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| **PROTOCOL** | | | | | | |
| Full Title: Comparison of microfracture and Autologous Bio-scaffold Enhanced Chondrogenesis (ABEC) in treatment of osteochondral lesions of the talus: A prospective, randomized study.  Short Title: Microfracture and ABEC in Osteochondral Lesions of the Talus (MALT) | | | | | | |
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List of abbreviations

| Abbreviation | Explanation |
| --- | --- |
| ABEC  ADL  ADE | Autologous Bio-scaffold Enhanced Chondrogenesis  Activities of Daily Living  Adverse Device Event |
| AE | Adverse event |
| AOFAS | American Orthopaedic Foot and Ankle Score |
| AOT | Autologous osteochondral transplantation |
| BMI | Body Mass Index |
| CRF | Case Report Form |
| CTA | Clinical Trials Authorisation |
| CTU | Clinical Trials Unit |
| DMEC | Data Monitoring and Ethics Committee |
| FAAM | Foot and Ankle Ability Measure |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonisation |
| MACI | Matrix-induced Autologous Chondrocyte Implantation |
| MCID | Mean Clinically Important Difference |
| MOCART | Magnetic resonance Observation of CArtilage Repair Tissue |
| MRI | Magnetic Resonance Imaging |
| OAT | Osteochondral Allograft Transplantation |
| OCL | Osteochondral Lesion |
| QOL | Quality of Life |
| R&D | Research and Development |
| RCT | Randomised Control Trial |
| SAE | Serious Adverse Event |
| SF-12 | Short Form 12 |
| SOCRATES | Standardised Orthopaedic Clinical Research and Treatment Evaluation Software |
| SOP  SUSAR | Standard Operating Procedure  Serious Unexpected Serious Adverse Reaction |
| TSC | Trial Steering Committee |

# Background

## Injury and burden of the condition

An osteochondral lesion (OCL) is a defect in the cartilage and subchondral bone of a joint, most commonly related to trauma – either a single event or multiple episodes1. Osteochondral lesions of the talus occur in 70% of acute ankle sprains or fractures2. Lesions may occur without trauma. The natural history of OCL is unclear, but symptoms may include pain, locking, stiffness and swelling. Symptoms may limit the ability to walk, perform activities of daily living (ADLs) and participate in sports. Progression to symptomatic arthritis has not been conclusively proven. Non-operative management includes rest and splinting, including casting. 55% of symptomatic lesions do not respond to non-surgical management3.

## Existing knowledge

Although many surgical treatment options are available, the gold standard for lesions less than 15mm in diameter remains micro-fracture4. Micro-fracture exposes chondral lesions to mesenchymal stems cells from the bone marrow in an attempt to regenerate cartilage. Often this leads to fibrocartilage rather than hyaline cartilage. Traditionally rehabilitation has been cautious to prevent breakdown of the blood-clot containing stem cells5; however, Lee et al6 identified no difference in outcomes for patients who weight bear at two weeks and those who weight bear at eight weeks, in small to midsized OCLs of the talus. Autologous bio-scaffold enhanced chondrogenesis (ABEC) is a single stage procedure where, following preparation and microfracture, a scaffold is applied to the lesion to aid stabilisation of the stem cells and increase rates of chondrogenesis. There are different application techniques available with fixation methods including sutures or fibrin glue. Joint Rep™ (Oligo Medic Inc., Laval Quebec Canada) is an injectable preparation. This process has been studied in the knee with osteochondral lesions7, with better results in medium sized lesions at 5 years compared with microfracture alone. However, treatment recommendations for larger lesions in the ankle are less clear8, although there are options which include:

Autologous osteochondral transplantation (AOT)

Osteochondral allograft transplantation (OAT)

Matrix-induced autologous chondrocyte implantation (MACI).

All have shown positive short and medium term9 outcomes, however, long term benefit has not been conclusively studied10.

A single study reviewed the use of a clot stabiliser with microfracture and microfracture alone in talus OCLs, identifying no statistically significant difference at 5 years for function, pain or satisfaction. This study was not randomised, but mean results for all areas showed higher absolute numbers in favour of the bio-scaffold11.

MRI has been shown to be highly sensitive and specific for diagnosis of OCLs of the talus12, however it may overestimate the size of the defect due to bone oedema13. The utility of post-operative MRI for assessment of operative success in OCLs of the talus is still controversial. Comparison of autograft and allograft techniques of osteochondral transplant show a correlation with better function and lower rate of MRI proven cartilage degeneration in autograft techniques14. However, in a review of one particular scaffold technique there was no correlation between American Orthopaedic Foot and Ankle Score (AOFAS) scores and magnetic resonance observation of cartilage repair tissue (MOCART) scores15. A further study in OCLs in ankles suggested that cyst formation on post-operative MRI scan did not correlate with poor short-term function16. However, in a review of patients with OCLs in the knee, a post-operative MRI scan did show a correlation between a number of subsets of MOCART scores (degree of defect fill, surface of repair tissue, and overall signal intensity) and long-term clinical function17.

## Hypotheses

The aim of this study is to compare 1-year functional outcome of patients treated with microfracture alone versus microfracture AND JointRep with symptomatic osteochondral lesions of the talus.

Study hypothesis:

In patients with symptomatic OCLs of the talus, augmentation of microfracture with JointRep will provide better outcomes in terms of function, pain, ADLs and sport at 1 year following surgery.

Null hypothesis:

There is no difference in clinical outcome between microfracture and microfracture AND JointRep at 12 months.

## Need for a trial

To date there has been one single cohort study comparing microfracture and autologous bio-scaffolds in osteochondral injuries of the talus. This was not randomised and had a low sample size. Results from this study suggested there was no statistically significant difference between groups at 5 years11. However, there have been other studies that have shown positive functional outcomes and pain scores in patients treated with this process18-22. It is currently unclear what the positive predictive value of post-operative MRI is on medium to long term function.

# TRIAL DESIGN

## Trial summary

Design and conduct a prospective multi-centre randomised control trial (RCT) to evaluate the clinical effectiveness of microfracture AND JointRep versus microfracture alone (duration: twenty-four months defined by recruitment rate).

Research Design and Questions:

A multi-centre prospective RCT, in multiple orthopaedic and trauma hospitals beginning in New Zealand and Australia, with the possibility of extension to North America and the European Union. Each centre will be trained in the use of Joint Rep and assessed for suitability of inclusion in this study.

What is the throughput of eligible patients at each participating site?

What number of eligible patients consent to be randomised?

What are the functional outcome scores and difference at 3, 6 and 12 months (primary aim)?  
Is there a radiological difference in cartilage quality at 12 months (secondary aim)?   
What is the frequency and difference in post-operative complications?

What are the longer-term outcomes at 2 and 5 years post operation?

Do the longer-term outcomes correlate with cartilage quality on MRI scan at 12 months?

## Patient selection

Inclusion criteria:

* Symptomatic osteochondral lesion of the talus where microfracture has been offered, with at least 6 months of non-surgical management, as confirmed on MRI, in patients with skeletally mature ankles to aged 60 years old.
* Able to consent to trial inclusion
* Medically fit for surgery

Exclusion criteria:

* Lesions too small to be considered for microfracture or a specific contra-indication to microfracture
* Declared intolerance or allergy to crustaceans or D-glucosamine
* Bipolar lesions (kissing lesions of the tibial plafond and talus)
* Diffuse arthritic changes
* Previous ankle operation
* Pregnancy
* Neuromuscular disorders
* Metabolic arthropathy
* Active infection23
* Self-funded surgery

Sample Size:

Power calculations utilise data from a similar population in a previous study with outcome measures performed at 2 years, so are approximate. A mean AOFAS hindfoot score of 83.6 (+/- 13.6) was found in patients treated with a bio-scaffold22, this scoring system is detailed in Appendix 8.1. Scaled minimally clinically important difference is an AOFAS score of 6.924. Utilising this as the allowable difference and with a two-sided equality power calculation, and decision criteria of Alpha equals 5% and Beta error equals 20%. A sample size of 148 total patients was suggested25, factoring for patient drop-out, 85 patients in each group will be recruited. Whilst other independent studies may have been used for comparative means patient groups, surgical techniques and follow-up were heterogenous, rendering direct comparison inadequate.

Recruitment:

Patients will be identified by the orthopaedic surgeon who initially assesses each patient upon presentation, or a research associate/nurse, at the included study hospitals. If the patient is deemed suitable for inclusion then they will be provided with the trial information and either consented; for inclusion and both procedures, at this clinic appointment or at a subsequent date if they require time for consideration and discussion with whanau. Patients will be required to undergo a pre-operative MRI scan of the affected limb for operative planning as per the surgeon’s standard practice. The enrolled study hospital orthopaedic departments will receive appropriate study information material to allow study implementation. Recruitment will be consecutive and there will be no additional exclusions beyond those detailed above.

Randomisation and Blinding:

Randomisation will be generated using a 1:1 randomisation sequence, which will be computer-generated by an independent on-line randomisation service. The treatment allocation will be obtained by research associate/nurse or surgery via accessing the online randomisation a minimum of one week prior to the day of surgery. Randomisation will not be stratified by institution.

It will not be possible to blind the clinician administering the intervention but attempts will be made to blind the patient receiving the intervention, this may not be possible due to differences in post-operative management. Additionally, analysis and data interpretation will be conducted on a blinded data set.

## Study Protocol

Planned Interventions:

At each participating centre, the person administrating the intervention will be a trained orthopaedic surgeon or designated registrar.

As a pragmatic prospective study, to ensure equipoise and allow better generalizability, exact surgical technique will be performed at the discretion of the operating surgeon within the following guidance, diagnostic ankle arthroscopy using medial and lateral portals. Lesion debrided with subsequent creation of stable smooth surrounding articular surface. Microfracture performed with an awl26. The subchondral plate is plate punctured 3-4mm apart, from the peripheral to the centre of the lesion. Additional procedures performed as required.

In randomised patients, JointRep to be utilised as per the manufacturer instructions: JointRep prepared during arthroscopy. The defect localised with a 14-gauge needle. The inflow irrigation is stopped, the arthroscope removed but the sleeve is left in. An air circulation is created inside the joint with an inflow sleeve and an outflow suction cannula which is allowed to run for a few minutes. Arthroscope returned to joint. Surgeon injects the desired volume of JointRep™ into the defect under direct visualization. After 2-3 minutes of immobilisation of the ankle, the joint is then closed.

Postoperative Management:

Post operatively up to 6 weeks of immobilisation and non-weightbearing is allowed. This is at the discretion of the operating surgeon. This will allow patients to be blinded, however, double blinding is not possible. Post-operative instructions must be recorded in the data set at the time of operation. Confounding is possible given the possible variability of immobilisation and weight bearing restrictions, however, the authors felt this would increase patient recruitment and reflect true practice. Patients will return for review at 2, 6, 12, and 52 weeks. Patients may also be reviewed at additional times as per the operating surgeons standard practice.

Outcome Measures:

The primary outcome is the Foot and Ankle Ability Measure (FAAM) at 12 months completed by the patient in the hospital setting. This is a validated tool for assessment of ankle function, with subsets for activities of daily living and sports, which would evaluate the functional demands in our expected population27 and is detailed in Appendix 8.2. A strong correlation has also been shown with the SF-1228. The minimal clinically important difference (MCID) for sports is 9%, for ADLs 8%.

Whilst other measures are available, FAAM provided a more relevant evaluation of our study population than some29,30 or are no longer recommended in isolation for research31.

Secondary measures will include range of motion, VAS pain scores, UCLA functional score and the rate of complications.

Patients will be clinically evaluated pre-operatively and at 3 and 12 months. Post-operative MRI scan will be performed at one year. Additional FAAM questionnaires will occur via email link or telephone conversation at 6, 24 and 60 months.

Pre-operative measures include:

* Age,
* Chronicity,
* BMI
* Aetiology (traumatic/atraumatic) – as defined by treating surgeon
* Smoking status (current, recent ex (<less than 3 months), ex <3/12),
* Gender,
* Ethnicity32
* Laterality,
* Berndt and Harty Classification33
* MRI Hepple classification34,
* MRI lesion location35,
* MRI recorded size of lesion4
* Interval between symptoms onset and time of surgery

Peri-operative factors include –

* Size and location of lesion
* Additional procedures performed
* Post-operative immobilisation and weightbearing protocol

As well as primary and secondary outcomes measures, post operation complications will be recorded. These include wound infection, venous thromboembolism and further surgical procedures.

Pre-operative imaging will be evaluated by an assessor blinded to intervention. Image guided grading of lesions will be evaluated by the previously utilised techniques 4,33,34. Each assessment will be repeated and agreement calculated. Arthroscopy size and location of lesion including depth will be performed by the operating surgeon and will utilise a standard sized probe for scale referencing. This process cannot be blinded, but sampling can occur with assessment of intra-operative arthroscopic photographs with a standard probe present for scale, and transfer of images to a research assistant.

Assessment technique

All imaging will be reviewed by a qualified musculoskeletal radiologist who is blinded to the surgical procedure and clinical outcome scoring. Images will be grouped, placed into a randomly ordered list and repeated after an appropriate interval to evaluate agreement.

Pre-operative radiographs will be utilised for Berndt and Hardy classification, as modified by Loomer36, described as:

Stage I: Subchondral compression (fracture)

Stage II: Partial detachment of osteochondral fragment

Stage III: Completely detached fragment without displacement from fracture bed

Stage IV: Detached and displaced fragment

Stage V: Subchondral cyst present

Pre-operative MRI will be utilised to evaluate for Hepple classification34, this is as follows:

Stage I: Articular cartilage injury only

Stage IIA: Cartilage injury with bony fracture and oedema (flap, acute)

Stage IIB: Cartilage injury with bony fracture and without bony oedema (chronic)

Stage III: Detached, nondisplaced bony fragment (fluid rim beneath fragment)

Stage IV: Displaced fragment, uncovered subchondral bone

Stage V: Subchondral cyst present

Lesion location will be reviewed utilising the description by Elias et al35, which is as follows:

“The articular surface of the talar dome was divided using a three-column by three-row grid into nine zones equal in area in an axial plane. The nine equal zones were assigned numerical identifiers from 1 to 9 beginning with the most anterior and medial region, and proceeding laterally, then posteriorly. Zone 1 was the most medial of the three anterior zones; zone 3 was the most lateral of the anterior three zones. Zone 5 was the mid talar dome with regard to both transverse and anteroposterior locations and zone 9 was the most lateral of the posterior three zones. The surface area of each zone of the articular talar dome was identical.”

Sizing will be calculated by the MRI technique by Choi et al4, which is summarised as:

Coronal length (horizontal extension measured from the coronal image),

Sagittal length (horizontal extension measured from the sagittal image),

Depth (vertical extension measured from the sagittal image),

Area - as calculated by the ellipse formula, from coronal and sagittal length:

A = abπ= coronal length × sagittal length × 0.79

Intra-operative

Evaluation as per Chuckpaiwong et al37, with grouping of locations into medial, lateral and bilateral. Diameter will be assessed by averaging the transverse and longitudinal diameters.

Post-operative MRI

Postoperative MRI will be obtained with use of fast-spin-echo proton-density sequences to analyse articular cartilage. Assessment of the cartilage around the graft site will utilise a modified Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) 2-D scoring system, this is detailed in Appendix 3. This involves an analysis of nine pertinent variables:

the degree of filling of the defect,

the integration to the border zone,

the description of the surface and structure,

the signal intensity,

the status of the subchondral lamina and subchondral bone,

the appearance of adhesions

and the presence of synovitis38.

Cyst formation to be measured along 3 orthogonal axes and the maximum diameter used. The cyst location will be categorized relative to the pre-operative OCL as either peripheral to, inferior to, or within. Chondral wear or fissures in the graft to be similarly assessed with use of postoperative MRI.

Additional imaging will be performed at the discretion of the treating surgeon if patients has persistent pain.

Follow-up:

As per routine practice, all patients will be clinically assessed at 2 weeks; 6 weeks; 3, 6 and 12 months (+/- 1 week) post treatment. This will be conducted by the operating surgeon in their clinic. At these time points, in co-ordination with a research officer via telephone, the above patient reported outcome measures will be collected, as well as patient reported complications.

Following approval by CCDHB data security team for the Socrates database that is hosted on the CCDHB server to be web-enabled, for those participants who consent, the 3, 6 and 12 month data collection will occur via a secure online survey that is accessed via a link sent directly to the participants email from the Socrates database. After these time points the outcomes will then be collected by the online survey system and / or telephone by the research associate/nurse.

Statistical Analysis and Health Economics:

This data will be presented using standard methods for statistical summaries of discrete and continuous data sets.

Standard statistical summaries (e.g. medians and ranges or means and variances, dependent on the distribution of the outcome) and graphical plots showing correlations will be presented for the primary outcome measure and the secondary outcome measures. Baseline data will be summarized to check comparability between treatment arms, and to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent. The main analysis will investigate differences in the primary outcome measure between the two treatment groups on an intention-to-treat basis at 12 months post-recruitment. The significance in responses between treatment groups will be formally assessed using an independent samples t-test; based on an assumed approximate normal distribution for this outcome measure. Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). Estimates of treatment effects will be presented with 95% confidence intervals.

T test analysis of mean values between the two groups will be recorded. Average time to returned employment will also be compared using a test.

## Recruitment

All patients will be invited to take part in the study by the orthopaedic surgeon who initially assesses the patient. They will discuss the study and the possible operative interventions. All patients will receive a patient information sheet from the research team detailing the purpose of the study and information regarding trial procedures, the requirements of the study, and the potential risks involved. They will be encouraged to ask questions and to discuss their decision to participate in research with family/whanau members. Due to the non-acute nature of the injury, a decision will not be required immediately, however it will be required in a timely fashion to allow for randomisation and planning of the designated operation.

Following informed consent, if the patient is willing, they will then sign and date an informed consent form before conducting any procedure specifically for the trial. Once the patient has agreed to participate in the study and signed the consent form, the patient will be registered with the study coordinator and allocated a unique study number. Individuals who decide not to participate will be treated by the standard surgical approach as the discretion of the surgeon caring for each patient.

The patient outcome questionnaires will primary occur via an online link but may take place in the outpatient clinic setting if patients are required to attend, or administered via the telephone at the above designated time points. Patients and whanau will be given the opportunity to ask questions of the clinical team.

Written informed consent for entry into the trial will be obtained prior to randomisation. Subjects will be randomised sequentially.

Randomisation procedures will be accessed by the research associate through a telephone/online service. At this point, the research associate will be asked to confirm eligibility details and consent procedures have been followed, prior to the allocation being administered. The randomisation sequence will be designed in conjunction with the trial steering committee, with specific advice being sought from the trial statistician. Randomisation will occur a minimum of one week prior to surgery to allow adequate time for operative planning.

## Post-randomisation withdrawals and exclusions

Subjects may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a subject explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial.

Subjects may be withdrawn from the trial at the discretion of the Investigator due to safety concerns.

# adverse event management

## Definitions

Adverse event reporting has been guided by ISO 14155 Annex F39.

### Adverse Events (AE)

An adverse event is defined as any untoward medical occurrence in a subject which does not necessarily have a causal relationship with this treatment.

All patients at each follow-up appointment will be asked if there have been any medical events since the last review. The Chief investigator and trial co-ordinator will then determine seriousness and requirement for onward reporting.

Adverse Device Events (ADE)

An adverse device event is any untoward event that is related to the insertion of the chosen medical device. This includes insufficient or inadequate instructions for use, deployment, installation or operation and any malfunction of the medical device. This also includes any event related to use for use error or intentional misuse of the medical device.

All surgeons will report any ADE on each case. The Chief investigator and trial co-ordinator will then determine seriousness and requirement for onward reporting and further actions required for surgeon or centre involvement with trial.

Serious Adverse Events

A serious adverse event is an AE that fulfils one or more of the following criteria:

* Results in death
* Results in serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic diseases, or

3) in-patient or prolonged hospitalisation, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

The causality of SAEs will be assessed for whether this represents a Serious Adverse Event or a Serious Adverse Device Event. This will be recorded on the SAE form. The chief investigator will assess whether the SAE is an expected event (i.e. a known potential complication of the procedure) or a Serious Unexpected Serious Adverse Reaction (SUSAR).

Events that are expected in this trial population and are being collected as outcomes of the trial include the following:

* Infection: deep and superficial
* Deep vein thrombosis/embolus
* Nerve injury
* Further surgery

These events will not be reported as SAEs

## Reporting SAEs and SUSARs

All SAEs that occur between trial entry and 30 days after the end of the trial period will be reported.

SAEs and SUSARs will be reported using the SAE form in the patient’s CRF during the first two follow up occasions, and then by postal follow-up for the remaining follow up time points. The Principal Investigator in each centre must report any SAEs to the Trial Co-ordinating Centre within 24 hours of them becoming aware of it. The SAE form should be completed and faxed. The trial co-ordinator will liaise with the Investigator to compile all the necessary information. The Trial Co-ordinating Centre is responsible for reporting adverse events to the sponsor and ethics committee within the required timelines.

## End of Trial

The trial will end when 170 patients have been recruited and completed their 12-month follow-up. 170 patients have initially been chosen to ensure all outcome sample sizes reach adequate power to produce significant results.

The trial will be stopped prematurely if:

* Mandated by the Ethics Committee
* Following recommendations from the Trial Steering Committee
* Funding for the trial ceases

The Health and Disability Ethics Committee (HDEC) will be notified in writing if the trial has been concluded or terminated early.

# Data ANalysis

Personal data collected during the trial will be handled and stored in accordance with the Health Information Privacy Code.

Patients will be identified using a unique trial number only and will be anonymised at the point of transcription.

## Data collection and management

The Case Report Forms (CRFs) will be designed by the Trial Co-ordinator in conjunction with the Chief Investigator, Statistician and with the help of the Standardised Orthopaedic Clinical Research and Treatment Evaluation Software (SOCRATES). This is a program well utilised particularly for Orthopaedic outcomes measures and data collection.

The research associate at each centre will collect the data for the RCT. The original de-identified copies will be sent to and stored in the Primary Study Centre (Wellington Regional Hospital) Research Facility. The data will be entered into the SOCRATES database and subject to audit through institutional mechanisms and the funding body. During initial consent procedures, multiple contact details will be collected. In the event of a patient not responding the research team will follow this up with a telephone call and letter re-scheduling the appointment/resending the questionnaires. In the event of a second non-response a further telephone call and appointment/re-sending the questionnaires will occur, followed by a third and final attempt. These will occur at four weekly intervals.

To an attempt to increase patient response rate, while also trying to lessen the clinic burden for both patient and staff, patient reported outcomes will be collected via an online secure survey system, that is generated from the SOCRATES database already in use. A specific and secure survey link is emailed to each individual. The survey will be automatically emailed out at the correct time points, and the encrypted data is then sent back to the SOCRATES database that is stored within the study’s primary hospital (CCDHB), upon patient completion for auto-population of the data set points relative to that individual’s study number. This ensures no data is stored off site

In the event of no response, the alternative contact number provided at the point of consent will be phoned. If there is no response from this contact the patient will be recorded as lost to follow up.

## Database

The database will be set up by the chief investigator and all specifications (i.e. database variables, validation checks, screens) will be agreed between the members of the trial steering committee. All data will be stored securely online using the SOCRATES database.

## Data Storage

All essential documentation and trial records will be stored by the primary study investigator and/or primary study research associate/nurse, in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

## Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial.

# Trial organisation and oversight

## Ethical conduct of the trial

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICHGood Clinical Practice and applicable regulatory requirements.

The protocol, final version of the Patient Information Sheet and Consent Form and all written information given to trial subjects will beapproved and given a favourable opinion in writing by an Ethics Committee as appropriate.

## Sponsor

Participating hospitals will act as co-sponsors to this study. Additional sponsorship is yet to be confirmed.

## Indemnity

Standard indemnity covers health service staff, medical academic staff with honorary contracts, and those conducting the trial.

## Administration

The trial will be co-ordinated from within the research group, who will be responsible for the day-to-day co-ordination and for the clinical aspects.

## Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as a ‘lay’ representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial, will take responsibility for:

* + Major decisions such as a need to change the protocol for any reason
  + Monitoring and supervising the progress of the trial
  + Reviewing relevant information from other sources
  + Informing and advising on all aspects of the trial

## Essential Documentation

A Trial Master file will be set up and held securely at the primary research co-ordinating centre (Wellington Regional Hospital). This will require password access and will be controlled by the trial co-ordinator will include data and supporting documents with identification and version history.

As adapted from ISO 1415539 Annex E, documents required prior to starting clinical investigation are:

* Clinical investigation plan – Trial protocol including design and procedures
* Investigation brochure – Instruction for indications and device use
* Ethics committee correspondence – Confirms ethical approval at local and national level
* Financial agreements – Demonstrates understanding of responsibilities and costing
* Case report forms – Data from each subject – this includes initial identification, results and all follow-up. Consent forms from each subject are included
* Adverse events forms – Documents all events as required by standard.
* Site/Training assessment – Ensures each site reaches pre-defined standard for inclusion and additional investigators are qualified and appropriately supported in device use.
* Log of principle investigator and members of investigator team at each site – Documents attribution of responsibilities at each site, including title, signature and responsibilities
* List of investigation sites – Evidences who is conducting investigation with names and addresses.

Amendments created during the trial will be logged, this includes additional correspondence with local or national ethics committees, additional sites or investigators and protocol or reported changes.

Details of randomisation, inclusion and exclusion will be created during the trial. A master file of included subjects and subsequent de-identification will be created and stored securely, so anonymised data is utilised for analysis and subsequent review.

# Dissemination and publication

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, physiotherapists and researchers from across NZ and Australia. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with standards for reporting trials and lay representatives on the TSC will work in collaboration with the chief investigator to produce lay summaries, which will be distributed by relevant clinical interest groups through website, meetings and conferences.

# Financial support

Funding is yet to be confirmed.

# Appendices

## AOFAS Score Ankle - Hindfoot Scale (100points Total)

**I Pain (40 points)**

None 40

Mild, occasional 30

Moderate, daily 20

Severe, almost always present 0

**II Function (50 points)**

Activity limitations, support requirement

No limitations, no support 10

No limitation of daily activities, limitation of recreational activities, no support 7

Limited daily and recreational activities, cane 4

Severe limitation of daily and recreational activities, walker, crutches, wheelchair, brace 0

Maximum walking distance, blocks

Greater than 6 5

4 – 6 4

1 – 3 2

Less than 1 0

Walking surfaces

No difficulty on any surface 5

Some difficulty on uneven terrain, stairs, inclines, ladders 3

Severe difficulty on uneven terrain, stairs, inclines, ladders 0

Gait abnormality

None, slight 8

Obvious 4

Marked 0

Sagittal motion (flexion plus extension)

Normal or mild restriction (30°or more) 8

Moderate restriction (15° - 29°) 4

Severe restriction (less than 15°) 0

Hindfoot motion (inversion plus eversion)

Normal or mild restriction (75% - 100% normal) 6

Moderate restriction (25% - 74% normal) 3

Marked restriction (less than 25% normal) 0

Ankle – hindfoot stability (anteroposterior, varus - valgus)

Stable 8

Definitely unstable 0

**III Alignment (10 points）**

Good, plantigrade foot, midfoot well aligned 15

Fair, plantigrade foot, some degree of midfoot malalignment observed, no symptoms 8

Poor, nonplantigrade foot, severe malalignment, symptoms 0

**Total=100**

American Orthopaedic Foot and Ankle Society

**8.2 Foot and ankle ability measure (FAAM)28**

**Activities of Daily Living Subscale**

Please answer **every question** with **one response** that most closely describes your condition within the past week. If the activity in question is limited by something other than your foot or ankle mark “Not Applicable” (N/A).

Because of your foot and ankle how much difficulty do you have with:

No Slight Moderate Extreme Unable N/A

Difficulty Difficulty Difficulty Difficulty to do

Standing

Walking on even ground

Walking on even ground

without shoes

Walking up hills

Walking down hills

Going up stairs

Going down stairs

Walking on uneven ground

Stepping up and down curbs

Squatting

Coming up on your toes

Walking initially

Walking 5 minutes or less

Walking approx. 10 mins

Walking 15 mins or more

Home responsibilities

Activities of daily living

Personal care

Light to moderate work

(standing, walking)

Heavy work (push/pulling

climbing, carrying)

Recreational activities

How would you rate your current level of function during your usual activities of daily living from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities.



### 0 100

**Foot and Ankle Ability Measure (FAAM) - Sports Subscale**

Because of your foot and ankle how much difficulty do you have with:

No Slight Moderate Extreme Unable N/A

Difficulty Difficulty Difficulty Difficulty Difficulty to do

Running

Jumping

Landing

Starting and

stopping quickly

Cutting/lateral

movements

Ability to perform

activity with your

normal technique

Ability to participate

in your desired sport

as long as you like

How would you rate your current level of function during your sports related activities from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities?



### 0 100

Overall, how would you rate your current level of function?

Normal Nearly Normal Abnormal Severely Abnormal

**8.3. 2D MOCART Score**

Defect fill Subchondral bone exposed 0

Incomplete < 50% 5

Incomplete > 50% 10

Complete 20

Hypertrophy 15

Cartilage interface Complete 15

Demarcating border visible 10

Defect visible < 50% 5

Defect visible > 50% 0

Surface Surface intact 10

Surface damaged < 50% of depth 5

Surface damaged > 50% of depth 0

Adhesions Absent 5

Yes 0

Structure Homogeneous 5

Inhomogeneous or cleft formation 0

Signal intensity Normal 30

Nearly normal 10

Abnormal 0

Subchondral lamina Intact 5

Not intact 0

Subchondral bone Intact 5

Granulation tissue, cyst, sclerosis 0

Effusion Absent 5

Yes 0

Total points 100

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