Treatment of Medial Tibial Stress Syndrome using an Investigational Lower Leg Device. A Randomised Controlled Trial.

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Declaration of the Principal Investigator: I have read and understood the protocol document and agree to conduct the study as outline in the protocol and also in accordance with Australia Research Guidelines.

NAME OF PRINCIPAL INVESTIGATOR: Brandi Cole

SIGNATURE OF PRINCIPAL INVESTIGATOR: 

DATE:13/2/17

SYNOPSIS

Treatment of Medial Tibial Stress Syndrome using an Investigational Lower Leg Device. A Randomised Controlled Trial.

Protocol version: 4

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Summary

Study title:	Treatment of Medial Tibial Stress Syndrome using an investigational Lower Leg Device. A Randomised Controlled Trial.
Protocol version	1
Objectives	Primary objective: Return to full-time sport/activity levels and recurrence of MTSS after return to full-time sport. Secondary objectives: Level of shin pain during rest, with ADLs and during rehabilitation running each week prior to return to activity, time to progress through each stage of the rehabilitation protocol prior to return to full activity, bilateral active dorsiflexion range of motion at initial assessment, at return to full-time activities and at 6 weeks, 3 months and 6 months after return to full-time activities, compliance with device use and overall patient satisfaction with the device.
Study design	Prospective, double-blinded, randomised controlled trial
Planned sample size	50
Selection criteria	Symptomatic medial tibial stress syndrome of at least 6 weeks duration diagnosed on the basis of history of diffuse, dull lower leg pain with activity, and palpable tenderness of the posteromedial tibial border.
Study procedure	Patients randomized to one of two groups to receive either the novel device or a placebo to be worn on the lower leg, first fitted at initial visit. They will then undergo a home rehabilitation program and be followed up at 6 weeks, 3 months, and 6 months in the clinic.
Statistical considerations	Sample size 50 Statistical analysis will be performed using SigmaPlot v11 (Systat Software, Inc. Chicago, IL,USA).
Duration of the Study	8 month follow up

Table of Contents

1. BACKGROUND

1.1. Disease Background*

Shin splints, also known as Medial Tibial Stress Syndrome (MTSS), is an overuse injury or repetitive-stress injury of the shin area. A range of stress reactions of the tibia and surrounding musculature occur when the body is unable to heal properly in response to repetitive muscle contractions and tibial strain[14].

MTSS occurs in approximately 4-20% of the general population[14] and has significantly increased prevalence (35%) in athletes, particularly runners, and military personnel [13].

The most common complaint is vague, diffuse pain of the lower extremity along the medial distal tibia and is associated with exertion[1,5]. Clinical examination of the distal one-third of the medial border of the tibia often reveals tenderness to palpation with the anterior tibia often being non-tender[13]. Patients with early phase MTSS experience the worst pain at the beginning of exercise and this gradually subsides during training or within minutes of cessation of exercise. As the disease progresses the pain presents with less activity and may occur at rest[13].

There are multiple risk factors for developing MTSS, however, muscle imbalance and inflexibility, especially tightness of the triceps surae (gastrocnemius, soleus, and plantaris muscles) has been documented heavily in the literature as being commonly associated with MTSS[1,6,7].

The pathophysiology is not well understood, however, it is believed to be a combination of tendinopathy, periostitis, periosteal remodelling, and stress reaction of the tibia[1-3]. Dysfunction of the tibialis posterior, tibialis anterior, and soleus muscles are also common implicated[1,2,3]. These various tibial stress injuries appear to be caused by alterations in tibial loading, as chronic, repetitive loads cause abnormal strain and bending of the tibia[1]. Studies have attributed the pain experienced in MTSS to the disruption of Sharpey fibers that are connected to the medial soleus fascia and run through the periosteum of the tibia to insert into the bone[22]. Interestingly, in patients with chronic MTSS radiography has shown periosteal involvement including periosteal exostoses[13]. Periosteal oedema and subsequent bone marrow oedema into the periosteum has also been shown as a significant feature of chronic MTSS[3].

There is also discussion that MTSS, as a result of calf tightening, may be associated with a myofascial pain disorder which is ‘composed of hypercontracted extrafusal muscle fibres’ characterised by the presence of tender, firm nodules called trigger points[21]. These nodules are hyperirritable upon palpation. One recommended treatment for myofascial pain disorder is mechanotherapy[20] to provide acute

symptomatic treatment and allow for more rapid commencement of an appropriate rehabilitation program.

In concordance with both bone loading and myofascial pain theories, other studies have suggested that MTSS develops as a result of repetitive impact forces that eccentrically fatigue the soleus leading to tibial bending or bowing and overloading the capacity for bone remodelling[1, 12].

Treatment is predominantly conservative (rest, ice, analgesia, stretching, massage), however, few advances have been made in the treatment of MTSS over the last few decades[13]. Current treatments are mostly based on expert opinion and clinical experience with few well-conducted randomised control trials (RCT)[4]. Rest has been shown to be the single most important treatment in acute MTSS[1,3,7,12]. For many athletes, however, prolonged rest is not ideal.

Other treatments include use of NSAIDs for analgesia along with ice for ~15-20mins in the acute phase[13.] Physiotherapy has been shown to be helpful (ultrasound, whirlpool baths, phonophoresis, soft tissue mobilisation, electrical stimulation, and unweighted ambulation have been shown to be effective in the acute setting)[1,3,5-7,9,12]. However, many athletes require more regular treatment that suggests a more athlete self-directed method of treatment could be helpful in the setting of MTSS.

Similarly, a regular program of stretching and strengthening exercises has been shown to be effective in prevention of, and in the rehabilitation period following, MTSS[1,3,5-7,9,12].

Appropriate footwear and orthotics has been shown to reduce the incidence of MTSS[1,3,4-8,12] and can prevent repeat episodes[1,4]. Shock-absorbing insoles have shown potential in prevention and treatment of MTSS in a military population, however, with unclear results due to methodological flaws[23]. Finally, a systematic review has highlighted that correction of musculoskeletal dysfunctions can improve pain and overall function and may be helpful in preventing recurrence[13].

Some studies have introduced a lower limb brace designed to treat MTSS, with particular focus on a military population[16,19]. However, statistical significant results were not demonstrated between experimental and control groups. This has been attributed to methodological limitations such as a small sample size (n < 25), compliance issues, non-validated outcome measures, and a short time period for evaluation of efficacy[17].

Despite previous studies showing little efficacy of a lower limb brace for the treatment of MTSS, this simple and patient self-directed option should not be disregarded for it's potential role in mechanotherapy[20]. With a carefully constructed study

methodology, appropriate sample size, using newly developed evaluation tools not previously available for use in clinical settings[18], over a longer period of time compared to previous brace studies we believe a more clinically relevant picture of the role of lower limb braces in the treatment of MTSS may be realised.

As agreed upon by a large body of evidence, the key to treatment of MTSS is prevention[1], however, to date, there is limited evidence to support our current treatment and interventions for MTSS[4].

The current literature regarding MTSS clearly demonstrates a multifaceted syndrome in its etiology and associations. To improve our current treatment, therefore, requires a multifaceted approach that addresses both bone loading and myofascial aspects of the condition.

1.2. Rationale for Performing the Study*

The proposed study is designed to determine whether current treatment methods with an adjuvant novel device for medial tibial stress syndrome are more effective than the current treatment methods without the novel device. Rest is currently the most effective treatment modality, however, many active individuals find this period of rest frustrating and detrimental to their goals, particularly amongst those competing in high level sport. The aim of the device is to reduce the amount of rest required to return to previous activity levels whilst also symptomatically treating the pain associated with medial tibial stress syndrome.

It is expected that we should be able to show a treatment effect of the device in terms of time taken to return to full activity load, recurrences after return to full activity load and overall shin pain. This will be compared to that of the placebo group to see if the device provides any additional treatment effect beyond that of the placebo group.

2. STUDY OBJECTIVES*

2.1. Primary Objective*

Time to return to full-time sporting activities, and recurrence of symptoms after return to full-time activities.

2.2. Secondary objectives

Level of shin pain during rest, with ADLs and during rehabilitation running each week prior to return to activity, time to progress through each stage of the rehabilitation protocol prior to return to full activity, bilateral active dorsiflexion range of motion at initial assessment, at return to full-time activities and at 6 weeks, 3 months and 6 months after return to full-time activities, compliance with device use and overall patient satisfaction with the device.

3.STUDY DESIGN*

3.1. DESIGN*

- Prospective, double-blinded, randomized controlled trial.

3.2. STUDY GROUPS

Normal Treatment with the Novel Device Group (Device group)

Normal Treatment with placebo Device Group (Placebo group)

3.3. NUMBER OF PARTICIPANTS*

50

3.4. NUMBER OF CENTRES

1

3.5. DURATION

- Start date May 2016, expected end date May 2020
- Expected time period for the recruitment phase of the study is 24 months

4. PARTICIPANT SECTION

4.1. INCLUSION CRITERIA*

- Symptomatic medial tibial stress syndrome of at least 6 weeks duration, diagnosed on the basis of:
  - History of diffuse, dull shin pain that is associated with exercise,
  - Palpable tenderness of the posteromedial tibial border

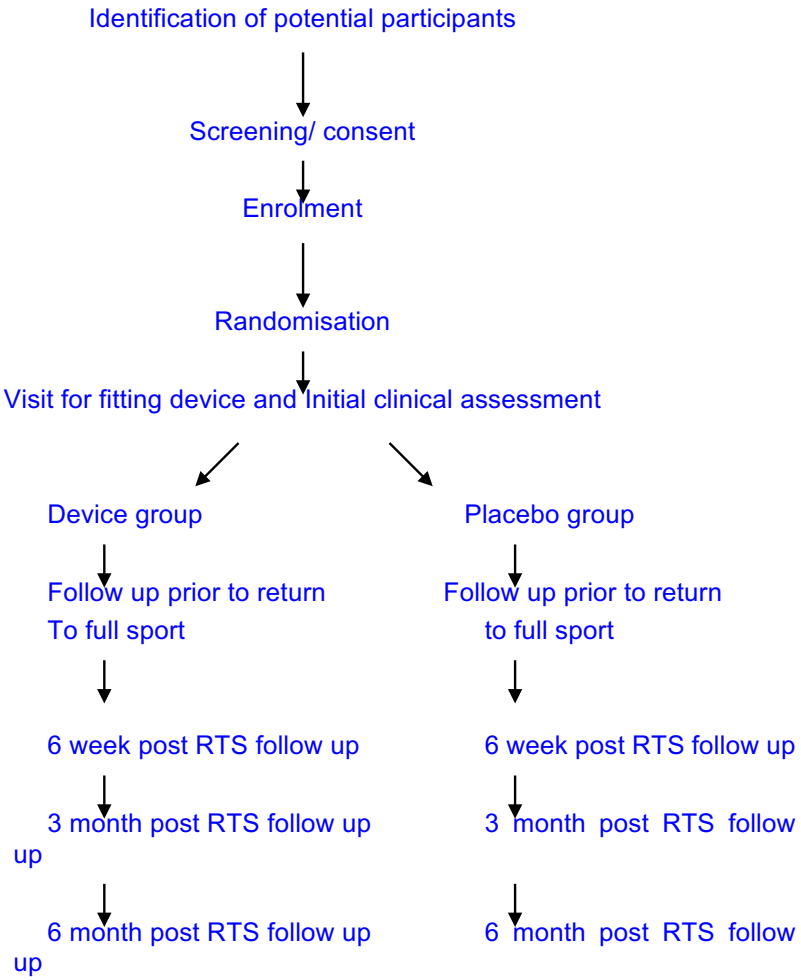
4.2. EXCLUSION CRITERIA*

- Diagnosis of stress fracture in the previous 6 months
- Clinical suspicion of a current stress fracture due to localised point tenderness on the anterior or medial border of the tibia unless ruled out by an MRI (MRI negative for bone stress reaction)
- Signs of plantar fasciitis including heel pain on first steps in the morning and tenderness to palpation over the posteromedial calcaneal tuberosity
- Previous diagnosis of compartment syndrome
- Suspicion of chronic exertional compartment syndrome on the basis of history of shin or calf pain brought on at a predictable point in activity, that worsens if exercise continues and is relieved by rest, unless excluded with compartment pressure testing
- Clinical signs of complex regional pain syndrome including pain out of proportion to the inciting event, allodynia, hyperalgesia, diffuse oedema, skin changes and difference in temperature between limbs
- Previous diagnosis of popliteal artery entrapment syndrome
- Clinical suspicion of popliteal artery entrapment syndrome based on disappearance of pedal pulses on repetitive plantarflexion
- Clinical suspicion of radicular leg pain including history of back pain associated with the leg pain and/or reproduction of leg pain on SLR testing with added dorsiflexion
- Neurological disease affecting the lower leg
- Coagulation disease
- Pregnancy

- Age less than 18
- Individuals with increased risk of fungal infection
- Individuals with disorders affecting the skin
- BMI > 35
- Any condition that increases risk of infection of the lower limb

5. STUDY OUTLINE*

5.1. STUDY FLOW CHART



5.2. INVESTIGATION PLAN*

List Interventions	Enrolment visit	Initial assessment	Assessment prior to	6 week follow up	3 month follow up	6 month follow up

		and fitting of device/placebo	return to sport			
Informed Consent	✓					
Inclusion / Exclusion critieria	✓					
Patient filled form - evaluation of shin pain and function (to be completed weekly)		✓	✓	✓	✓	✓
Physical examination		✓	✓	✓	✓	✓
Treadmill testing		✓	✓	✓	✓	✓
Adverse Event & Serious Adverse Event Assessment			✓	✓	✓	✓

At the enrolment visit, patients will be examined to determine a clinical diagnosis of MTSS according to the inclusion and exclusion criteria. Following confirmation of eligibility for enrolment in the study, patients will be asked to read a patient information sheet that outlines the purpose of the study and what is involved. They will then be given a consent form and asked to complete it if they wish to partake in the study.

Once informed consent is obtained, the patient's age, gender, occupation, duration of symptoms, leg(s) involved, highest level of sport achieved, and previous history of MTSS will be recorded.

Participants will be randomised to the novel device group or the placebo group. The novel device group will receive the Solushin (Solushin Pty Ltd, Australia), complete with compressive hemispheres and rod, fitted to the patient. The placebo group will receive a garment that appears to look the same as the Solushin, however, it will lack the functional elements of the device. If participants have bilateral MTSS they will be given the same device for both legs – that is, a participant randomized to the investigational device group with bilateral MTSS will receive one investigational device for each leg and vice versa.

All patients will be instructed on the correct application of the Solushin device or the placebo, respectively, with both groups being required to wear their device from commencement of the study up until 6 weeks after return to full-time activity. Patients will be instructed to wear their device for at least 2 hours prior to undergoing their return to full activity program and 2 hours after completing their activities. If patients do not participate in exercise in any day, they will be instructed to wear their device for at least 2hrs in the morning and 2hrs in the afternoon during those days.

Participants will be instructed by the clinician to follow a standardized return to full activity protocol with graded progression based on symptoms. They will be asked to refrain from any other running or load bearing activities other than activities of daily living and the rehabilitation exercises until return to full activity. They will be permitted to cycle, swim and participate in resistance programs should they choose to.

All participants will also have the option to undergo other treatment procedures such as ice, stretching, massage and soft tissue techniques recommended by their usual treating clinician.

Initial assessment of MTSS will require participants to perform an active range of dorsiflexion test followed by a treadmill running test whereby patients will be progressed through a modified Bruce protocol (Appendix 1) (see my note on appendix) and asked to stop at the point at which their leg pain is elicited. The end of the test will occur when they complete the protocol or when they reach their maximal heart rate (220 – age) if no symptoms occur. Patients will be asked to complete a VAS Score to rate their pain prior to, immediately after and 5 minutes after treadmill testing. The same assessments will be made at follow-up appointments in the clinic prior to return to full activity and again at 6 weeks, 3 months and 6months after return to full load activities.

The nominated Medical Monitor is Dr Donald Kuah who will follow up with any participants who are unhappy with their management or any other aspect of the trial. Participants will be able to contact Dr Kuah for review whether that is a medical review, a second diagnostic opinion or a conversational review about the conduct of the study. In addition the first 5 participants enrolled in the study will be closely monitored in the early stages of use of the device for adverse effects. This will be done via a clinical examination once a week for the first two weeks, then fortnightly for the next two fortnights for a clinical examination. Additionally, there will be a phone interview every two days for the first week prior to the in-person clinical examination allowing the investigators to identify and act on issues earlier than the one week visit.

Patients will be asked to complete a questionnaire and send it to the clinician once a week until return to full-time activity, then every fortnight for the duration of the study (Appendix 2).

The nominated Data Safety Monitoring Committee consists of Dr Donald Kuah and Professor George Murrell who will monitor safety during the trial via reviewing the results of the first 5 participants enrolled in the study and any other participants who report adverse events throughout the trial.

5.3. Study Procedure Risks*

The risks in this study are related to the device material. There is a low risk that the material in both the device group and the placebo group can promote fungal or bacterial colonization of the skin that is in direct contact with device. This risk is lowered by the use of an antifungal and antibacterial material that is machine washable. Due to the compressive nature of the device, there is a low risk that it will produce a tourniquet effect that could compromise haemodynamics and lead to formation of thromboemboli. However, the device is not designed to reach pressures consistent with torniquets.

5.4. Recruitment and Screening*

Participants will be recruited via face to face discussion, sending of letters and/or flyers to Sydney physiotherapists, doctors as well as using social media platforms such as Facebook and Instagram.

Any patients who fit the inclusion criteria (identified from their initial history and clinic examination) will be considered as potential participants. Eligible patients will then be informed about the study and invited to attend a clinic appointment where they will be further examined to ensure they fit the inclusion criteria, don't meet any exclusion criteria and are willing to participate in the trial. Patients who fit the criteria will be given the PICF and given time to consider whether they would like to be a part of the study and if they are not sure we suggest that they go home to think about it and call to make another appointment if they wish to partake.

5.5 INFORMED CONSENT PROCESS*

The study will be explained verbally to the suitable participants and if they agree to participate they will be provided with a written explanation of the study and will fill out and sign a written informed consent form which will be put in their medical file.

5.6 ENROLMENT PROCEDURE*

If the participant meets inclusion criteria, has no exclusion criteria and agrees to participate in the trial they will be enrolled into the study after informed consent has been completed. The participant will receive a study enrolment number and this will be documented in the participant's medical record and on all study documents.

5.7 RANDOMISATION PROCEDURE

After enrollment participants will be randomized into one of two groups using a computer generated randomization code that will be held by an administrative staff member with no other involvement in the trial.

6. SAFETY*

6.1. ADVERSE EVENT REPORTING*

Adverse events will be assessed at each follow up and recorded in the participant's medical notes. We will also keep a log of all adverse events. We are considering adverse events to be any untoward medical occurrence in a participant which does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavorable or unintended sign, symptom or condition and/or an observation that may or may not be related to the study treatment.

If participants feel that their shin pain has worsened, they will be re-evaluated at the 6 week follow-up visit for possible other causes of lower leg pain.

Participants are able to call or return to clinic at any time between the initial visit and the prior to return to sport visit. They have the option of obtaining an external second opinion of their condition at any time and proceeding with any other recommended treatment. Any other treatment received will be recorded at each subsequent visit.

All adverse events will be recorded in a case report form. It will not be reported to the ethics review committee immediately unless it impacts on the research and action is planned.

All serious adverse events will be recorded and reported individually to HREC if the information materially impacts the continued ethical acceptability of the trial or indicates a need for change to the trial protocol, otherwise they will be included in the annual Serious Adverse Events Summary Report.

7. BLINDING AND UNBLINDING

Patients will be blinded to which group they have been assigned and all groups will be given an identically shaped device. The clinician fitting the device and instructing treatment protocol will not be blinded as it is important to fit the device correctly and provide instructions for correct application. This clinician will not be involved in collection or reporting of any data for the research project. The outcome assessors will be blinded to treatment group.

8. STATISTICAL CONSIDERATIONS*

Fifty participants will be recruited into the study and equally randomized into two groups of 25. The sample size was chosen based on a similar previous study conducted by Johnston et al. (2006) that examined the use of a lower leg brace in the treatment of

MTSS[20]. Based on data from this RCT, a sample size calculation using an ANOVA model was performed:

Minimum detectable difference = 7 days return to full-time activity

Expected Standard deviation of residuals = 3.47 days (Based on previous RCT (SEM data) and sample size for one group is 23, maximum standard deviation is (SEM=STD/SQRT(23)), or (SEM*SQRT(23)=STD) => (6*SQRT(23)= 7 days)

Number of groups = 2

Desire Power = 0.8 (80%)

Alpha = 0.05 (p-value)

The minimum sample size for each group is 23, and 46 in total, ie 23 patients in each group will be enough to detect a difference between the groups in return to full load activities.

For parametric data such as active range of dorsiflexion, VAS pain scores and patient device use data un-paired student's t-test will be used to assess differences between groups at different time points, with significant level set at 0.05.

For non-parametric data such as patient satisfaction with the device we will use a repeated measures ANOVA.

Statistical analysis will be performed using SigmaPlot v11 (Systat Software, Inc. Chicago, IL,USA).

9.STORAGE AND ARCHIVING OF STUDY DOCUMENTS*

Information will be stored in a computer file in the ORI, on USB backup and a paper copy stored in the medical records. Electronic data is stored in password protected files and physical data will be stored in a locked cabinet. Data will be stored for 15 years after the completion of the project and then destroyed.

10.ETHICAL CONSIDERATIONS

The study has been devised so as to adhere to the guidelines set out in chapter 4.3: People in Dependent or Unequal Relationships of the National Statement on Ethical Conduct in Human Research (2007). Consent will be negotiated in the form of a thorough patient information and consent form which outlines the purpose of the study and the requirements of each participant. Potential participants will be encouraged to discuss participation in the study with their regular clinician who is not involved.

The study is designed to minimize potential detrimental effects of the researcher-participant relationship by making sure the researchers are not involved with the treatment of the patient outside of the study parameters and within the study participants are asked that they report any difficulties, complaints or adverse events to the researchers so that participants can be assessed immediately followed by the appropriate course of action.

Potential participants who are already involved in a separate study will be advised to remain in that study as a participant and not engage in another.

Researchers will minimize any dependency of participants by following the strict study protocol and instructing participants to do the same. Realistic participant explanations will be ensured through provision of the patient information sheet and consent form. Persons who decline participation or withdraw from the study will not be denied any treatment or be disadvantaged in any way.

Throughout the study, participants will be treated with respect, consent will be sought by an investigator who has no pre-existing relationship with potential participants and all information will be kept confidential as per section 9 of this protocol.

This protocol has been reviewed by Bellberry Human Research Ethics.

11.FINANCING AND INSURANCE

The researchers will conduct the study voluntarily in their free time. The experimental devices and placebo will be provided by Solushin Pty Ltd for no fee. Participants will be allowed to keep their device after completion of the study if they so wish. All clinicians (principal researcher and first author) have medical indemnity insurance that encompasses clinical trials.

12.PUBLICATION POLICY

Participants will be provided with a patient information and consent form which outlines the purpose of the study and the methodology, informing them that their information will be kept confidential, they may receive a placebo device and they have the right to withdraw from the study at any time. The plan for the study is to improve the management of medial tibial stress syndrome. Therefore, on completion the study will be submitted to publication to an appropriate peer-reviewed journal.

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14. APPENDIX 1: MODIFIED BRUCE PROTOCOL

Patients will spend 2 minutes on each stage before progressing.

Stage	Speed (km/hr)	Gradient
1	5.47	14
2	6.76	17
3	8.05	20
4	8.85	23
5	9.65	26
6	10.46	29
7	11.26	32
8	12.07	35
9	12.67	38
10	13.29	41

15. APPENDIX 2: PARTICIPANT QUESTIONNAIRE

Medial Tibial Stress Syndrome Score
Name: **Date:**

I have complaints in:

Both shins	☐
Only the left shin	☐
Only the right shin	☐

In case of complaints in both shins:

I have most complaints in:

My left shin	☐
My right shin	☐

Instructions:

- While completing this questionnaire, keep in mind the pain as you have experienced maximally over the past days, and check the answer that fits **best** this shin pain
- While completing this questionnaire, keep in mind your **shin with most** complaints.
- Please read **all** options before you select a checkbox.
- **For all questions, choose one answer per question only.**

Sporting activities

For military: Marching is considered to be a sporting activity.

1) Presently:		**P**
I perform all of my usual sporting activities	☐	0
I am forced to do less of my usual sporting activities due to pain in my shin	☐	1
I am forced to do alternative sporting activities only due to pain in my shin	☐	2
I cannot do any sporting activity due to pain in my shin	☐	3

2) While performing sporting activities:

I have no pain in my shin	☐	0
I have some pain in my shin	☐	1
I have a lot of pain in my shin	☐	2
I cannot do any sporting activity due to my shin pain	☐	3

Walking

3) While walking:		**P**
I have no pain in my shin	☐	0
I have some pain in my shin	☐	1
I have a lot of pain in my shin	☐	2
I cannot walk due to pain in my shin	☐	2

Pain at rest
e.g. sitting or laying down

4) At rest, my shin is:		
Not painful	☐	0
Sensitive	☐	1
Painful	☐	2
Very painful	☐	2

5) Number of exercise sessions per week

6) Average minutes per session

7) Activity type during each session (e.g. hopping, running, swimming)

8) Surface types (e.g. concrete, grass, water)

9) Average rate of perceived exertion in sessions

/10

10) How many pre-sessions/post- sessions/days in the past week did you wear the device?

11) On average, for how long do you wear the device each day? (please circle one)

Not at all 30mins-1hr 1hr-2hrs 2hrs+

12) Have you used any other treatments for your shin splints instructed by your clinician in the past week (stretching, icing, strengthening, massage

etc)? If so, what were they and how often did you use them? (NB: please indicate If there is no change since your previous response)

13) Overall, how happy are you with the device? (please circle one)

useless

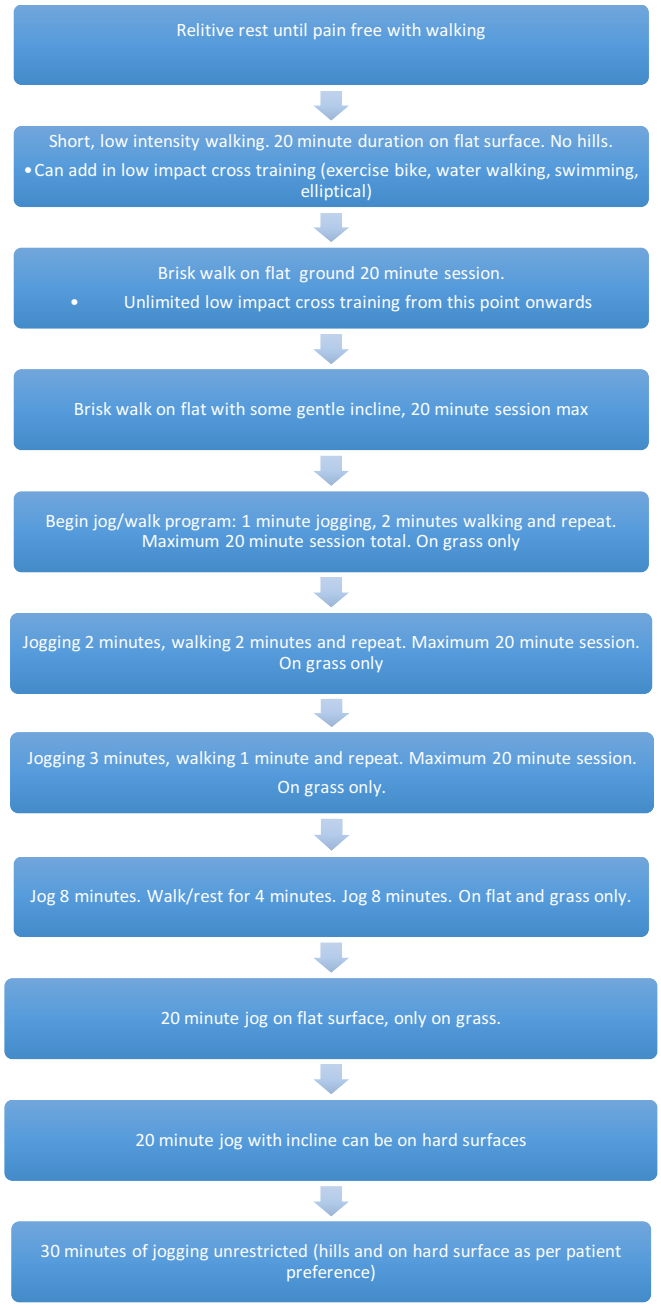
little use

neutral

useful

very useful

16. APPENDIX 3: RETURN TO FULL ACTIVITY PROGRAM



- **Patients can progress each stage every 3 days if no pain with or following activity. No more than 2 running days in a row (i.e. one rest day out of every three)**
- **If experiences pain during or after activity or at rest – must have relative rest for 24 hours and continue with flow chart from one step back.**
- **Lack of progression or regression on flow chart will need medical review by trial doctor(s).**
- **Present for return to full training/sport assessment when completed flow chart pain free. Absolute minimum time is 33 days.**