# A Cohort Study of Bioabsorbable Screws for Syndesmosis Fixation in Ankle Fracture

# *SYNFIX* trial

## Aberdeen Royal Infirmary

# Study contact information

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|---|---|
| Protocol Number: | 7 |
| Protocol Date | 04/07/2022 |
| Principle Investigator: | Prof Alan Johnstone, Aberdeen, Scotland UK |
| Investigators: | Mr Harry Sargeant<br>Miss Mariam Sattar |

**Investigator's Statement**

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; modifications to the study are acceptable only if they are mutually agreed upon protocol amendment as approved by the sponsor and ethics review board. I agree to await ethics review board approval of the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrollment in the study, to collect and record data as required by the protocol and case report forms, and to maintain study documents for the period of time required.

| **Investigator Signature** | **Date of Signature** |
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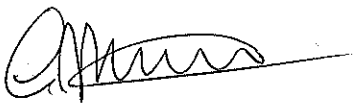
|  | 6/7/22 |

# Introduction

Ankle fractures represent about 9% of fractures presenting to an orthopaedic service.[1] Although suprasyndesmotic injuries represent approximately 10% of these injuries, unpredicted syndesmotic instability has been demonstrated in 33% of all external rotation ankle fractures.[2,3] Syndesmotic disruption has been demonstrated in 39% of unstable Weber B ankle fractures.[4] The syndesmosis is a complex ligamentous arrangement which is crucial in stabilising the ankle mortise, whilst allowing some movement during plantar and dorsiflexion.[5]

Surgical management and anatomical fixation of these injuries is the accepted gold standard treatment due to the incidence of post operative arthritis and poor outcome with mal-reduction or missed syndesmosis injury.[6] Cadaveric studies have demonstrated a reduction in tibiotalar contact area of 45% with one millimetre of talar lateral displacement.[7] Options for syndesmotic fixation vary and is an ongoing topic for debate. Recent surveys have shown wide variation in practice, with use of one or two 3.5 or 4.5 mm screws, engaging three or four cortices as the most common options. A high proportion of surgeons then routinely remove these at 3 months.[8,9] Routine removal of metallic screw fixation is another debated topic, however, and there are no randomised controlled trials looking at this question. Screw breakage is common, however there is no evidence to suggest this results in worse outcome, on the contrary it may be that intact screws are more problematic and require removal.[10] A general review of this literature concluded that routine removal is probably not indicated, and that the incidence of this is decreasing however still commonplace.[11] Hardware related pain can be seen in 31% of patients and which may explain the high incidence of removal, however improvement following hardware removal can occur in only 50% of patients.[12] Furthermore removal of syndesmosis screws has been shown to have a relatively high complication rate of 22.4%.[13] This explains some of the desire to find alternative options for fixation including bioabsorbable screws and suture button methods.

# Evidence for Bioabsorbable screws

Bio-absorbable screws have been shown to have similar biomechanical strength when comparing 5mm tri-cortical single screw fixation of the syndesmosis.[14] Equal fatigue and failure strength has also been shown with 4.5mm screws.[15]

Three small case series have reported use of these screws with good or excellent outcomes, and maintenance of mortise reduction (n=7,4 and 23).[16,17,18] Sinisaari et al showed no significant difference in outcome in 18 patients treated with bioabsorbable screws compared with 12 treated with standard metallic screw fixation.[19] Thodarson et al showed no significant difference in a prospective randomised trial between the two methods of fixation in 32 patients (PLA).[20] Kaukonen et al reported higher rates of patients returning to previous pre-injury activity levels, and less swelling with bioabsorbable screw fixation (PLLA) in a randomised trial of 38 patients.[21] Sun et al found a higher rate of foreign body reaction in those treated with bioabsorbable screws (PLLA) in a randomised trial of 168 patients, however functional recovery was similar.[22] A meta-analysis on these papers found no significant difference in functional outcome, or complication rate, however overall higher complication rates with bioabsorbable screws.[23]

The studies mentioned above have used bioabsorbable screws composed of either Polylactide acid (PLA), or polylevolactic acid (PLLA). The logic behind the design of these screws is that they undergo hydrolysis into lactic acid and glycolic acid which in turn are further broken down and excreted by the body. PLA and PLLA lose their mechanical resistance from 3 months to 1 year, with PLLA degrading slower the PLA.[24] PLLA can have a resorbtion time of over 5 years and there has been question to whether this can even be classified as bioabsorbable.[25] There has been concern historically with foreign body reactions, sterile abscess formation, sinus tract, fistula formation and osteolysis relating to some bioabsorbable implants, particularly PGA screws which can have a faster resorbtion time of 4-8 weeks.[26]

This study proposes to use a 5$^{th}$ generation bioabsorbable screw (Activascrew™, Bioretek) which is a co-polymer of PLLA and PGA; poly L-lactide-co-glycolide (PLGA). This should maintain mechanical strength for at least 8 weeks and bioresorb within 2 years.[27] Modulus of stiffness is similar to bone and allows gradual transfer of load during resorbtion. This is ideal for fixation of the syndesmosis, allowing for healing in a reduced position, then undergoing resorbtion to allow the small increments of movement that happen normally at the syndesmosis and removing the need for removal of metalware in a second operation.

# Study Aim

**Primary objective**

- To assess syndesmosis fixation and maintenance of reduction, with bioabsorbable screws, measured with CT scanning immediately post operatively and at one year post operatively.

**Secondary objectives**

- To identify patient reported outcome scores in the first year after the injury
- To identify the length of procedure
- To identify the duration of image intensifier use
- To measure complication rates in the first year after injury
- To measure range of movement and functional scoring
- To measure pain scores in the first year after the injury
- Weight bearing distribution test

# Surgical Technique

The operation requires the patient positioned supine with a sandbag beneath the ipsilateral buttock to internally rotate the leg to permit the ankle and foot to sit in neutral. Appropriate antibiotics as per local guidelines should be administered prior to insufflation of a tourniquet. Fluoroscopy is required throughout the procedure and should be positioned on the contralateral side to the injured limb to improve the access for the surgical team.

Depending on the injury type the fibula may or may not require fixation (maissoneuve or weber B/C type injury). This will be performed if necessary via a direct lateral approach to the fibula, and fixation as per surgeon preference appropriate for the fracture configuration. Typically a lag screw and one-third tubular neutralisation plate is used. Plates should be applied to the posterolateral surface of the fibula to permit passage of the syndesmosis screw through the plate and for increased mechanical stability. Following this the syndesmosis will be reduced with the foot plantigrade using large pointed reduction forceps with or without a K-wire. Medial malleolar fixation, if required, is performed after fibula fixation.

**Bio-absorbable screw fixation**

A single 4.5 mm fully threaded Activascrew™ (2094913CE01) is placed through four cortices if the fibula fracture is being fixed, through the plate if feasible. Two are used in the case of high fibula or maissoneuve injuries. These will all be through four cortices. A countersink may be used. The screws should be placed parallel to the tibial plafond, 2-4cm proximal to the tibio-talar joint and 30° from posterior to anterior. In the case of fibula

fixation this should be though the plate if feasible. The reduction of the syndesmosis and appropriate placement of the positioning screw(s) should be checked intra-operatively with fluoroscopy. The syndesmosis is reduced, using reduction forceps. A hole is drilled with the 3.5mm drill, then tapped with the 4.5mm tap and measured. The Activascrew™ holder and screwdriver are used to pick up and insert the desired screw. Once the screw is in position the insertion adapter is removed and discarded.

**Standardised rehabilitation protocol**

Post operatively the patient remains non weight-bearing in a Plaster for a total of 6 weeks with a cast change, wound check and removal of sutures at 2 weeks. Following this the patient would then remain partial weight bearing in a protective boot for a further 6 weeks. The patients should be prescribed 6 weeks of Low Molecular Weight Heparin for venous thromboembolic prophylaxis as per local protocol.

# Study Design

Please see appendix 1 for information on how the study will be run during the COVID-19 pandemic.

**Sample size considerations**

A total number of 40 patients should be sufficient to assess the outcome of fixation using this device.

**Patients selection and enrolment**

Patients will be thoroughly screened to assess their suitability for the study and must fit the inclusion and exclusion criteria.

**Inclusion criteria**

- Patient has a Weber C fibula fracture with or without a medial malleolus fracture and evidence of radiological syndesmotic widening on intra-operative stressing
- Patient has a Weber B fracture with evidence of syndesmosis widening radiologically on stressing intra-operatively
- Patient has a maissoneuve type injury with evidence of syndesmotic diastasis
- Patient mobilises independently, with or without aids.

- Patient has given formal consent to be involved in the trial and has completed the study consent form
- Patient is likely to comply with study requirements
- Age range of patients in the study is 18-64 (inclusive).

**Exclusion criteria**

- Immobility
- Presence of a posterior malleolus fracture involving >25% of articular surface
- Open fractures
- Pathological fractures
- Other fractures involving the same lower extremity
- Patient unwilling to give informed consent to be included in the trial
- Patient has other injuries that would influence the study
- Any ankle fracture that the treating surgeon feels inappropriate to be included in the study

**Outcome measures**

***Primary Outcomes***

**CT Scanning**

All patients will undergo focused CT scanning two weeks post operatively and at one year. A customised foot holding device will enable to scan to be taken with both feet in neutral alignment (Evolution supine foot positioner, Vasocare Ltd). Assessment will be made in comparison with the contralateral side to assess reduction of the syndesmosis. Quantative measurement of reduction will be measured using the technique as described by Phisitkul et al.[28]

***Secondary Outcomes***

Peri-operative

- Procedure duration
- X Ray exposure duration

Ability to weight bear

- Assessment of ability to load share on the affected limb on initial weight bearing and the change in weight distribution on timed weight bearing over a 60 second period. Measured using scale analysis, with the patient being blinded to the readings

Complications

- Surgical Wound Review for delayed or complicated wound healing
- Secondary Operations
- Adverse events

*Patient Reported Outcome Scores:*

Visual Analogue Scale (VAS).

- Patients will be divided into the following categories;
    - Mild or no pain: 0 – 3
    - Moderate pain: 4- 7
    - Severe pain: 8 – 10.

American Academy Orthopaedic Surgeons Foot & Ankle Outcomes[29]

- A validated, self- administered outcome questionnaire. It involves 25 questions regarding foot and ankle health from patient's perspective. There are 5 subscales: pain (9 questions), function (6 questions), stiffness and swelling (2 questions), giving way (3 questions), and shoe comfort (5 questions). It has good usability, reliability and validity.

Olerud and Molander Ankle Score[30]

- a self-administered patient questionnaire. It is a good outcome tool for assessing symptoms after an ankle fracture. The score is based on nine different items: pain, stiffness, swelling, stair climbing, running, jumping, squatting, supports and work/activities of daily living. The scoring system correlates well with parameters considered to summarise the results after this type of injury and is therefore recommended for use in scientific investigations.

EuroQol EQ-5D[31]

- a validated, generic health-related quality of life measure consisting of 5 dimensions each with a 3-level answer possibility. Each combination of answers can be converted into a health utility score. It has good test-retest reliability, is simple for patients to use, and gives a single preference-based index value for health status that can be used for broader cost-effectiveness comparative purposes.

# Assessment methods

**Pre Clinical Evaluation**

Demographic factors including age, gender, co-morbidities and primary diagnosis will be obtained. A lateral and antero-posterior mortise X ray will be obtained to evaluate and classify fracture

**Operative Recording**

The lead operator will complete a standardised, structured operation note.

**Assessment & Clinical Evaluation**

The patients in the study will be asked to attend for follow-up and assessment for 12 months post surgical intervention, as outlined in figure 1.

## Data handling

Case report forms (CRFs) will be supplied by the Chief Investigator and all data will be recorded on the case report forms (CRFs). Upon enrolment into the clinical study, a unique Patient Study ID will be assigned in numerical order and will be prefixed by a unique lettered code for different sites. Only the Research Associate (RA) for each site will have the key to identify individual patients.

The RA is responsible for completion of the CRFs in a timely and accurate manner. All CRFs must be legible and completed in black or blue ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision, beside the relevant box and must be signed and dated by the investigator or his or her representative. Data is not to be obliterated by blacking out, using correction fluid or by erasing the original entry. Any documents related to the study must be archived at the study site or in a central archive. This includes anonymising the identities of the subjects involved in the study. This list and the signed informed consent forms are key documents in the files that need to be stored by the investigator in a secure environment for between 3-7 years, depending upon each participating hospitals current practice.

| Time Point | Data Collection |
|---|---|
| Baseline | X Rays, Patient questionnaire, Pre-injury PROMS |
| Operation | Classification, operative time and Duration of XR exposure |
| 2 weeks | X Rays, focused CT of syndesmosis, Wound review, Record of Complications |
| 6 weeks | X Rays, Wound review, Record of Complications |
| 3 months | X Rays, OMAS, EQ-5D, AA0S:FA, Weight bearing test, Record of complications |
| 6 months | OMAS, EQ-5D, AAOS:FA, Weight bearing test, Record of complications |
| 12 months | X Rays, OMAS, EQ-5D, AAOS:FA, Weight bearing test, Record of complications, focused CT of syndesmosis |

*Figure 2; Follow up and data collection outline*

# Further considerations

**Pre-study procedure**

Prior to the study commencing, ethics approval will be required.

**Patient information**

The investigator will provide the patient with written trial information prior to obtaining consent for trial inclusion. The terminology used must be chosen so that the layman can fully understand the content.

**Patient's informed consent**

Each patient's agreement to participate in the clinical trial must be given in writing. Copies of the written informed consent forms will be inserted into the investigator's study file and in the patient's medical notes. An additional copy will be given to the patient. The patients will be given ample time to consider participating in the clinical evaluation. Patients may withdraw their consent to participate in the trial at any time, and for any reason.

**Adverse event management**

Adverse events are defined as any untoward medical occurrence in a clinical trial subject and which do not necessarily have a causal relationship with the treatment. Serious adverse events are defined as any untoward and unexpected medical occurrence that:

- Results in death, [1 SEP]
- Is life-threatening [1 SEP]

- Requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- Results in persistent or significant disability or incapacity,
- Any other important medical condition that, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed.

All adverse events will be listed on the appropriate Case Report Form for routine return to the central office and all serious adverse events will be entered onto the Serious Adverse Event reporting form and emailed to Mrs Carol Carnegie within 24 hours of the investigator becoming aware of them. Once received, the Chief Investigator will confirm causality and expectedness. Serious adverse events that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee within 15 days.

Serious adverse events that may be expected as part of the surgical interventions, and that do not need to be reported to the main Research Ethics Committee are: complications of anaesthesia or surgery (e.g. wound complications, infection, damage to a nerve or blood vessel and thromboembolic events) and secondary operations for infection, mal-union, non-union or for symptoms related to the metalwork.

**Trial Report and publications**

At the end of the trial a report will be written, which will include a statistical evaluation and an assessment of the results from the medical point of view. The report will be based on the points laid down in this protocol. All grouped patient data will be anonymised.

**Study Schedule**

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| Expected date of first inclusion: | 01/12/2020 |
| Estimated date of last patient's inclusion | 31/12/2024 |


1. Charles M. Court-Brown, Ben Caesar, Epidemiology of adult fractures: A review, Injury, Volume 37, Issue 8, August 2006, Pages 691-697, ISSN 0020-1383, http://dx.doi.org/10.1016/j.injury.2006.04.130.
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14. Cox, S., Mukherjee, D.P., Ogden, A.L., Mayuex, R.H., Sadasivan, K.K., Albright, J.A. and Pietrzak, W.S., 2005. Distal tibiofibular syndesmosis fixation: a cadaveric, simulated fracture stabilization study comparing bioabsorbable and metallic single screw fixation. *The Journal of foot and ankle surgery*, *44*(2), pp.144-151.
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# Appendix 1

# A Cohort Study of Bioabsorbable Screws for Syndesmosis Fixation in Ankle Fracture

This appendix describes the process to be used during the COVID 19 pandemic. Once advised by the sponsor that it is appropriate, we will revert to the original protocol.

## Study design

**Sample size**
This study involves patients who have sustained a traumatic injury therefore no change in study size is required as this should not be affected by the pandemic.

**Patient selection and enrolment**
All patients will be screened for suitability through the routine trauma service by staff who currently work there. Selection should not increase the frequency of patient/staff interaction. Consent will be taken by the trauma unit staff, as it would if they are not partaking in the study.

**Surgery**
Patients will follow the routine pathway through trauma theatre in ARI. COVID safety measures and precautions are in place.

**Inclusion and exclusion criteria**
Patients who are suspected of having or do have COVID will not be included in this study.

**Outcome measures**

Primary outcome measure - CT scanning
This will take place during the fracture clinic follow up for patients at two weeks. This is not in addition to the usual follow up for this fracture and will not increase numbers at clinic. Fracture clinic is currently running with social distancing and patient safety measures in place and trial patients will be managed in the same way as non-trial participants at fracture clinic.

Secondary outcome measures
Patient reported outcome measures will be documented at fracture clinic, and as above this should not increase frequency at clinic, and will be carried out by staff who currently work in fracture clinic. Routine X-rays will also be carried out as they

would at routine fracture clinic follow up for non trial patients. Social distancing measures are in place in the X-ray department.

**Time point data collection**
There will be no changes to the data collection time point. These are standard for the routine care of an ankle fracture patient.

**Patient information sheet**
This has been amended to notify the patient of measures in place, and that there is approval for the study during the pandemic.