taken following local anaesthetic infiltration. The harvested tissue will be processed to isolate and culture the stem cells, for future injections. The isolated stem cells will be suitably stored meeting TGA biological product/treatment requirements.

Visit 3 – Post Adipose Tissue Harvest Procedure

You will be seen by the lipo-suction procedural doctor as routine post operative care 1 week post the procedure.

Visit 4 – Week 0 - Injection 1

At this visit, you will complete pain and functionality questionnaires prior to your first injection. You will receive the first of two injections. All injections into your knee will be done under Ultrasound guidance to ensure correct placement of the needle into the joint space. A sample of knee joint fluid will be taken prior to the injection. All procedures will be performed under sterile conditions. This visit is estimated to take 60 minutes.

Visit 5 – Week 1 - Pain assessment

You will be seen by the study doctor for routine post procedural review. You will complete pain score questionnaires and record medication use over the previous 24 hours.

Visit 6 – Week 4 – Pain assessment

You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours.

Visit 7 – Week 12 - Pain assessment

You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours.

Visit 8 – 6 months - 6 month injection

At this visit, you will have a 6month MRI performed after which you will receive the 6 month stem cell injection and complete pain score and outcome questionnaires. All injections into your knee will be done under Ultrasound guidance to ensure correct placement of the needle into the joint space. A sample of knee joint fluid will be taken prior to the injection. All procedures will be performed under sterile conditions. This visit is estimated to take 2 hours. You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours.

Visit 9 – 6 Months + Week 1 - Pain assessment
You will be seen by the study doctor for routine post procedural review. You will complete pain score questionnaires and record medication use over the previous 24 hours.

Visit 10 – 12 months – Pain and Outcome Score assessment + MRI
You will receive a 12month follow up MRI at this visit. You will complete pain and outcome score assessment. This visit is estimated to take 60 minutes, plus the time required for the MRI.

8. Specimens

A total of about 68 mL of blood (2x34mls) and between 4-20mls (2x2-10mls) of knee joint fluid will be collected. All blood collected during the study will be made up by your body within a few days of the blood draw. Your blood and synovial fluid samples will be stored for no more than 5 years after the end of the study at which time your samples will be destroyed. The samples will be tested to develop an understanding of the biological environment within the body in symptomatic osteoarthritis, and whether the injection of the autologous stem cells changes this environment. The storage allows for the analysis of the samples for any reason related to the study

9. Participant Responsibilities

As a study participant, you are responsible for following the study directions and those of your study doctor. This includes returning promptly to the study clinic for all necessary study follow-up visits, reporting any changes in your medications (over-the-counter and prescription), and reporting any changes in how you feel to the study doctor and the study staff.

You will be responsible for completing questionnaires regarding your condition.

If you experience any illness or discomfort during the study, you should notify your study doctor. Your study doctor will then evaluate you to determine if you should continue the study. During this study, your study doctor will notify any doctor who is taking care of you that you are participating in a research study that involves the use of this study medication.

If you cannot attend a scheduled visit, you should inform the study clinic as early as possible so that the visit can be rescheduled.

10. Reasonably Foreseeable Risks or Discomfort to the Participant

The harvesting liposuction and injection procedure may cause some discomfort to the participant. Where appropriate local anaesthetic infiltration will be used. There also exists a risk of infection. Medical doctors will perform all the procedures. They will have an equivalent of a Bachelor of Surgery and Bachelor of Medicine degree and will have a current medical registration and medical indemnity.

You will be given the opportunity to ask questions about the procedure to allay any fears that you might have about the potential discomfort and risks. Study participants will be able to contact the treating doctor at any time if they have concerns regarding side effects experienced.

8.1 Harvesting Liposuction Procedure
a. Discomfort : It is possible that some participants may experience discomfort during the liposuction procedure. All liposuction will be performed after infiltration of a local anaesthetic tumescence which is an internationally accepted practice.
b. Infection – participants will be monitored for adverse events such as infection. The risk of this occurring is low. Subjects will receive a course of antibiotics to commence prior to the liposuction procedure.
c. Bruising - participants may experience minor bruising at the site of liposuction.

8.2 Intra-articular Knee Stem Cell Injections
a. Discomfort : Patients may experience some discomfort at the time of injection. Prior to injection the area will be anaesthetised using 2mls of 1% xylocaine. Stem cell injections can be associated with a flare up of pain for 1-2weeks. This will be managed with appropriate pain relief.
b. Infection – participants will be monitored for adverse events such as infection. If infection did occur participants will be referred for surgical opinion and may require surgical washout and a period on intra-venous antibiotics. The risk of this occurring is low.
c. Bruising - participants may experience minor bruising at the site of injection.

> **Note : Medical doctors will perform all the procedures. They will have an equivalent of a Bachelor of Surgery and Bachelor of Medicine degree and will have a current medical registration and medical indemnity. Those doctors performing lipoharvesting will have appropriate qualifications within this area.*

8.3 Mesenchymal Stem Cell Therapy : Safety Data
Systematic review of published clinical trials indicates that mesenchymal therapy is safe. Importantly no association has been made between mesenchymal stem cell therapy and adverse events such as infection, death or malignancy. Although malignant transformation may be a theoretical risk, malignancy has only been noted in studies where participants had ongoing or previous malignancies – no de novo malignancies have been observed. Importantly any history of present malignancy is an `exclusion criteria' in this proposed study.

Stem cell administration has been shown to be associated with a transient and self limiting febrile episode (fever). Intra-articular mesenchymal stem cell injections have been occasionally associated with self limiting discomfort and swelling. This is not uncommon and any increased discomfort should not last more than 48hours.

8.4 Culture Media
Bovine culture media will be used. Given the use of this culture media, the cells will be triple washed with clinical grade/ GMP grade Phosphate Buffered Saline (PBS) to remove any traces of media. Bovine deprived culture media is used commercially in the development of many clinical products including vaccines. All procedures will be performed in a sterile environment, Grade A area or ISO 5, where air quality of room is constantly monitored by a particle counter with HEPA filtered air circulating in the laboratory to inhibit any environmental contamination and to limit any risk of c infection. All the laboratory staff handling the lipoaspirate and the cells will be well trained and experienced in aseptic techniques.

10.5 Antibiotics

Participants will use prophylactic antibiotics (Cephalexin 500mg 4 times a day) commencing 24hrs prior to the liposuction harvest procedure and for a further 4 days (5 days in total) or a single dose of IV antibiotics (ceftriaxone) during the liposuction. Those with an allergy to cephalosporins or a documented anaphylaxis to penicillin will be prescribed a suitable alternative antibiotic (ie. Doxycycline). You should take pro-biotic/live culture preparations (ie. yoghurt) during this time period to replenish the normal bacteria of the digestive tract.

10.6 Pain Relief

Participants will be prescribed suitable analgesic medication post procedures such as endone or paracetamol + codeine. There is a risk of drowsiness and opiate dependence. You will only be given a limited script

11. Possible Benefits

Autologous stem cell therapy is an emerging treatment. Our study will be the first to use appropriate methodology to explore benefits and adverse events. Initial in vitro and in vivo studies suggest the participants will substantially benefit in terms of reduced pain and activity limitation. Recent publications have highlighted the ability of stem cells to regrow cartilage in human subjects. It is anticipated that stem cell therapy will have disease modifying properties and hence possibly prevent later requirement for knee replacement surgery.

12. Alternative Treatments

Alternative treatments are available to treat your osteoarthritis. Your study doctor will discuss with you the advantages and disadvantages of alternative treatments. This includes conservative traditional treatments including simple analgesia and weight loss and other available injectable therapies.

13. Use of Data and Confidentiality

This study will involve the collection and processing by your doctor of personal data about you, including sensitive data regarding your health and other personal details. MRI imaging will be assessed off site.
All personal data that is removed from the study site, where possible, will be de-identified.

Your personal records will be stored in secure locations such as locked filing cabinets, and amongst the other electronic medical records at the Study Doctor's clinic.

An independent Data and Safety Management Committee will oversee the study. It is foreseeable that participant anonymity will be difficult to maintain when the committee are assessing aspects of the research – ie. participant feedback questionnaires.

In the event that you are admitted to another hospital during the course of or arising out of your participation in the trial, we will ask for your permission for the release of any relevant records from that hospital.

A report of the results of this study may be published, but your name will not be disclosed in these documents. Appropriate precautions will be taken to maintain

confidentiality of medical records and personal information. It is a requirement that your study records must be retained for 15 years after the completion of the study. After this period, the records will be shredded, incinerated or securely recycled.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. Your GP will be informed of your participation in this study.

14. Use of data for other purposes

Relevant collected information may be used for future research purposes. This will only include de-identified data and would only be used for other projects that have been granted appropriate ethics approval.

15. Medical Treatment Compensation

Every reasonable precaution will be taken to ensure your safety during the course of the study. If you are injured as a direct result of participation in the trial, reasonable medical treatment will be provided. Any compensation made necessary by the study will be made according to the Medicines Australia, guidelines on compensation for drug induced injury. These guidelines are available for your inspection at: http://medicinesaustralia.com.au/files/2010/09/Clnical-Trials-Compensation-Guidelines.pdf. However as guidelines, they do NOT in any way dictate the pathway you should follow to seek compensation.

Your participation in this study will not affect any other right to compensation that you might have under statute or common law. It is the recommendation of the independent ethics committee responsible for the review of this trial that you seek independent legal advice before taking any steps towards seeking compensation for injury.

16. Will I be paid for involvement in the study ?

Your involvement in this data collection study is voluntary. You will not receive any financial compensation for your involvement.

17. Financial Conflict of Interest

Please note that some of the involved researchers are partners at Magellan Stem Cells and Melbourne Stem Cell Centre where the treatments will take place.

The study doctor will also be your treating doctor.

Your study doctor will not allow a conflict of interest to compromise their position, the research study or your clinical care.

18. Contact details

You are encouraged to ask the study doctor or study staff any questions about this study or this consent form, and you should receive satisfactory answers to your questions. If you experience any research-related injuries during the study, you should contact the Principle Investigator Professor Richard Boyd or the study doctor Dr Julien Freitag – contact details are attached on the first page of this form.

19. Participation

Your participation in this study is entirely voluntary. You may refuse to participate or may withdraw from this study at any time without penalty or loss of any rights or benefits to which you are otherwise entitled. Your study doctor may also stop your participation in the study at any time. If you decide to withdraw from the study you should contact your study doctor or his study staff immediately on 03 92708000.

Furthermore, you may demand that existing data arising from your participation are not used in the research project provided that this right is exercised within four weeks of the completion of your participation in the project. If this is the case, you are asked to complete the "Withdrawal of Consent Form" or to notify one of the researchers by e-mail or telephone that you wish to withdraw your consent for your data to be used in this research project.

20. New Information

The study doctor will inform you (or if applicable your legally authorized representative) of any new information about the study medication that might develop during the course of this research and might influence your willingness to participate in the study. If appropriate, your study doctor will ask you to sign a revised informed consent form approved by the Human Research Ethics Committee.

21. Study Results

The study doctor will discuss directly with you your individual results. When available the study outcome will also be made available to you.

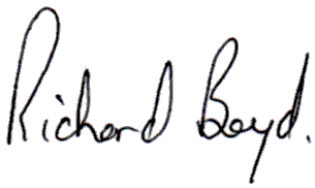
22. Complaints

Should you have any concerns or complaints about the conduct of the project, you are welcome to contact the
Executive Officer, Monash University Human Research Ethics (MUHREC):

Executive Officer
Monash University Human Research Ethics Committee
(MUHREC)
Room 111, Building 3e
Research Office
Monash University VIC 3800

Tel: +61 3 9905 2052 Email: muhrec@monash.edu Fax: +61 3 9905 3831

Thank you,



Professor Richard Boyd