PARTICIPANT INFORMATION

Evaluation of Adipose-Derived Mesenchymal Stem Cells for the Treatment of Arthritis – A Prospective Case Series Data Collection.

Chief Investigators: *Dr James Wickham* (Lecturer, School of Biomedical Science, Charles Sturt University) & *Associate Professor Julien Freitag* (Clinical Director and Study Doctor, Melbourne Stem Cell Centre).
Co-Investigators: Professor Richard Boyd, Dr Kiran Shah, Dr Dan Bates, Dr Leesa Huguenin, Dr Matt Chamberlain, Megan Walton, Joshua Thomas.

Invitation
You are invited to participate in a research study that aims to explore the effectiveness of using your own stem cells to treat your arthritis.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. What is the purpose of this study?
The purpose of this study is to formally follow up and record the effectiveness of stem cell injections in the treatment of arthritis. 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 arthritis.

2. Why have I been invited to participate in this study?
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.

3. What does this study involve?
Participation in this study will require you to make a number of visits to the Melbourne Stem Cell Centre, undergo MRI scans and the filling out of online questionnaires. Each one of these tasks has been termed a visit and the details of what will happen at each visit are described below.

Visit 1 – Baseline Assessment (from 30min - 2 hours).
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 affected joint. Pregnancy testing will be performed on all females of child bearing age and 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 to be formally enrolled in the study. A baseline scan (MRI) – if not already done - will also be required prior to undergoing your scheduled therapy.

Visit 2 - Adipose Tissue Harvest Procedure (3 hours).
You will undergo a mini-liposuction to harvest stem cells. Approximately 20-100 ml of abdominal fat will be taken following local anaesthetic in filtration. 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. A blood sample (approx. 50 ml) from a vein at the elbow may be collected at the Melbourne Stem Cell Centre by the Study Doctor for the creation of a blood derived carrier media for the stem cells.

Visit 3 – Post Adipose Tissue Harvest Procedure (15 minutes).
You will be seen by the lipo-suction procedural doctor or clinic nurse as routine post-operative care at 1 week post-adipose tissue harvest procedure. You will then wait another 7 weeks for your stem cells to grow and be purified before your first stem cell injection.

Visit 4 – Week 0 – Stem Cell Injection 1 (from 15 - 60 minutes).
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 arthritic joint will be done under ultrasound or fluoroscopy guidance to ensure correct placement of the needle into the joint space.

Visit 5 – Week 4 – Pain Assessment (10 minutes).
You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours.

Visit 6 – Week 12 – Pain Assessment (10 minutes – online questionnaire
You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours.

Visit 7 – 6 months – 6 month Stem Cell Injection 2 (from 15 – 60minutes).
At this visit, you will receive the 6 month stem cell injection and complete pain score and outcome questionnaires. All injections into your arthritic joint 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. You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours.

Note: *The second stem cell injection is to be completed at approximately 6 months. Variation to this schedule is allowed in order to maintain appropriate research participant care and safety. The timing of the second injection will be recorded for purpose of documentation at time of study publication. The timing of the second injection does not influence the results of the stem cell therapy.*

Visit 8 – 12 months – Pain and Outcome Score Assessment (1 hour) + MRI scan.
You will receive a 12 month follow up MRI at this visit. You will also complete pain and outcome score assessments. This visit is estimated to take 60 minutes, plus the time required for the MRI.

Visits 9 to 14 – Pain and Outcome Score Assessment (10minutes)
You will complete online pain score and outcome questionnaires and record medication use over the previous 24 hours. These online questionnaires will be completed every 6 months until 4 years

of follow-up noting that you can withdraw consent to data collection beyond 12 months and also have the ability to withdraw consent to data collected up until 12 months.

*'**Note:** Where necessary to maintain research participant care and safety follow-up visits may be conducted remotely (online or by telephone consultation). In addition to this and for the same reason of ensuring participant care and safety follow-up testing may be done off-site at appropriately accredited sites if required.'*

4. Are there risks to me in taking part in this study?

All medical procedures involve some risk of injury. Listed below are the potentials risks and discomforts of your involvement in this study.

Risk 1 – Specimens.

Blood will be collected from a vein near the elbow. This may cause some minor discomfort with the initial insertion and possible minor bruising afterwards. Your blood 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 arthritis, 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.

Risk 2 – Non-compliance of Participant Responsibilities.

As a study participant, you are responsible for following the study directions and those of your study doctor. Failure to do this may put you at harm which is not something we want to see happen. Responsibilities include 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 and if you experience any illness or discomfort during the study, you should notify your study doctor.

Risk 3 – Lipoharvest Procedure.

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. Infection is possible, but the risk of this occurring is low. To safeguard against this, subjects will receive a dose of antibiotics prior to the liposuction procedure. Another risk factor for the liposuction procedure is bruising which you may experience (minor) at the site of liposuction. Note that medical doctors will perform all the procedures and they will have an equivalent of a Bachelor of Surgery/Bachelor of Medicine degree and will have a current medical registration and medical indemnity.

Risk 4 - Intra-articular Joint Stem Cell Injections.

Patients may experience some discomfort at the time of injection. Prior to injection the area will be anaesthetised using 2 mls of 2% xylocaine. Stem cell injections can be associated with a 'flare up' of pain for 1-2 weeks. This can be managed with appropriate pain relief. Participants will be monitored for adverse events such as infection from the injection. If infection does 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. Bruising at the injection site is possible as

well although this is unlikely. As with the lipoharvest procedure, medical doctors will perform all the injections.

Injections will be performed using ultrasound or fluoroscopy guidance. Ultrasound is not associated with radiation. The radiation dose of fluoroscopy guidance (either X-Ray or CT) is 3-10% or what you would naturally be exposed to each year.

Risk 5 – The Mesenchymal Stem Cell Therapy.
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 past or present malignancy is an exclusion criteria in this proposed study.

Risk 6 - 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 infection. All the laboratory staff handling the lipoaspirate and the cells will be well trained and experienced in aseptic techniques.

Risk 7 – Antibiotics.
There is a small risk of an infection with the lipoharvest procedure. A prophylactic oral antibiotic (Cephalexin 500 mg 4 times a day) commencing 24 hrs 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 is a necessary preventative measure to combat this possible infection. Those with an allergy to cephalosporins or a documented anaphylaxis to penicillin will be prescribed a suitable alternative antibiotic (i.e. Doxycycline). You should take pro-biotic/live culture preparations (i.e. yoghurt) during this time period to replenish the normal bacteria of the digestive tract.

Risk 8 - Pain Relief.
Participants will be prescribed suitable analgesic medication post procedures such as endone or paracetamol + codeine. There is a very small risk of drowsiness and opiate dependence with these drugs and hence you will only be given a limited script.

5. Are there benefits to me in taking part in this study?
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 joint replacement surgery.

6. How is this study being paid for?

All treatment and investigations performed are as a private patient and are not funded. Costs are met by each patient as this study is patient funded and Medicare or your private health insurer will not cover your treatment costs.

7. Will taking part in this study (or travelling to) cost me anything, and will I be paid?

Your involvement in this data collection study is voluntary. You will not receive any financial compensation for your involvement. Participation in this study will incur substantial costs to you. Cost of mesenchymal stem cell therapy is $7,000-$11,500 for a single joint - this includes day case admission, the lipoharvest fee, the treatment fee, the fee to Magellan Stem Cells to cover the isolation and expansion of your stem cells and the MRI imaging. Note that there are no additional costs to you within your 12 months of treatment.

8. What if I don't want to take part in this study?

Your participation in this study is entirely voluntary and hence if you wish not to take part in this study you are free not to participate at all.

9. What if I participate and want to withdraw later?

You may withdraw from this study at any time without penalty or loss of any rights or benefits to which you are otherwise entitled. If you decide to withdraw from the study you should contact your study doctor or his study staff on (03) 9270 8000. Furthermore, if you do decide to withdraw from the study you will still be able to continue to receive treatment. You may also 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.

10. How will my confidentiality be protected?

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, where possible, will be de-identified and not made available to the general public, however you will have access to your specific data. 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. It is foreseeable that participant anonymity will be difficult to maintain when the committee (the Chief Investigators of the study) are assessing aspects of the research – i.e. 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.anzctr.org.au 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.

11. What should I do if I want to discuss this study further before I decide?

If you would like further information about this project please contact the Study Doctor - Associate Professor Julien Freitag (Phone: 03 9270 8000) at the Melbourne Stem Cell Centre, Level 2, 116-118 Thames Street, Box Hill North, VIC.

12. Who should I contact if I have concerns about the conduct of this study?

Note that Charles Sturt University's Human Research Ethics Committee has approved this project. If you have any complaints or reservations about the ethical conduct of this project, you may contact the Committee through the HREC secretary:

HREC Secretary
Human Research Ethics Committee
Tel: (02) 6933 4213
Email: ethics@csu.edu.au

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.

CONSENT FORM

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- I agree to participate in the above research project and give my consent freely.
- I understand that the project will be conducted as described in the participant information sheet, a copy of which I have retained.
- I understand that this is a patient-funded study and that I will need to pay up front $7000-$11500.
- I understand that I am free to withdraw from the study at any stage but am aware that if I do withdraw after payment that there will be no refund of my money.
- I understand that the purpose of this research study is to improve the quality of medical care, and that it has also been explained that my involvement may not be of any direct benefit to me.
- I agree that I have been told that no information regarding my medical history will be divulged to unauthorised third parties and that the results of research data gathered from me may be published, provided that I cannot be identified.
- I consent to my GP being notified of my participation in this study and of any clinically relevant information noted by the study doctor in the conduct of this study.
- I understand that if I have any questions relating to my participation in this research, I may contact A/Prof Julien Freitag on email info@mscc.com.au

PRINT name _____

Signature _____**Date**_____