MONASH University

EXPLANATORY STATEMENT

Project: ***Evaluation of mesenchymal stem cells in the treatment of knee osteoarthritis***

Chief Investigator : Prof Richard Boyd
Department of Anatomy and Developmental Biology,
School of Biological Sciences
Phone: 9905 0630
email: **richard.boyd@monash.edu.au**

Chief Study Doctor : Dr Julien Freitag
Melbourne Stem Cell Centre
Phone: 92708000
email: **julien.freitag@mscc.com.au**

Sites: Melbourne Stem Cell Centre – Suite 2.16, Level 2, 114 – 118 Thames Street Box Hill North, Vic 3129

You are invited to take part in this study. Please read this Explanatory Statement in full before deciding whether or not to participate in this research. 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. You will not bare any costs for this study.

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.

You have been invited to participate in a research study for patients with knee joint osteoarthritis (OA). This study aims to explore the effectiveness of autologous mesenchymal stem cell (MSC) injections in treating OA. This study involves the use of autologous MSC, 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 MSC are expected to reduce pain and assist in bone and cartilage tissue repair, supporting their potential in the treatment of osteoarthritis.

You will be randomly allocated to four groups. Groups 1,2, and 3 will receive stem cell therapy. Group 4 will be a control group and will not receive any stem cell treatment.

If significant and clear disease modifying benefit occurs at follow up intervals 6months or 12months then Group 4 will be offered stem cell therapy based on applying best clinical practice.

The MSC 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 is to assess the effectiveness of autologous MSC injections in the treatment of knee joint OA. A secondary objective is to determine whether MSC therapy offers disease modifying potential and therefore whether it can limit, prevent or possibly reverse progression of osteoarthritis.

All participants will be instructed to cease any analgesic or other anti-inflammatory medications, except Paracetamol, for three weeks prior to the first intervention and for the duration of the trial.

3. Why were you chosen for this research?

You have been invited to participate in this research as you have either been referred by a treating practitioner/doctor or have personally responded to advertising regarding this study. 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, between 5-14 visits may be required, along with 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 three MRIs. You will also be required to complete follow-up questionnaires at regular intervals to allow us to determine the results of treatment.

5. Study Procedures

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

MONASH University

Group 1 ☐

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 blood and synovial fluid sample will be taken. 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 stromal cells. Approximately 100 ml of abdominal fat will taken following local anaesthetic infiltration. This is a very common procedure used extensively by cosmetic surgeons; it has a strong safety profile and patient acceptance. The harvested tissue will be processed to isolate the mesenchymal stem cells (MSC), for future injections. The isolated MSCs 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. All injections into your knees will be done under local anaesthetic and with the assistance of 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. You will be required to use crutches for 4 weeks after this injection.

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.

MONASH University

Visit 8 – 6 months – Pain and Outcome Score assessment and MRI
You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours

Visit 9 – 12 months - Pain and Outcome Score assessment and 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.

Group 2 ☐

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 blood and synovial fluid sample will be taken. 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 stromal cells. Approximately 100 ml of abdominal fat will taken following local anaesthetic infiltration. The harvested tissue will be processed to isolate and culture the MSC cells, for future injections. The isolated MSCs 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 knees 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. You will be required to use crutches for 4 weeks after this injection.

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.

MONASH University

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 MSC injection and complete pain score and outcome questionnaires. All injections into your knees 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.

Group 3 ☐

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 blood and synovial fluid sample will be taken. 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 stromal cells. Approximately 100 ml of abdominal fat will taken following local anaesthetic infiltration. The harvested tissue will be processed to isolate the mesenchymal stromal cells, for future injections. The isolated MSCs 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.

MONASH University

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 four injections occurring at monthly intervals. All injections into your knees 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. You will be required to use crutches for 4 weeks after this initial injection.

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 and Injection 2

At this visit, you will be asked to complete pain score and outcome questionnaires and record medication use over the previous 24 hours. You will also receive the second of four injections occurring at monthly intervals. All injections into your knees will be done under Ultrasound guidance to ensure correct placement of the needle into the joint space. A sample of knee joint fluid and a blood sample will be taken prior to the injection. All procedures will be performed under sterile conditions. This visit is estimated to take 60 minutes.

Visit 7 – Week 5 - Pain assessment

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

Visit 8 – Week 8– Pain assessment and Injection 3

At this visit, you will receive the third of four injections occurring at monthly intervals and complete pain score questionnaires. All injections into your knees 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 9 – Week 9 - Pain assessment

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

Visit 10 – Week 12 – Pain assessment and Injection 4

At this visit, you will receive the fourth of four injections occurring at monthly intervals and complete pain score questionnaires. All injections into your knees 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 11 – Week 9 - Pain assessment

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

Visit 12 – 6 months - 6 month injection + MRI
At this visit, you will have a 6month MRI performed after which you will receive the 6 month MSC injection and complete pain score and outcome questionnaires. All injections into your knees 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 13 – 6 Months + 1 Week - Pain assessment
You will be seen by the study doctor for routine post procedure review. You will complete pain score questionnaires and record medication use over the previous 24 hours

Visit 14 – 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.

Group 4 ☐

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 – Week 4 – Pain assessment
You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours

Visit 3 – Week 12 – Pain assessment
You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours

Visit 4 – 6 Month – Pain assessment
You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours

Visit 5 – 12 month – Pain Assessment
You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours

6. Specimens

If enrolled in Groups 1 or 2, 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 MSC changes this environment. The storage allows for the analysis of the samples for any reason related to the study

7. 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.

8. 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.

Participants will be informed of potential discomfort and risks in the participant information sheet. In the unusual circumstance that a participant has an increase in symptoms following the procedure it is unlikely to last for greater than 48 hours. Participants will be informed of potential discomfort and risks in the participant information sheet. Participants will be given the opportunity to ask questions about the procedure to allay any fears they 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 single dose of intravenous antibiotics prior to the liposuction procedure.
c. Bruising - participants may experience minor bruising at the site of liposuction.

8.2 Intra-articular Knee MSC Injections
a. Discomfort : Patients may experience some discomfort at the time of MSC injection. Prior to injection the area will be anaesthetised using 2mls of 1% xylocaine .
b. Infection – participants will be monitored for adverse events such as infection. They will be provided with a one-week course of 500mg Cephalexin to minimise the risk of infection post MSC injection. 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 MSC 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 MSCs therapy is safe (Lalu et al. 2012). Importantly no association has been made between MSC therapy and adverse events such as infection , death or malignancy. This pertains to both allogeneic and autologous treatments where the MSCs have undergone expansion/culture. 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 past or present malignancy is an `exclusion criteria' in this proposed study.

MSC administration has been shown to be associated with a transient and self limiting febrile episode (fever). Review of studies involving both autologous or allogeneic MSCs therapies indicates fever in up to 39% of patients.

Intra-articular mesenchymal stem cell injections have been occasionally associated with self limiting discomfort and swelling Participants will be warned of this and reassured that this is not uncommon and that 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.

9. Possible Benefits

Autologous MSC 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 publicatons have highlighted the ability of MSC to regrow cartilage in human subjects. It is anticipated that MSC therapy will have disease modifying properties and hence possibly prevent later requirement for knee replacement surgery.

10. 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.

11. 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. All personal data that is removed from the study site will be de-identified and will only be marked with your initials and a participant number that will be assigned to you at the beginning of the study.

Your personal details and identity will be known only by the study doctors, the principal researcher (Prof Richard Boyd), and an administrative assistant. Your personal records will be stored in secure locations such as locked filing cabinets, and amongst the other medical records at the Study Doctor's clinic. An identification code rather than your name will be used on questionnaires that you fill in. You will therefore remain anonymous throughout the study.

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.

12. 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.

13. 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.

14. Will taking part in this study cost me anything and will I be paid ?

As a research participant in this study, there will be no cost to you to participate and receive the autologous MSC treatment.

15. 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.

This study is being internally funded/supported by Magellan Stem Cells and the Melbourne Stem Cell Centre.

Your study doctor will not allow a conflict of interest to compromise their position or this research study. No money is paid directly to individual researchers. Those doctors performing procedures will be recompensed for their time through internal study funding.

16. 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.

17. 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.

18. 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.

19. 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.

20. 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