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PARTICIPANT INFORMATION STATEMENT

Project title: INTRA-ARTICULAR MESENCHYMAL STEM CELL INJECTIONS FOLLOWING ARTHROSCOPIC MICROFRACTURE VERSUS ARTHROSCOPIC MICROFRACTURE ALONE FOR KNEE CARTILAGE DEFECTS: A PILOT STUDY

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Aims of project:

The purpose of this pilot study is to assess whether autologous mesenchymal stem cell (MSC) injections in addition to arthroscopic knee microfracture will improve the quality of knee cartilage repair when compared to microfracture alone.

This study also aims to evaluate the efficacy of magnetic resonance imaging (MRI) in assessing cartilage health.

Funding / sponsorship: The treatment in the trial is being carried out at Melbourne Stem Cell Centre. It is funded by the Melbourne Stem Cell Centre and Magellan Stem Cells Pty Ltd.

Participants not suitable for the trial :

- Pregnancy or attempting pregnancy
- Have other causes of their knee symptoms
- Blood disorder
- MRI confirmed displaced menisicial tear.
- MRI confirmed Grade II-IV degenerative osteoarthritis
- History of cancer

Description of research procedures:

Up to 8 clinic 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 from 30 minutes to 2 hours each. During this study you will also have up to two MRIs (prior to the microfracture procedure and subsequently at 12 months post microfracture). You will also be required to complete follow-up questionnaires at regular intervals to allow us to determine the results of treatment.

In order for this study to be successful and allow accurate data collection it is important that you acknowledge the following responsibilities:

- Come to all scheduled consultations
- Carefully follow instructions
- Fill out questionnaires honestly
- Inform staff of any health concerns and/or medications that you are taking before and/or during the study
- Inform study staff if you no longer wish to be part of the study

If you agree to participate in the study, you will be allocated to one of the two groups (MSC injection following microfracture surgery or microfracture surgery alone). The details of what will happen at each visit are described below.

Group 1. MSC + Microfracture Group

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 who accept to be part of the study will be asked to complete a formal written consent and formally enrolled in the study. You will be randomly allocated to a treatment group (MSC + Microfracture or Microfracture Alone) and will not be blinded to your treatment arm. A baseline magnetic resonance imaging scan (MRI) will be required prior to undergoing your scheduled microfracture surgery. Following this baseline assessment and random allocation to the MSC + MIcrofracture group arrangements will be made for your next appointment and stem cell harvest procedure. Visit 1 is estimated to take up to 1 hour, plus the time required to undergo the MRI.

Visit 2 – Adipose Tissue Harvest Procedure

All participants assigned to the stem cell treatment group will undergo a mini-liposuction to harvest stem cells. Approximately 100 ml of abdominal subcutaneous adipose tissue (fat) will taken after local anaesthetic infiltration. The isolated stem cells (MSC) will be suitably stored under TGA (government) biological product/treatment requirements.

Visit 3 – Post Adipose Tissue Harvest Procedure

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

Visit 3 – Baseline prior to arthroscopy/microfracture

You will complete online or in person pain and function score questionnaires and record medication use over the previous week. This visit is estimated to take less than 30 minutes.

Visit 4 – Week 1 post arthroscopic microfracture surgery - Injection 1

You will complete pain scores and record medication use over the previous week. You will receive the first of two injections. Pregnancy testing will be performed on all females of child bearing age. All injections into your knees will be done under ultrasound guidance to ensure correct placement of the needle into the joint space. All procedures will be performed under sterile conditions. This visit is estimated to take 60 minutes.

Visit 5 – Week 5 - Pain assessment

You will complete online or in person pain and outcome score questionnaires and record medication use over the previous week. This may be performed online.

Visit 6 – Week 13 post microfracture – Pain assessment

You will complete online or in person pain and outcome score questionnaires and record medication use over the previous week. This may be performed online.

Visit 7 – 6 months post microfracture – Injection 2
You will complete online or in person pain and outcome score questionnaires and record medication use over the previous week. You will receive the 6month 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. All procedures will be performed under sterile conditions.

Visit 8 – 12 months post arthroscopic microfracture surgery
You will complete online or in person pain and outcome score questionnaires and record medication use over the previous week. A follow up MRI will be also be required at this visit. This visit is estimated to take 60 minutes, plus the time required for the MRI. This will be your last official study visit. At your study doctor's discretion, you may be contacted after you finish the study to follow up on your treatment and any ongoing medical conditions.

Group 2. Microfracture Only Group

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. Routine pathology will be requested including full blood count, renal and liver function. 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. You will be randomly allocated to a treatment group (MSC + Microfracture or Microfracture Alone) and will not be blinded to your treatment arm. A baseline MRI scan will be required prior to undergoing your scheduled microfracture surgery. Following this baseline assessment, arrangements will be made for review by your study doctor week 1 post surgery. Visit 1 is estimated to take up to 1 hour, plus the time required to undergo the MRI.

Visit 2 – Baseline prior to arthroscopy/microfracture
You will complete online or in person pain and function score questionnaires and record medication use over the previous week. This visit is estimated to take less than 30 minutes.

Vist 3-6 – Months 1, 2, 3 and 6 post microfracture - Pain assessment
You will complete online or in person pain and outcome score questionnaires and record medication use over the previous week. This visit is estimated to take less than 30 minutes.

.Visit 7 – 12 months post microfracture – Pain assessment and Medical review
You will complete online or in person pain and outcome score score questionnaires and record medication use over the previous 24 hours. You will attend a 12 month MRI. This visit is estimated to take less than 60 minutes. This will be your last official study visit. At your study doctor's discretion, you may be contacted after you finish the study to follow up on your treatment and any ongoing medical conditions.

Procedures
Adipose-derived stem cell harvest

Preliminary research on MSCs was done using bone marrow derived cells. Bone marrow harvest procedures are however painful and yield low numbers of MSCs. An alternative source of autologous adult MSCs – due to its abundance and ease of harvest (liposuction) - is adipose tissue.

Participants will be receive a course of a antibiotics (cephalexin or another sutiable antibiotic if allergic to cephalosporins – ie. doxycycline) to commence the day prior and for 4 days post liposuction. Whilst the relative risk of infection is low the use of antibiotic prophylaxis is common and accepted clinical practice. The area of abdominal liposuction will be infiltrated with local anaesthetic prior to the liposuction. Participants will not require a general anaesthetic.

The practitioner performing the lipoharvest will be appropriately certified to perform liposuction.

All patients will be reviewed 1 week after liposuction by the treating doctor. Participants will also be provided with the treating physician's contact details to discuss any concerns following the procedure.

Injections

Mesencymal Stem Cell Injections

Participants will receive autologous MSC injections at 1week and 6months post arthroscopic microfracture. Upon each visit, the knee will be prepared using standard sterile procedures. The area of injection site will be anaesthetised using local anaesthetic and then 100 million MSCs will be injected under ultrasound guidance into the knee joint,.

Intra-articular stem cell injections have been occasionally associated with self limiting discomfort. There will be no activity restriction requirements for participants following the injection.

Participants will be provided with appropriate analgesia (ie. paracetamol and codeine).

Pregnancy testing will be performed on all female participants prior to an MSC injection. Participants with a positive pregnancy test will be withdrawn from the study. The reason for withdrawal is due to lack of safety data on the use of stem cells in pregnancy. No adverse events have been documented in previous publications.

Participants will also be provided with the treating physician's contact details to discuss any concerns following the procedure

Possible benefits:

Whilst arthroscopic microfracture has been shown to be effective in treating cartilage defects, long term data indicates that it has a short functional lifespan and that benefits are not prolonged. Post operative injections of mesenchymal stem cells will potentially improve the resultant healing at the site of microfracture and therefore improve both pain and function for the short and long term and also prevent development of further joint degeneration/osteoarthritis.

Possible risks:

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 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. Participants will be receive a course of a antibiotics (cephalexin or another sutiable antibiotic if allergic to cephalosporins or have a history of anaphylaxis to penicillin) to commence the day prior and for 4 days post liposuction.
c. Bruising - participants may experience minor bruising at the site of liposuction.
d. Uneven skin surface over treated area of liposuction

Rare complications/risks :

a. drug toxicity to the local anaesthetic
b. fluid overload – low risk as only a minimal liposuction procedure
c. abdominal organ puncture
d. fat emboli : whereby fat is loosened and enters the blood through broken blood vessels. This can cause serious injury and can be fatal.

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 local anaesthetic.
b. Infection – participants will be monitored for adverse events such as infection. The risk of this occurring is low and all injections will be performed using sterile techniques
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.*

Mesenchymal Multipotenital Stromal Cell Therapy : Safety Data
Systematic review of published clinical trials indicates that MSCs therapy is safe. Importantly no association has been made between MSC 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. 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. MSC injections have also been occasionally associated with self limiting discomfort and swelling.

Culture Media
The culture media used in the isolation and expansion of stem cells is a bovine (cow) serum. Participants with a history of bovine allergy will be excluded from the study.

Medications
Post procedural analgesia including codeine may cause drowsiness. Participants must not drive or operate machinery whilst under the effect of these analgesics. Regular use of narcotic analgesics (including codeine) can lead to psychological and physical dependence and caution is advised.

Use of data and confidentiality:
Your personal details and identity will be known only by the study doctor, the principal researcher (Dr Jon Ford), 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 written on questionnaires that you fill in. You will therefore remain anonymous throughout the study.

The results of this study will be shared through journal articles and conference presentations. You will not be identifiable in any of these reports. It is possible that the data may be used for other research projects by members of the La Trobe University in the future to answer different research questions. This would only occur with the permission of the current researchers, and none of your personal or identifiable information would be given to other researchers.

All computer records relating to this study will be kept on password-protected computers of Dr Jon Ford and Dr Julien Freitag. All hard-copy records will be kept at the Study Doctor's clinic, and in a locked filing cabinet at La Trobe University, Bundoora, for a period of 15 years after publication. The raw data and computer files will then be destroyed.

Project results:
If you would like to know your individual results or the results of the trial overall, a summary of these will be available from Dr Ford upon request.

Follow-up procedures:
If you choose to participate in the trial, you will be required to fill out online questionnaires at 1 month, 3 months, 6 months, and 12months post surgery. If you do not have access to the online questionnaires they will be posted.

While your name will not appear on the questionnaire, they will be coded so we can tell if you have returned them or not. If you do not complete and return the questionnaires within one-week of receiving them, your Study Doctor or the administrator will contact you or one of the alternative contact people that you designated on your personal details form.

Participation is voluntary:
Participation in this research project is voluntary, and hence you are not obliged to take part. You are also free to withdraw from the project at a later stage if you change your mind.

If you choose not to participate, or withdraw from the project at a later stage, there will be no penalties for this decision. If you do not participate, or if you withdraw from the trial at a later stage, your Study Doctor will continue to see you at no out of pocket expense for any medical care relating to your involvement in the study.

Declaration of dual interests
Co-Investigator Dr Julien Freitag is a partner at Melbourne Stem Cell Centre – the clinic in which the treatment will occur.

Co-investigators Dr Julien Freitag, and Professor Richard Boyd are partners in Magellan Stem Cells.

Further questions or information:

Any questions regarding this project may be directed to the Investigator(s) Dr Jon Ford, Faculty of Health Sciences, on 0422 244 183 or j.ford@latrobe.edu.au or Dr Julien Freitag, Melbourne Stem Cell Centre on 9270 8000 or julien.freitag@mscc.com.au.

Complaints:
If you have any complaints or concerns about your participation in the study that the researcher has not been able to answer to your satisfaction, you may contact the Executive Officer, University Human Ethics Committee, Research Services, La Trobe University, Victoria, 3086, (P: 03 9479 1443, E: humanethics@latrobe.edu.au). Please quote UHEC application reference number HEC14-016.

Withdrawing from the project:
You have the right to withdraw from active participation in this project at any time. If you are unable to continue with the treatment for any reason, we would still value your responses on the follow-up questionnaires that we send to you. However, if you wish to take no further part in the project (including the follow-up questionnaires), you may withdraw from the project completely.

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.**