PROTOCOL

V-CILL (Vitamin C in Lower Limb) Trial

Can Vitamin C prevent Complex Regional Pain Syndrome in lower limb surgery? A double-blinded randomised, multi-centre, controlled feasibility study.

Protocol Number (if applicable): 1.0
Protocol Version 1.0 and date: 27/1/2021

Document history:

Version Number and Date	Summary of changes
Version 1	

Statement of Compliance

This clinical trial will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016).

This clinical trial is not sponsored by any pharmaceutical company or other commercial entity.

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PROTOCOL SYNOPSIS

TITLE	Can Vitamin C prevent Complex Regional Pain Syndrome in lower limb trauma? A double-blinded randomised, controlled feasibility study.
TRIAL DESCRIPTION	This is a randomised controlled feasibility trial conducted at five sites: • Peninsula Health • Frankston Private Hospital • Holmesglen Private Hospital • Cabrini Brighton Private Hospital • Beleura Private Hospital The trial will recruit patients who present for elective and emergency surgery of the foot and ankle. Patients will be randomised into two groups – placebo and 500mg vitamin C. Patients will then be assessed at regular intervals up to six months post injury/surgery to determine whether chronic regional pain syndrome was diagnosed.
OBJECTIVES	Primary objective – to determine if the proposed protocol is feasible with regards to: • Recruitment capability • Data collection procedure • Suitability of intervention • Resource availability • Participant response Secondary objectives: 1. to determine if vitamin C prevents CRPS in patients with lower limb extremity trauma in a dose-response manner 2. to determine the incidence of CRPS in lower limb extremity trauma and elective surgery. 3. To determine the demographics and characteristics of patients who develop CRPS of the lower limb
OUTCOMES AND OUTCOME MEASURES	The outcome is development of CRPS at any stage following trauma or surgery within the six-month time frame. The outcome measure is the validated Clinical Diagnostic Criteria for CRPS, also known as the 'Budapest Criteria'(1).
TRIAL POPULATION	Adult patients (defined as aged 18 and over) who undergo elective or trauma surgery on their foot and ankle at the following sites: • Peninsula Health • Frankston Private Hospital

	• Holmesglen Private Hospital • Cabrini Brighton Private Hospital • Beleura Private Hospital Patients who are unable to provide informed consent will not be enrolled in the study.
DESCRIPTION OF SITES ENROLLING PARTICIPANTS	• Peninsula Health (Frankston public hospital) • Frankston Private Hospital • Holmesglen Private Hospital • Cabrini Brighton Private Hospital • Beleura Private Hospital
DESCRIPTION OF INTERVENTIONS	Patients will be allocated to one of two groups: • Placebo • Vitamin C 500mg daily 50 capsules will be given to a patient in a box and patients will be asked to take one capsule daily for fifty days.
TRIAL DURATION	It is expected the trial will take 12 months to complete. Patients will be enrolled for six months and it is expected the trial will take six months to recruit appropriate numbers. Data analysis is expected to take six months.
PARTICIPANT DURATION	Participants are enrolled in the study for six months from the date of their index surgery. Patients will be reviewed at four points post-operatively: • between 7 and 14 days, combined with post-operative wound check and provision of standard post-operative orthotics/devices • five to six weeks, combined with post-operative x-ray if appropriate • eleven to fourteen weeks • twenty-six weeks following their injury

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
AR	Adverse Reaction
CRF / eCRF	Case Report Form / electronic Case Report Form
CRPS	Complex regional pain syndrome
DMC SMC	Data Monitoring Committee / Safety Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HREC	Human Research Ethics Committee
ISO	International Organization for Standardization
ITT	Intention To Treat
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
NHMRC	National Health and Medical Research Council
NSAIDS	Non-steroidal Anti-Inflammatory Drugs
PI / CPI	Principal Investigator / Coordinating or Chief Principal Investigator
PI	Product Information (available for an approved drug or device)
QA	Quality Assurance
QC	Quality Control
RGO	Research Governance Office
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SMC	Safety Monitoring Committee
SoA	Schedule of Assessments
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration
UAR	Unexpected Adverse Reaction
USM	Urgent Safety Measure

INVESTIGATOR AGREEMENT

I have read the protocol entitled “Can Vitamin C prevent Complex Regional Pain Syndrome in lower limb trauma? A double-blinded randomised, controlled feasibility study”.

By signing this protocol, I agree to conduct the clinical trial, after approval by a Human Research Ethics Committee or Institutional Review Board (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki and the good clinical practice

guidelines adopted by the TGA [Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments].
Changes to the protocol will only be implemented after written approval is received from the Human Research Ethics Committee or Institutional Review Board (as appropriate), with the exception of medical emergencies.
I will ensure that trial staff fully understand and follow the protocol and evidence of their training is documented on the trial training log.

Name	Role	Signature and date
Professor David Hunter-Smith	Senior investigator	
Dr Amy Touzell	Co-investigator	
Associate Professor Cylie Williams	Co-investigator	
Dr Taya Collyer	Co-investigator	

1. ADMINISTRATIVE INFORMATION

1.1. Trial registration

1.1.1. Trial registry

The trial will be registered with the Australian New Zealand Clinical Trials Registry (ANZCTR).

1.2. Sponsor

Trial Sponsor	Peninsula Health
Contact name	Dr Amy Touzell – 0484739550
Address	Frankston Public Hospital Department of Surgery Hastings Road Frankston VIC 3199
Sponsor-Investigator (where applicable)	not applicable

1.3. Expected duration of study

The recruitment period will be six months. The length of the treatment period is fifty days and the follow-up period is six months. It is expected the study will be completed within twelve months.

1.4. Contributorship

Name	Summary of contribution
Professor David Hunter-Smith	Senior investigator
Dr Amy Touzell	Co-investigator
Associate Professor Cylie Williams	Co-investigator
Dr Taya Collyer	Co-investigator

1.5. Stakeholder involvement

Investigators have engaged with the following stakeholders:

- Orthopaedic Department at Peninsula Health
- Podiatry Department at Peninsula Health
- Allied health employees of South East Orthopaedic Surgery
- Chief Executive Officer of the following private hospitals:
    - Frankston Private Hospital
    - Beleura Private Hospital
    - Holmesglen Private Hospital
    - Cabrini Private Hospital

The investigators have discussed the nature of the trial with these key stakeholders and incorporated preliminary feedback. The investigators will continue to engage with these stakeholders for ongoing feedback given the nature of the feasibility trial.

2. INTRODUCTION AND BACKGROUND

2.1. Trial rationale and aim

We aim to perform a feasibility study, with the potential for a larger trial in the future.

Primary objective – to determine if the proposed protocol is feasible with regards to:

- Recruitment capability
- Data collection procedure
- Suitability of intervention
- Resource availability
- Participant response

Secondary objective:

- to determine if vitamin C prevents CRPS in patients with lower limb extremity trauma in a dose-response manner
- to determine the incidence risk of CRPS in lower limb extremity trauma and elective surgery

The role of vitamin C and the prevention of CRPS has been demonstrated in upper limb trauma(2) but not clearly proven in lower limb trauma and elective surgery. A randomised controlled trial is yet to be published on this important topic, but several quasi-randomised trials have demonstrated the efficacy and safety of vitamin C in CRPS prevention(3)(4).

It is the experience of the senior author that complex regional pain syndrome was a common complication of lower extremity trauma and any means to prevent this debilitating disease was worth investigating to see if a simple, cheap intervention such as vitamin C, which has been demonstrated to prevent CRPS in upper limb trauma, would also be effective in lower limb trauma.

As a trial of this nature has not been conducted before, a feasibility trial is appropriate to assess the effectiveness of the protocol.

2.2. Background

Complex regional pain syndrome can be debilitating for patients. It is described as sustained sympathetic activity in a perpetuated reflex arc characterised by pain out of proportion to examination findings(5). It is commonly associated with crush injuries, surgery and prolonged immobilisation. The condition responds poorly to conservative and surgical treatments and is frustrating for both patient and clinician to treat. Early diagnosis and treatment is generally associated with better outcomes, but diagnosis is often delayed(6). Preventative treatment is the mainstay of therapy due to the poor clinical response of the condition following diagnosis and prolonged recovery rate with severe cases(7).

Type I CRPS is more common and is not associated with any demonstrable nerve lesions. It can be associated with trauma, casting or compression bandaging. Type II CRPS occurs in the setting of identifiable nerve injury(8).

The pathophysiology of the condition is still poorly understood. In patients who have sustained major trauma, standard homeostasis can be inundated resulting in a massive

systemic inflammatory response. Complex regional pain syndrome and burn wounds can involve a similar cascade of inflammatory exaggeration and severe symptoms including severe swelling, skin changes, hyperaemia and pain. Patients experience a triad of sensory, motor and autonomic nervous dysfunctions with long-standing pain and temperature differences of the affected and contralateral limb(9). An increase in inflammatory markers such as TNF-alpha and calcitonin are present both locally and systemically.

CRPS can affect patients of all ages with a 4:1 female to male ratio and medial age of 46 years at onset(10). The incidence has been described as up to 37% following distal radius fractures and 30% following tibial shaft fractures. Trauma is the commonest precipitating event(8).

Current treatment is generally via a multidisciplinary team. At Peninsula Health, this involves a physiotherapist, pain specialist and hand therapist or podiatrist depending on the extremity. The goals of treatment are pain control, rehabilitation, restoration of function and preservation of current function. Anti-epileptic medication such as gabapentin is commonly prescribed and has been shown to have reduction of symptoms(11). Antidepressents and non-steroidal anti-inflammatory medication have also been described with limited effectiveness. Topical agents such as lidocaine patches have not been studied in a controlled trial but are part of the treatment process. Nerve blocks, peripheral nerve stimulation and spinal cord stimulation have also been described. Physiotherapy and occupational therapy are the mainstay of treatment and aim to control oedema, stretch the affected limb to prevent contraction. Massage, contrast baths and transcutaneous electrical stimulation can be used to desensitize the affected limb. There is good-quality evidence to support physiotherapy management in CRPS patients(9).

It was noted that vitamin C given in high doses during the first twenty-four hours of burn resuscitation reduced resuscitation fluid requirements and wound oedema. Vitamin C has been shown to scavenge hydroxyl free radicals which protects the delicate vascular epithelium and inhibits vascular permeability and subsequently reduces oedema(12). Zollinger et al extrapolated this theory to upper limb trauma and demonstrated a dose-response reduction in complex regional pain syndrome in distal radius fractures in a large multi-centre randomised controlled trial(2). Besse et al (2009) performed a quasi-randomised prospective trial that also demonstrated a dose-response relationship between vitamin C and the prevention of CRPS(3).

Zollinger described a statistically significant reduction in the diagnosis of CRPS in patients taking 500mg of vitamin C with no statistically significant difference between patients taking 500mg and 1000mg, but a difference between placebo and 250mg(3). In Australia, the most common available dose of vitamin C in capsule is 500mg. The efficacy and safety of Vitamin C in this dosage has been demonstrated(4). For this feasibility study we are therefore randomising patients to placebo and vitamin C 500mg.

Valid outcome measures of CRPS have been described(13)(14). Similar to the protocol described by Zollinger(2), patients will undergo a clinical assessment two weeks post injury, six weeks post injury, twelve weeks post injury and twenty-six weeks post-injury. This

correlates to standard routine practice, where patients are assessed at two weeks post-operatively for a wound check, six weeks post-operatively for clinical review and also commonly twelve and twenty-six weeks post-operatively for ongoing assessment of response to surgery.

Patients will be assessed by their treating clinician according to the Budapest Criteria(1):

- A: continuing pain, which is disproportional to any inciting event
- B: The patient must report at least one symptom in three of the four following categories:
    - Sensory- reports of hyperaesthesia and/or allodynia
    - Vasomotor – reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
    - Sudomotor/oedema – reports of oedema and/or sweating changes and/or sweating asymmetry
    - Motor/trophic – reports of decreased range of motion and/or motor dysfunction (weakness/tremor/dystonia) and/or trophic changes (hair/nail/skin)
- C: The clinician must observe at least one sig at the time of the evaluation in two or more of the following categories:
    - Sensory- evidence of hyperalgesia (to pinprick) and/or allodynia and/or deep somatic pressure and/or joint movement
    - Vasomotor – evidence of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
    - Sudomotor/oedema – evidence of oedema and/or sweating changes and/or sweating asymmetry
    - Motor/trophic – evidence of decreased range of motion and/or motor dysfunction (weakness/tremor/dystonia) and/or trophic changes (hair/nail/skin)
- D: There is no other diagnosis that better explains the signs and symptoms

A randomised controlled trial to investigate the dose-response relationship between vitamin C and the prevention of complex regional pain syndrome in the lower limb has yet to be reported in the literature and can potentially revolutionise how we treat these patients. It is a relatively cheap, safe, potentially effective preventative in lower limb trauma that may help prevent the catastrophic consequences of complex regional pain syndrome in the lower limb.

2.3. Risk/Benefit assessment

2.3.1. Known potential risks

Trauma is known to increase vitamin C requirements. However, in patients exceeding 1000mg of vitamin C daily the multivariate relative risk of kidney stone formation in men was 41% higher than in those consuming 90mg a day. Vitamin C in high doses (in excess of 5000mg a day) has been suggested to cause haemolysis in glucose-6-phophatase dehydrogenase deficient patients, which has a high prevalence rate amongst persons of

African, Asian or Mediterranean descents(15). Neither Zollinger nor Besse described any complications from their vitamin C dosing (maximum 1000mg) in their published trials (2)(3).

2.3.2. Known potential benefits

Vitamin C has been proven to prevent the development of complex regional pain syndrome in patients who experience upper limb trauma. Should this finding be extrapolated to the lower limb, there will be a lower rate of this condition in the trial population. The side effects of opioid analgesia and non-steroidal anti-inflammatory medication (NSAID's) are well known and more severe than vitamin C(16). It is therefore reasonable that the potential analgesic benefits of vitamin C are considered.

2.3.3. Assessment of potential risks and benefits

Vitamin C is a relatively safe, commonly taken, over-the-counter vitamin supplement given to children and adults. Vitamin C is available in Australia and New Zealand without a prescription in chemists in doses of up to 1000mg. It is also the experience of the senior author that patients are 'prescribed' vitamin C by some local naturopaths in massively high doses, in excess of 2000mg daily. Despite these high doses, complications were not noted by the senior author. There have been described cases of kidney stones in high doses (>1000mg a day)(9). In massively high doses (up to 10 times our proposed intervention dose) it can be associated with haemolysis in glucose-6-phosphatase dehydrogenase deficiency. Renal failure has been reported in massively high doses (up to 100 times what we are proposing) given intravenously(17).

Previous studies of vitamin C in the doses we are proposing have not described any complications in patients taking the supplement. The potential benefit (prevention of a debilitating, difficult-to-treat condition in both the study population and in future patients), far outweigh the risks of a vitamin supplement that many people take as an over-the-counter medication.

3 TRIAL OBJECTIVES AND OUTCOMES

3.1 Objectives

3.1.1 Primary objective

Primary objective – to determine if the proposed protocol is feasible with regards to:

- Recruitment capability
- Data collection procedure
- Suitability of intervention
- Resource availability
- Participant response

3.1.2 Secondary objectives

Secondary objective:

1. to determine if vitamin C prevents CRPS in patients with lower limb extremity trauma in a dose-response manner

2. to determine the incidence of CRPS in lower limb extremity trauma.
3. To determine the demographics and characteristics of patients who develop CRPS of the lower limb

3.1.3 Exploratory objectives

There are no exploratory objectives for this study.

3.2 Outcomes

Table listing objectives and outcomes

OBJECTIVE	OUTCOME & OUTCOME MEASURE
Primary	
Primary objective – to determine if the proposed protocol is feasible with regards to: • Recruitment capability • Data collection procedure • Suitability of intervention • Resource availability • Participant response	Recruitment capability: • Successful recruitment of pre-determined patient numbers Data collection procedure: • Successful follow up at established time-points • Qualitative clinical feedback about ease of assessment/data collection • Lost to follow up rate Suitability of intervention: • Patient-reported compliance with medication • Patient-reported complication • Qualitative assessment of patient feedback Resource availability • Establishing paid and unpaid labour costs required for the trial • Availability of medication and placebo Participant response: • Qualitative participant feedback • Participant engagement/follow up
Secondary	
1. To determine if vitamin C prevents CRPS in patients with lower limb extremity trauma in a dose-response manner 2. to determine the incidence of CRPS in lower limb extremity trauma	To determine if vitamin C prevents CRPS in patients with lower limb extremity trauma in a dose-response manner: Patients are evaluated at four points post-operatively: • 10-14 days • 5-6 weeks • 10-12 weeks • 26 weeks The outcome of a positive diagnosis for CRPS will be made if the patient meets the 'Budapest criteria' at any of their four post-operative review appointments. This is a combination of asking patients about their symptoms and

OBJECTIVE	OUTCOME & OUTCOME MEASURE
	examining them for positive signs as per the below criteria: A: continuing pain, which is disproportional to any inciting event B: The patient must report at least one symptom in three of the four following categories: • Sensory- reports of hyperaesthesia and/or allodynia • Vasomotor – reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry • Sudomotor/oedema – reports of oedema and/or sweating changes and/or sweating asymmetry • Motor/trophic – reports of decreased range of motion and/or motor dysfunction (weakness/tremor/dystonia) and/or trophic changes (hair/nail/skin) C: The clinician must observe at least one sig at the time of the evaluation in two or more of the following categories: • Sensory- evidence of hyperalgesia (to pinprick) and/or allodynia and/or deep somatic pressure and/or joint movement • Vasomotor – evidence of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry • Sudomotor/oedema – evidence of oedema and/or sweating changes and/or sweating asymmetry • Motor/trophic – evidence of decreased range of motion and/or motor dysfunction (weakness/tremor/dystonia) and/or trophic changes (hair/nail/skin) D: There is no other diagnosis that better explains the signs and symptoms This outcome method has been validated(1).
To determine the demographics and characteristics of patients who develop CRPS of the lower limb	Patient demographics will be collected: • Age • Gender • Mechanism of injury (high energy/low energy) • Workers compensation injury • Smoking status

OBJECTIVE	OUTCOME & OUTCOME MEASURE
	• Diabetes • Pre-existing history of CRPS This information will be used to comment on the demographic of patients who do develop complex regional pain syndrome with the aim of predicting and preventing the condition in this patient population.

4 STUDY DESIGN

4.1 Overall design

This is a randomised, controlled, double-blinded feasibility study. The intervention is randomisation to one of two treatment arms:

- Placebo
- Vitamin C 500mg

Patients and clinicians will be blinded to their intervention arm until the end of the study. Medication will be dispensed in boxes of exact same shape, size and colour. The treatment period will be for fifty days with a six-month follow up.

The trial will be conducted at five sites in Bayside Melbourne:

- Frankston public hospital
- Frankston private hospital
- Beleura Private Hospital
- Holmesglen Private Hospital
- Cabrini Brighton Private Hospital

4.2 Justification for dose

Patients will receive an oral dose of vitamin C or placebo. Patients will receive an identical box with either placebo or 500mg.

In Australia, vitamin C is usually dispensed in 250mg, 500mg or 1000mg capsules. 500mg dosing was selected as previous studies have not demonstrated any complication in patients taking 500mg vitamin C. It has been demonstrated that 250mg is less effective compared to 500mg dosing in the prevention of CRPS(2). There has also been a very small complication rate in dosing greater than 1000mg/day(18). Therefore 500mg was determined as most appropriate for this feasibility study.

4.3 Trial population

Patients aged 18 and over will be eligible for the trial. Patients undergoing elective or emergency foot and ankle surgery and the five sites will be invited to participate.

Patients who are unable to provide informed consent to participate in the trial will be excluded.

4.4 Eligibility criteria

Participants will be assigned to a randomised trial treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

4.4.1 Inclusion criteria

Each patient needs to meet the following criteria to be eligible to participate in the trial:

- Patients need to be aged 18 and over to participate in the trial. This is because most fractures in the lower limb in children are treated non-operatively. In addition, most sites have limited numbers of younger patients who have surgery for foot or ankle problems, recruitment of people under the age of 18 is unfeasible.
- Patients need to be able to provide informed consent for the trial via a signed and dated consent form. Patients who are unable to provide informed consent because of (for example) cognitive impairment will be excluded.
- Patients who present to Peninsula Health, Frankston Private Hospital, Holmesglen Private Hospital, Beleura Private Hospital or Cabrini Brighton Private Hospital for surgery of the foot and ankle, either elective or emergency, will be eligible to participate.

4.4.2 Exclusion criteria

Patients meeting the following criteria will be excluded from the trial:

- Current or recent (ie less than three months prior to randomization) use of vitamin C, either as an isolated substance or as part of a multi-vitamin tablet. This is because the vitamin C dosing will not be standardized if patients are also taking the vitamin, and there is potential for overdosing. Vitamin C has a half-life of 10-20 days and therefore a long exclusion period is required.
- Patients who are pregnant or breastfeeding will be excluded due to the unknown safety risks in this patient population.
- Patients who are unable to commence taking the placebo/vitamin C medication within 72 hours after their surgery will be excluded from the trial
- Patients unable or unwilling to take oral medications.
- Patients who are vegan (as the placebo acidophilus is diary based)

4.5 Lifestyle considerations

Patients will be required to take one capsule once per day for fifty days. It is not expected this will inconvenience patients and compliance in other trials has been excellent.

4.6 Screen failures

Eligibility information will be obtained:

- Via the patient themselves – contacting the researcher/s directly
- Via the medical records, operating lists and referral screening after approval from the Human Research Ethics Committee

Patients will then have their willingness to participate recorded in the electronic medical record.

Those who are found, during the screening procedures, to be ineligible for trial inclusion are termed “Screen failures and they are not assigned to the intervention / are not randomised” and will be ineligible to continue in the trial.

4.7 Recruitment and identification of potential participants

Patients will be recruited in the following ways:

- Following HREC approval, elective and trauma theatre lists will be screened and potential patients with elective and trauma foot and ankle surgery will be identified and asked to participate in the trial. They will then be contacted by a member of the research team.
- A poster advertising the trial will be available in fracture clinic and elective orthopaedic clinic and patients will have an opportunity to discuss participating in the trial directly with their treating clinician who will then pass on the details to a member of the research team.
- Clinicians in the fracture and elective clinics will invite eligible patients to participate in the trial.

Contact details for the patients, including an email address and mobile phone number, will be passed on to a member of the research team for contact as well as access to the electronic medical record for patient contact information.

The target trial population is all patients aged 18 and over who present for elective or trauma surgery of the foot and ankle. For this feasibility study, is estimated that approximately 100 patients will need to be enrolled to assess the feasibility of the trial
The recruitment period will be six months.
Recruitment will be done at the following sites:

- Peninsula Health – Frankston Hospital
- South East Orthopaedic Surgery – Frankston Private Hospital, Beleura Private Hospital, Holmesglen Private Hospital, Cabrini Brighton Private Hospital

Recruitment will most commonly occur in the outpatient setting. For patients presenting with trauma-related conditions, recruitment may occur in the inpatient setting.

Prior to performing any trial-specific intervention, a signed consent form will be obtained for each participant. The process will be that the investigator or delegated member of the trial team will discuss the trial with the potential participant. The investigator will provide the Participant Information and Consent Form to the patient. This document will describe the purpose of the trial, the procedures to be followed, and the risks and benefits of participation.

The investigator will conduct the informed consent discussion and will check that the participant comprehends the information provided. The investigator will answer any questions about the trial. The patient will be invited to provide written consent. Consent will be voluntary and free from coercion. The investigator who conducted the consent discussion will also sign the informed consent form. A copy of the consent form will be given to the participant where the participant has signed.

It will be documented in the participant's record that consent has been provided. When the all the inclusion/exclusion criteria have been addressed and the eligibility of the participant confirmed, the participant may be assigned to a trial arm/intervention.

4.8 Consent

Patients will be contacted by a member of the research team prior to participating in the trial or receiving any intervention once detected as being eligible for the trial.
The following conditions will be met for each patient:

- Disclosure of relevant information to prospective research participants
- Comprehension of the information provided
- Voluntary agreement of the participant, free from coercion

Prospective patients will receive written and verbal information about the trial, the risks involved and the follow up required for the study.
Consent from minors will not be sought as only patients aged 18 and over are eligible for the trial. A member of the research team will obtain informed consent. Patients will verbally consent to participating in the trial and this will be confirmed in writing and also documented in the patient's Electronic Medical Record.
If patients are deemed ineligible for participation, or decline to participate, they will be recorded anonymously with reason as to why they did not participate in the trial.
Recruitment and consent may be performed by the investigators as well as other members of the investigative team. Patients will be given opportunity to consider their involvement in the study, and to discuss their involvement with family members or support persons. It will be made clear that participation is voluntary, and the patient's decision to participate will not affect their relationship with any of the treating practitioners including Dr Amy Touzell. It will be made clear that should patients choose not to participate in the study, their surgery and/or follow up will not be adversely affected and will not differ from those who chose to participate in the study.

5 INTERVENTION

5.1 Treatment arms

There will be two treatment arms: placebo and vitamin C 500mg. Patients will be randomised to one of the two arms.

5.2 Trial Intervention(s)

Placebo and Vitamin C 500mg capsules will be sourced from Peninsula Health pharmacy and kept in a locked office in all sites. Boxes will be labelled with a randomised number only.
Pharmacy will have access to the randomised number and its allocation to placebo or vitamin C 500mg. The patient, clinicians and researchers will not be privy to the randomised group.
Other labelling of the intervention will be as applicable on the vitamin C packet. This includes:

- Expiry date
- For clinical trial use only
- Keep out of reach of children
- Store in a cool, dry place

Placebo and both vitamin C doses will be of similar size and taste. Patients will take one capsule orally once per day for fifty days. Capsules are stored in a cool, dry place and prepared by pharmacy.

5.2.1 Description of trial investigational products

5.2.1.1 Placebo

Active substance	*Lactobacillus acidophilus and Bifidoobacterium animalis*
Trade or Generic name	*Blackmores Acidophilus*
Dosage form	Capsule
Route of administration	Oral one capsule daily for fifty days

5.2.1.1 Vitamin C 500mg

Active substance	Ascorbic Acid (Vitamin C) 500mg Citrus bioflavonoids extract 50mg
Trade or Generic name	Amplio Vitamin C
Dosage form	Capsule
Route of administration	Oral one capsule daily for fifty days

5.2.2 Dosage

Patients will be randomised to placebo or vitamin C 500mg. They will be blinded to their intervention arm until the end of the study.
Patients will take one capsule once per day, for fifty days. There is no restriction on the timing of the capsule and they can be taken with or without food.

5.2.3 Dose modification

In the very rare event that patients develop a complication from Vitamin C toxicity such as renal stones or gastrointestinal upset (this has never been documented in previous studies using this dose of vitamin C), they will be advised to cease taking the medication altogether. They will still be analysed using the intention to treat principle.

5.2.4 Storage, preparation, dispensing and administration of trial drug

The five sites will be allocated a box of medication from Peninsula Health pharmacy. This will be kept in a locked office with access only by the primary researcher at that site. Whilst on-site at Peninsula Health, this medication will be stored in pharmacy.

Patients will be educated on the dosage, timing and frequency of the medication and will be advised to take the capsules until the box is finished (50 days). Medication is self-administered.

In the setting of delayed or missed doses, patients will be told not to "make up" the dose but instead continue their normal daily dosing.

Patients will be asked at their review whether they have adhered to the medication schedule, if they had any problems with taking the medication or if any side effects such as gastrointestinal upset had occurred.

5.2.5 Product accountability

The trial medication will be sourced through pharmacy at Peninsula Health. The pharmacist will be responsible for randomising the medication and only the pharmacist will have access to the randomisation results. The patient and investigators will be blinded to the intervention. The pharmacist will maintain accurate records of the receipt of all trial medication including dates of receipt. Pharmacy will distribute the medication to the other three sites and these will be stored in a locked office.
Patients will be instructed to return leftover medication at the end of the fifty days (ideally there will be no leftover product as only fifty days' supply will be provided) and reasons for departure from the expected dispensing regimen will be recorded. At the end of the trial, there will be final reconciliation of the trial drug received, dispensed, consumed and returned. Any discrepancies will be investigated, resolved and documented by the trial team. Unused trial drug will be destroyed in compliance with applicable regulations.

5.2.6 Measurement of participant adherence

Patients will be asked at their two-week, six-week, twelve-week and twenty-six week reviews whether they had been adherent with taking their medication. Adherence will be recorded in the medical record. If patients miss more than three doses at any stage in the preceding two weeks, they will be deemed non-adherent to the treatment protocol and participation withdrawn. Data up to that point will be analysed in the groups to which they were randomised following the intention-to-treat principle, but adherence will be noted and documented.

5.2.7 Excluded medications and treatments

Patients will be advised not to take additional vitamin C supplementation and check the labels of over-the-counter or homeopathic medication, prescribed or otherwise.
There may be the following drug interactions:

- High doses of vitamin C (>1000mg a day) may result in increased absorption of aluminium in medications containing aluminium and subsequent increased susceptibility to kidney stones.
- Anti-oxidants (e.g. vitamin C) may reduce the effect of some chemotherapeutic agents.
- Taking eostrogen and vitamin C may increase oestrogen levels
- Oral vitamin C may reduce the effectiveness of some antivirals such as protease inhibitors
- Vitamin C combined with niacin can reduce niacin's effect

- High doses of vitamin C (>2000mg a day) may reduce the response to warfarin.
- Any reaction to the above medication will result in cessation of treatment and analysis as per intention to treat.
- If patients had taken vitamin C or vitamin C-containing multivitamin in the preceding three months prior to enrolment in the trial they will be ineligible to participate due to the long half life (10 – 20 days) of vitamin C.

5.2.8 Concomitant therapy

Patients will be told prior to commencement of the study not to take vitamin C supplements during the course of the trial and to check labels of any multivitamin supplements.

Patients are advised to inform the researchers if they are to commence chemotherapy during their fifty days of treatment. In this rare instance, the researcher will liaise with the treating oncologist to determine that 500mg vitamin C is appropriate for their chemotherapy regime and the trial treatment will be stopped immediately if deemed unsuitable.

5.2.9 Discontinuation from trial intervention

Participants who discontinue trial treatment will remain in the trial. The remaining trial procedures should be completed as indicated by the trial protocol.

Participants may discontinue trial treatment for the following reasons:

- Participant / legal guardian request to discontinue trial intervention
- Investigator decision to discontinue a participant from the trial intervention if the participant:
    - Is pregnant
    - Experiences a serious or intolerable adverse event such that continued trial intervention would not be in the best interest of the participant
    - Develops, during the course of the trial, symptoms or conditions listed in the exclusion criteria
    - Requires a medication that is prohibited by the protocol
    - Requires early discontinuation for any other reason

The investigator may also withdraw all trial participants from the trial treatment if the trial is terminated.

The procedure for transitioning a participant off the trial drug and/or onto alternate therapy is as follows: patients will be advised to cease taking the medication immediately and return the unused medication to the researcher.

For the safety of all participants ceasing trial treatment, the protocol-specified safety evaluations should be undertaken to capture new safety events and to assess existing, unresolved safety events. All scheduled follow-ups of trial participants should also occur following treatment discontinuation, where possible.

In addition to the safety evaluations, the data to be collected at the time of trial intervention discontinuation will include the following:

- Reason for discontinuing medication
- Any adverse effects
- Involvement of other practitioners in treatment of adverse events

A dedicated Case Report Form (CRF) page will capture the date and the specific underlying reason for discontinuation of the trial intervention.

The participant should remain in the trial for scheduled visits for trial assessments (follow-up) per protocol.

6 RANDOMISATION AND BLINDING

An investigator not directly involved in the analysis of the trial results will prepare the randomisation schedule using block randomisation to maintain balance between treatment arms. This will be Associate Professor Cylie Williams as she will not be directly involved in the analysis. The schedule will be provided to the pharmacist and sealed envelopes containing the treatment allocation of each randomisation code will be provided to the investigator in case of emergency.

6.2 Concealment mechanism

	Allocation concealment	Blinding (masking)
Definition	Unawareness of the next trial group assignment in the allocation sequence	Unawareness of the trial group to which trial participants have already been assigned
Purpose	Prevent selection bias by facilitating enrolment of comparable participants in each trial group	Prevent ascertainment, performance, and attrition biases by facilitating comparable concomitant care (aside from trial interventions) and evaluation of participants in each trial group
Timing of implementation	Before trial group assignment	Upon trial group assignment and beyond
Who is kept unaware	Trial participants, individuals enrolling them **and clinicians assessing outcome measures.**	One or more of the following: Trial participants, investigators, care providers, outcome assessors.
Always possible to implement?	Yes	No

6.3 Breaking of the trial blind

6.3.1 On trial

The randomisation code for an individual participant may only be unblinded in emergency situations, where the Investigator decides a participant cannot be adequately treated without knowing the identity of their treatment allocation. Specifically, if the patient reports symptoms of vitamin C toxicity such as severe gastrointestinal upset or kidney stones, the randomisation code will be broken in order to communicate to the patient's treating physician(s) the vitamin C dosing. To break the randomisation code the Investigator must open the emergency unblinding envelopes provided, or contact the randomisation

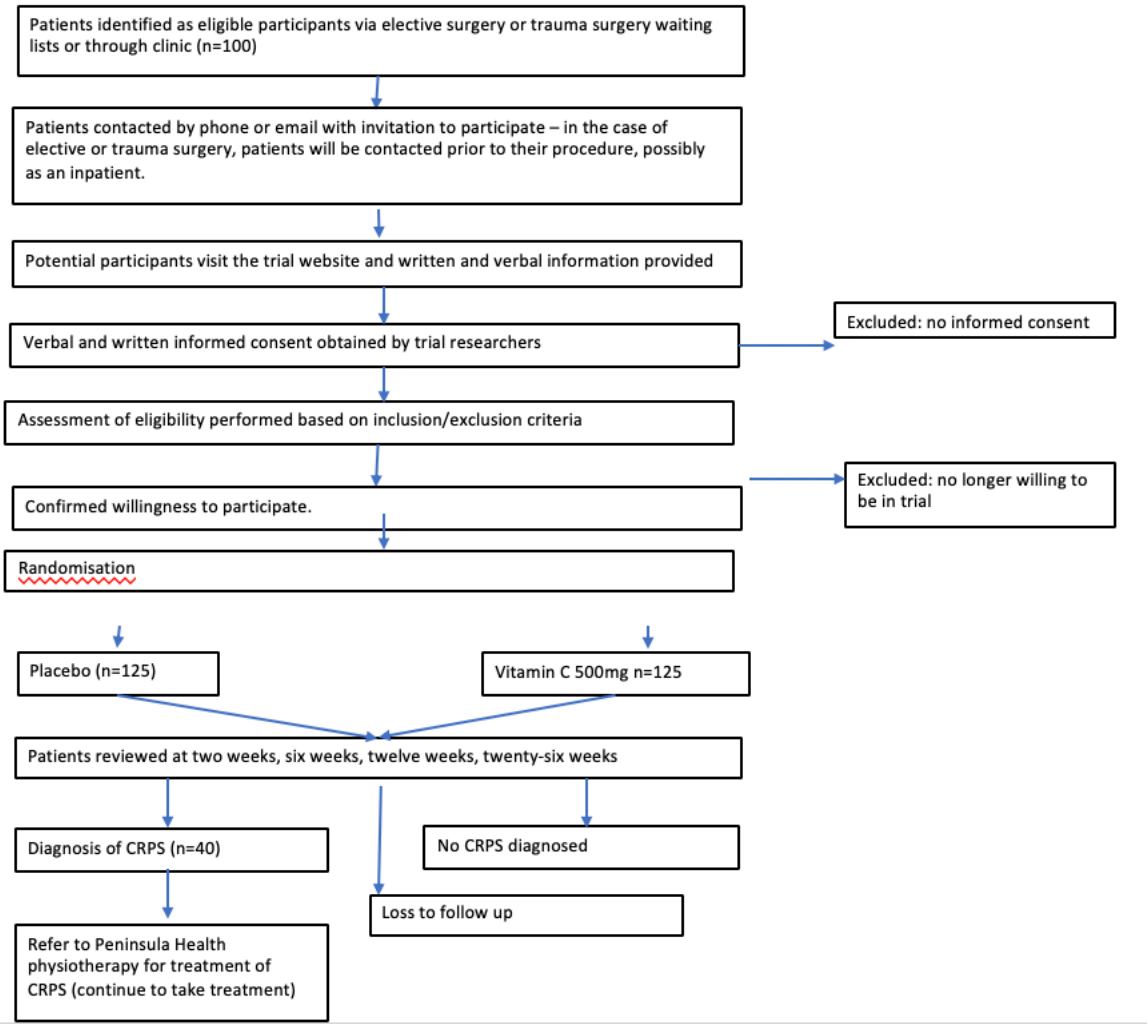
facility/personnel. If any unblinding envelope is opened, the time, date, participant number and reason for opening must be documented.
Blinding is imperative in this trial to avoid bias and answer the specific research question and all researchers are aware of the importance of this.
It is not expected that inadvertent unblinding will occur due to strict randomisation and blinding protocols.

6.3.2 On completion of the trial

Trial drug codes and dosing will only be available once all data collected has been entered into the trial database for every participant and the database has been finalised, except in the case of emergency as detailed above.
Patients will receive a written letter or email informing them of their treatment arm allocation as well as preliminary trial results at the end of the trial.

7 TRIAL VISITS AND PROCEDURES

7.2 Trial timeline



7.3 Schedule of assessments

	TRIAL PERIOD							
	Enrolment	Allocation to intervention	Post-surgery					Close-out
TIME POINT**	$-t_1$	0	*Two weeks*	*Six weeks*	*Twelve weeks*	*Fifty weeks*	*Six months*	*Six months*
ENROLMENT:	Prior to surgery							
Eligibility screen	Prior to surgery							
Informed consent	Prior to surgery							
Reference material given	Prior to surgery							
Allocation to intervention		X						
INTERVENTIONS:								
Placebo		←	—	—	—	→		
Vitamin C 500mg		←	—	—	—	→		
ASSESSMENTS:								
Two weeks post surgery			X					X
Six weeks Post surgery				X				X
Twelve weeks post surgery					X			
Twenty-six weeks post surgery							X	X

7.4 Description of procedures

All members of the orthopaedic team involved in assessing post-operative patients undergo an education session about the project and how to assess for CRPS. CRPS is a relatively common diagnosis that doctors of all grades should confidently be able to detect although the importance of documentation according to our diagnostic criteria will be made during the briefing. The briefing will be repeated during each rotation as the junior doctors rotate through different terms.

To determine suitability for inclusion, all elective and trauma orthopaedic theatre lists will be screened to determine patient eligibility and enrol participants. Adult patients identified as undergoing foot and ankle elective or trauma surgery, as defined as any procedure at or below the level of the distal one third of the tibia, will be deemed a potential participant. Patients will be contacted by a researcher prior to their surgery via telephone or email. If patients were admitted as an inpatient, seen in an outpatient clinic or after hours, they will be contacted by a researcher within 72 hours following their surgery. They will be

randomised and commenced on their treatment within 72 hours of injury or surgery. If patients are unable to commence their vitamin C/placebo treatment within 72 hours of injury or surgery they will be deemed ineligible to participate as comparative studies have commenced vitamin C supplementation the following day after surgery or injury.

If patients consented to their own surgical procedure, they will be deemed of sound mind to consent to the trial as well. Patients will be asked specifically the following questions:

- Have you taken vitamin C or any other multivitamin supplementation that contains vitamin C, in the last three months? If they answer yes, or are unsure they will be deemed ineligible to participate.
- What date and time was your surgery? If this was greater than 72 hours prior to randomisation and commencement of treatment they will be deemed ineligible.
- Are you pregnant or breastfeeding?

The following information will be collected during the initial contact with the patient should the patient consent to participation in the trial:

- Patient identifiers:
    - Age
    - Sex
    - First name/last name
    - Email address
    - Contact phone number.
- Patient demographics
    - Date of birth
    - Sex
    - Previous history of CRPS
    - Previous history of mental health condition
    - Compensable status (public patient, private health insurance, self-funded patient in private, workers' compensation, TAC, other)
- Surgical demographics
    - Date of surgery
    - Hospital where surgery was performed
    - Surgery type (elective, emergency, other)
    - Surgical site (forefoot, midfoot, hindfoot, tibia, combination, other)

The trial intervention will be administered by a researcher and commenced within 72 hours of surgery or injury. In the event that a patient sustains an injury the subsequently has surgery, their 72 hour 'clock' will commence immediately following their surgery.

At each trial visit, patients will be assessed as per the outcome criteria. Patients will be asked about their symptoms and examination documented by the clinician to specifically address the Budapest Criteria for CRPS diagnosis:

A: Does the patient report a history of:	☐ sensory changes (hyperaesthesia and/or allodynia) ☐ vasomotor changes (temperature asymmetry, skin colour changes and/or skin colour asymmetry) ☐ sudomotor/oedema changes (oedema, sweating changes or sweating asymmetry) ☐ motor/trophic changes (decreased range of motion and/or motor dysfunction and/or weakness/tremor/dystonia and/or trophic changes of hair/nails/skin?
B: Does the clinician observe:	☐ sensory changes (hyperaesthesia and/or allodynia) ☐ vasomotor changes (temperature asymmetry, skin colour changes and/or skin colour asymmetry) ☐ sudomotor/oedema changes (oedema, sweating changes or sweating asymmetry) ☐ motor/trophic changes (decreased range of motion and/or motor dysfunction and/or weakness/tremor/dystonia and/or trophic changes of hair/nails/skin?
C: Is there another diagnosis that better explains the signs and symptoms during today's history and examination?	◯ Yes ◯ No
D: Is the patient's pain disproportionate to the inciting event?	◯ Yes ◯ No
If the patient responds yes to three out of four questions in part A, AND the clinician observes two out of four signs in part B, AND answers yes to C and D, the patient meets the criteria for CRPS diagnosis. Does the patient meet the criteria for CRPS diagnosis?	◯ Yes ◯ No

Patients will be examined at their review appointment by a member of the research team or treating clinician according to the following Budapest Criteria:

- A: continuing pain, which is disproportional to any inciting event
- B: The patient must report at least one symptom in three of the four following categories:
    - Sensory- reports of hyperaesthesia and/or allodynia
    - Vasomotor – reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
    - Sudomotor/oedema – reports of oedema and/or sweating changes and/or sweating asymmetry
    - Motor/trophic – reports of decreased range of motion and/or motor dysfunction (weakness/tremor/dystonia) and/or trophic changes (hair/nail/skin)
- C: The clinician must observe at least one sig at the time of the evaluation in two or more of the following categories:
    - Sensory- evidence of hyperalgesia (to pinprick) and/or allodynia and/or deep somatic pressure and/or joint movement
    - Vasomotor – evidence of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
    - Sudomotor/oedema – evidence of oedema and/or sweating changes and/or sweating asymmetry

    - Motor/trophic – evidence of decreased range of motion and/or motor dysfunction (weakness/tremor/dystonia) and/or trophic changes (hair/nail/skin)
- D: There is no other diagnosis that better explains the signs and symptoms

If a patient is unable to attend their appointment in person, a Telehealth appointment and videoconference examination will be utilised instead of a face-to-face appointment.

This information will be recorded in RedCap database managed by Monash University. Patients who meet the above criteria will be diagnosed with complex regional pain syndrome and referred to physiotherapy for management of this condition. They will be told to continue their treatment medication. Patients will then be removed from the trial follow-up (as you cannot have CRPS twice from the same event).
Patients diagnosed with CRPS will be communicated to the lead researcher via email and subsequently entered into the trial database as meeting the outcome.
All hospital registrars and orthopaedic consultants will be given a verbal presentation to introduce the research project and the study investigators involved in the trial. This will be done at an orthopaedic weekly business meeting for approximately one hour. Education on trial design and CRPS examination and history will be provided. Study researchers will conduct follow-up history and examination.
Assessment at two weeks, six weeks, twelve weeks and twenty-six weeks is standard treatment for most bony and soft tissue injuries of the lower limb and does not deviate from normal procedure.

If a patient is diagnosed with CRPS, they will be referred to physiotherapy as per usual care. The method for which they are referred will depend on whether the patient is referred in the public or private systems:

- Public: a written referral will be made to the Physiotherapy Department at Peninsula Health. This is standard practice for a patient diagnosed with CRPS in this institution.
- Private: a written referral will be made to the patient's regular physiotherapist. If the patient does not have a regular physiotherapist, a choice of local, experienced physiotherapists will be offered for a referral and a written referral will be made. This is standard practice for management of CRPS in this system.

Patients will also be asked at each review appointment if they have adhered with the medication and if they are experiencing any side effects.

How has the patient felt since their last visit? (eg. fine, unwell, nauseated, in pain)	_____
Has the patient had any side effects to the medication such as abdominal upset, back pain, nausea or vomiting?	◯ Yes ◯ No
Has the patient taken the medication as prescribed?	◯ Yes ◯ No

If patients have skipped up to three consecutive dose of their medication, they will be

deemed 'non adherent and a note will be made on their Electronic Medical Record but will still be analysed to where they were randomised. If patients skip one dose they will be advised to simply continue the medication and not 'make up' a dose.

7.5 Notes on specific trial visits

7.5.1 Screening

Patients will be recruited via two methods:

- Elective surgery theatre lists
- Trauma surgery theatre lists

In the event of trauma and elective surgery, patients will be contacted prior to their surgery by a member of the research teach and invited to participate.

In the event of presentation in an outpatient setting, patient referrals from their general practitioner or emergency department will be reviewed and patients will be contacted via phone or email to participate in the study.

Patients who are undergoing surgery or have sustained an injury at or distal to the distal one third of the tibia will be eligible.

Patients will be consented and enrolled in the trial prior to surgery and randomisation and commencement of treatment will occur immediately afterwards. In an outpatient setting, if patients have presented within 72 hours of injury, eligibility criteria will be assessed and patients will be consented, enrolled, randomised and treatment commenced during that outpatient visit. If patients are unable to commence their treatment within 72 hours of injury they will not be deemed eligible to participate.

7.5.2 Final trial visit

The final trial visit will occur six months following the patient's surgery. There are no special procedures or evaluations at this time except the standard questions. Trial results and randomisation results will be shared with participants via email at the conclusion of the trial. It is not expected patients will need to be contacted in the future.

Any adverse events as a result of the medication will be followed until resolution and appropriate referrals followed up.

7.5.3 Unscheduled visit

Patients will be advised to contact a member of the research team should they have an unscheduled visit (for example, to the Emergency Department) with either an exacerbation of their condition or side effect of their medication. Patients will be asked at each review whether they had presented to another centre for their injury or side effect at any stage.

7.5.4 Telehealth consultations

In light of the recent coronavirus pandemic and shift to telehealth consultations, the need for potential telehealth follow up has been made. It is expected that patients will be followed up by standard face-to-face appointments but, if required, follow up can be via videoconference using secure videoconference programs as recommended by the Department of Health – these are Health Direct (Peninsula Health) or Coviu (Frankston Private Hospital, Holmesglen Private Hospital, Cabrini Brighton Private Hospital and Beleura Private Hospital). These videoconferencing systems and secure and recommended by the federal Department of Health for telehealth consultations.

5.2 Treatment discontinuation, participant withdrawals and losses to follow up

5.2.1 Discontinuation of treatment - participant remains in trial for follow up

Participants who discontinue trial treatment will remain in the trial. The remaining trial procedures should be completed as indicated by the trial protocol.

Participants may discontinue trial treatment for the following reasons:

- Participant request to discontinue trial intervention
- Investigator decision to discontinue a participant from the trial intervention if the participant:
    - Demonstrates significant non-adherence with the trial intervention
    - Experiences a serious or intolerable adverse event such that continued trial intervention would not be in the best interest of the participant
    - Develops, during the course of the trial, symptoms or conditions listed in the exclusion criteria
    - Requires a medication that is prohibited by the protocol
    - Requires early discontinuation for any other reason

The investigator may also withdraw all trial participants from the trial treatment if the trial is terminated.

The procedure for transitioning a participant off the trial drug and/or onto alternate therapy is as follows – immediate cessation of the intervention medication and opening of randomization envelope so treating clinicians are aware of the dosage.

For the safety of all participants ceasing trial treatment, the protocol-specified safety evaluations should be undertaken to capture new safety events and to assess existing, unresolved safety events. All scheduled follow-ups of trial participants should also occur following treatment discontinuation, where possible.

In addition to the safety evaluations, the data to be collected at the time of trial intervention discontinuation will include the following:

- Reason for discontinuation
- Assessment for CRPS

A dedicated Case Report Form (CRF) page will capture the date and the specific underlying reason for discontinuation of the trial intervention.

The participant should remain in the trial for scheduled visits for trial assessments (follow-up) per protocol.

5.2.2 Withdrawal of consent - participant withdraws from all trial participation

Participants are free to withdraw from the trial at any time upon their request or the request of their legally acceptable representative. Withdrawing from the trial will not affect their access to standard treatment or their relationship with the hospital and affiliated health care professionals.

For the safety of all participants ceasing trial treatment, reasonable efforts should be made to undertake protocol-specified safety evaluations to capture new safety events and to assess existing, unresolved safety events following withdrawal.

If patients have severe symptoms they will be referred to the most appropriate treating clinician (for example, urology in the setting of kidney stones). Patients will be advised to cease treatment and randomization treatment arm will be made known to patient and clinician.

A dedicated Case Report Form (CRF) page will be used to capture the date of participant withdrawal of consent.

5.2.3 Losses to follow-up

A participant will be considered lost to follow-up if they fail to return for two scheduled visits and is unable to be contacted by the trial site staff. The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address, a letter to the patient's general practitioner and also an email to the patient). These contact attempts will be documented in the participant's medical record or trial file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

5.2.4 Replacements

Participants who sign the informed consent form and are not randomised / assigned trial intervention may be replaced.
Participants who have been randomised / assigned trial intervention may NOT be replaced.

5.2.5 Trial Closure

A participant is considered to have completed the trial if he or she has completed all phases of the trial including the last visit or the last scheduled procedure shown in the Schedule of Assessments,

The end of the trial is defined as completion of the last visit in the Schedule of Assessments in the trial at all sites. At this stage, the Sponsor-Investigator will ensure that all HRECs and RGOs as well as all regulatory and funding bodies have been notified.

This trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the trial is prematurely terminated or suspended, the Sponsor-Investigator will promptly inform trial participants, HREC and RGO, the funding (where applicable) and regulatory bodies, providing the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of an unexpected, significant, or unacceptable risk to participants that meets the definition of a Significant Safety Issue (SSI) (for the definition refer to Section 8.1).
- Insufficient adherence to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Demonstration of efficacy that would warrant stopping
- Determination that the primary endpoint has been met
- Determination of futility

In the case of concerns about safety, protocol adherence or data quality, the trial may resume once the concerns have been addressed to the satisfaction of the sponsor, HREC, RGO, funding and/or regulatory bodies.

5.2.6 Continuation of therapy

Patients will only be given a 50 day supply of treatment medication. It is expected they will cease this medication before the trial finishes so no continuation of medication will be required.

6 SAFETY EVENTS AND RISKS

Please note – the risk of an adverse event with this over-the-counter, commonly used vitamin supplement is very low. In other trials, no adverse events using the medication had been reported, even in doses that are double what we are proposing.

6.2 Definitions

6.2.1 Definitions for use in trials involving investigational medicinal products

Participant-specific adverse events

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and does not necessarily have a causal relationship with this treatment.

Adverse Reaction (AR): Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an investigational medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR): Any adverse event/adverse reaction that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect.

Note: Life-threatening refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in this definition should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both serious and unexpected. A SUSAR will be immediately reported to all stakeholders including the sponsor, investigators, HREC, local governance office and TGA.

Safety issues (requiring expedited reporting)

The following definitions describe additional safety events that require expedited reporting to stakeholders including the Sponsor, Investigators, HREC, local governance office and TGA.

Significant Safety Issue (SSI): A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
A SSI is a new safety issue or validated signal considered by the Sponsor in relation to the investigational medicinal product that requires urgent attention of stakeholders. This may be because of the seriousness and potential impact on the benefit-risk balance of the investigational medicinal product, which could prompt regulatory action and/or changes to the overall conduct of the clinical trial, including the monitoring of safety and/or the administration of the investigational medicinal product.

Urgent Safety Measure (USM): A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This is a type of SSI that can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

6.2.2 Definitions for use in trials involving investigational medical devices

Participant-specific adverse events

Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device

Note: This definition includes adverse events resulting from insufficient or inadequate instruction for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device.

Note: This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

Device Deficiencies: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

Serious Adverse Device Effect (SADE): An adverse device effect that has resulted in any of the consequences of a Serious Adverse Event (SAE).

Serious Adverse Event (SAE): An adverse event that:

a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalisation, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death or a congenital anomaly or birth defect.

Note: Planned hospitalisation for a pre-existing condition, or a procedure require by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE): A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report. USADEs require expedited reporting to stakeholders including the Sponsor, Investigators, HREC, local governance office and TGA.

Safety issues (require expedited reporting)

Significant Safety Issue (SSI): A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

Urgent Safety Measure (USM)
A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

6.3 Capturing and eliciting adverse event/reaction information

Adverse events and adverse reactions (non-serious and serious) will be captured from the time of administration of the medication until 30 days following the final dose (fifty days after commencement of the trial) and will be followed until resolution or stabilisation.

At every trial visit participants will be asked "How have you felt since your last visit?" in order to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, used any new medication or changed concomitant medication regimens. In addition, AEs will be documented from physical examination

findings, clinically significant lab results or other documents (including participant diaries and correspondence from their primary care physician) that are relevant to participant safety. This will be recorded in the patient's medical record as well as communicated with members of the research team.

6.4 Documentation of AEs

For the purposes of this trial the investigator is responsible for recording all Adverse Events, regardless of their relationship to trial drug, with the following exceptions:

- Conditions that are present at screening and do not deteriorate will not be considered adverse events.
- Abnormal laboratory values will not be considered adverse events unless deemed clinically significant by the investigator and documented as such.

The AE will be described in the source documents (e.g. medical record or trial shadow file) and captured on the CRF and will include:

- A description of the AE
- The onset date, duration, date of resolution
- Severity (mild, moderate or severe – what is the impact on the participant's daily life?)
- Seriousness (i.e. is it an SAE?)
- Any action taken, (e.g. treatment, follow-up tests)
- The outcome (recovery, death, continuing, worsening)
- The likelihood of the relationship of the AE to the trial treatment (Unrelated, Possible, Probable, Definite)

Changes in the severity of an AE will be reported. AEs characterised as intermittent will be documented for each episode. All AEs will be followed to adequate resolution, where possible.

6.5 Assessing the seriousness of a participant's AE

The seriousness of an AE will be assessed by an investigator according to the definition in in the preceding section on definitions with the following exception(s):

- Hospitalisation due to progression of disease will not be considered an SAE for the purposes of this trial.

* The severity and relationship of an AE will be assessed as per the following section.

** The seriousness of an AE will be assessed by an investigator according to the definition in Section 8.1, with the following exceptions:

- Hospitalisation due to progression of disease will not be considered an SAE for the purposes of this trial.
- Elective surgery planned at the time of enrolment.

6.6 Assessing the relatedness (causality) of a participant's AE

All adverse events must have their relationship to trial intervention assessed by the investigator who evaluates the adverse event based on temporal relationship and his/her clinical judgment.

The degree of certainty about causality will be graded using the categories below. In a clinical trial, the trial product should always be suspected.

The relationship of the event to the trial intervention will be assessed as follows:

- Unrelated: There is no association between the trial intervention and the reported event. AEs in this category do not have a reasonable temporal relationship to exposure to the test product, or can be explained by a commonly occurring alternative aetiology.
- Possible: The event could have cause or contributed to the AE. AEs in this category follow a reasonable temporal sequence from the time of exposure to the intervention and/or follow a known response pattern to the test article, but could also have been produced by other factors.
- Probable: The association of the event with the trial intervention seems likely. AEs in this category follow a reasonable temporal sequence from the time of exposure to the test product and are consistent with the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgement based on the investigators clinical experience.
- Definite: The AE is a consequence of administration of the trial intervention. AEs in the category cannot be explained by concurrent illness, progression of disease state or concurrent medication reaction. Such events may be widely documented as having an association with the test product or that they occur after rechallenge.

6.7 Assessing the expectedness of a participant's AE

The investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the trial intervention.

The severity of an Adverse Event will be assessed as follows:

- Mild: Events that require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate: Events that cause sufficient discomfort to interfere with daily activity and/or require a simple dose of medication.
- Severe: Events that prevent usual daily activity or require complex treatment.

6.8 Reporting of safety events

Site Principal Investigator Reporting Procedures

The Site Principal Investigator/delegate is responsible for recording all safety events in the source document.

The Investigator is responsible for expedited reporting (within 24 hours of becoming aware of the event) to the Sponsor-Investigator the following local safety events:

1. USMs
2. SUSARs
3. All SAEs /SARs, except those that are identified below as expected in the trial population:

a. Mild gastro-intestinal discomfort
b. Mild discomfort when swallowing the capsule

The Site Principal Investigator is responsible for reporting SAEs (including SUSARs) to the Sponsor-Investigator as soon as possible but within 24 hours of the first knowledge of the event. These reports should be submitted using the trial Expedited Safety Report Form (see Appendix 3).

The Site Principal Investigator is also responsible for reporting SSIs, local USMs and local SUSARs to their research governance office within 72 hours of becoming aware of the event and in accordance with their local governance authorisation.

Sponsor-Investigator Reporting Procedures

The Sponsor-Investigator must assess and categorise the Expedited Safety Reports received from Investigators and report these to all Site Principal Investigators, the approving HREC and TGA in accordance with the NHMRC's 'Safety monitoring and reporting in clinical trials involving therapeutic goods' (November 2016) and any additional requirements of the approving HREC. All safety reports must clarify the impact of the safety event on participant safety, trial conduct and trial documentation.

The Sponsor-Investigator is responsible for the following reporting to PIs, the HREC(s) and TGA:

1. All SSIs that meet the definition of a USM within 72 hours of becoming aware of the issue.
2. All other SSIs within 15 calendar days of instigating or becoming aware of the issue
3. For SSIs leading to an amendment of trial documentation:
    a. Submit details of the SSI without undue delay and no later than 15 calendar days of becoming aware of the issue.
    b. Submit amendment to the HREC without undue delay.
4. For SSIs leading to temporary halt or early termination of a trial for safety reasons:
    a. Communicate reasons, scope of halt, measures taken, further actions planned without undue delay and no later than 15 calendar days of decision to halt.
    b. For a temporary halt, notify the PIs, HREC and TGA when the trial restarts, including evidence that it is safe to do so.

The Sponsor will also report SUSARs to the TGA as follows:

1. Fatal or life-threatening SUSARs immediately, but no later than 7 calendar days after being made aware of the issue (follow up info within a further 8 calendar days)
2. All other SUSARs no later than 15 calendar days of being made aware of the issue

The Sponsor is responsible for providing the additional safety information to the approving HREC:

1. Provide an annual safety report, including a summary of the evolving safety profile of the trial
2. Provide any updated Product Information/Investigator's Brochure for the investigational products (if applicable)

The Sponsor is also responsible for providing any updated Product Information/Investigator's Brochure to Investigators.

7 DATA MANAGEMENT

9.1 Overview

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of trial participants, including accurate case report forms (CRFs), and source documentation. The Investigators must use maintain a record that details the location of essential documents, including those documents stored outside the Investigator Site File. Consider locations of all source documents, e.g. pharmacy, pathology, radiology, Investigator's office.

9.2 Data Collection, processing and storage

9.2.1 Source Data

Outcome data will be recorded in online database RedCap through Monash University, and notes made in the patient's electronic medical record. Data analysis will be performed using patient hospital numbers only, and additional information about the data (such as notes about study write-up and thesis drafts) will be stored on locked laptop.

Patient consent forms will be stored in a locked office in the department of surgery, Frankston Hospital.

Study investigators will enter the data directly into RedCap and make a note in the patient's electronic medical record that this has been performed.

9.2.2 Data Capture Methods and Storage

Study investigators will be briefed on how to record information in their assessment and consultation notes for the trial as per the protocol using RedCap. Education material and training on the use of RedCap will be provided by the Principal Investigator.

Clinicians will document the following assessment criteria in RedCap at each two week, six week, twelve week and twenty-six week follow up point:

A: Does the patient report a history of:	☐ sensory changes (hyperaesthesia and/or allodynia) ☐ vasomotor changes (temperature asymmetry, skin colour changes and/or skin colour asymmetry) ☐ sudomotor/oedema changes (oedema, sweating change or sweating asymmetry) ☐ motor/trophic changes (decreased range of motion and/or motor dysfunction and/or weakness/tremor/dystonia and/or trophic changes of hair/nails/skin?
B: Does the clinician observe:	☐ sensory changes (hyperaesthesia and/or allodynia) ☐ vasomotor changes (temperature asymmetry, skin colour changes and/or skin colour asymmetry) ☐ sudomotor/oedema changes (oedema, sweating change or sweating asymmetry) ☐ motor/trophic changes (decreased range of motion and/or motor dysfunction and/or weakness/tremor/dystonia and/or trophic changes of hair/nails/skin?
C: Is there another diagnosis that better explains the signs and symptoms during today's history and examination?	◯ Yes ◯ No
D: Is the patient's pain disproportionate to the inciting event?	◯ Yes ◯ No
If the patient responds yes to three out of four questions in part A, AND the clinician observes two out of four signs in part B, AND answers yes to C and D, the patient meets the criteria for CRPS diagnosis. Does the patient meet the criteria for CRPS diagnosis?	◯ Yes ◯ No
How has the patient felt since their last visit? (eg. fine, unwell, nauseated, in pain)	_____
Has the patient had any side effects to the medication such as abdominal upset, back pain, nausea or vomiting?	◯ Yes ◯ No
Has the patient taken the medication as prescribed?	◯ Yes ◯ No

The diagnosis of CRPS will be made if the patient meets the Budapest criteria, and patients will be referred to physiotherapy for pain management. The investigator will record whether the patients was diagnosed with CRPS in the EMR and communicate this back to the patient's General Practitioner via a clinical letter (this is standard practice in the event of a post-operative complication).

Randomisation data will be stored on a locked computer in the Department of Surgery.

Data analysis will be performed using non-identifiable hospital UR numbers only, stored on a locked laptop by the senior researcher and in a password protected file and using RedCap.

9.2.3 Record Retention

Data will be kept for 15 years after the completion of the trial. Hard-copy consent forms will be stored in a locked office in the department of surgery. Electronic data will be stored on a

locked laptop using a password protected file. Records will not be destroyed without the written consent of the primary investigator. Dr Amy Touzell, primary researcher, will have access to the stored data and will be responsible for deleting data at the end of the archival period. Hard-copy consent forms will be shredded.

9.2.3.1 Registration of a Biobank

Not applicable.

9.2.3.2 Sample Storage and Management

Not applicable.

10 STUDY OVERSIGHT

10.1 Governance structure

10.1.1 Trial Management Group (TMG)

The Site Principal Investigator is responsible for supervising any individual or party to whom they have delegated tasks at the trial site. They must provide continuous supervision and documentation of their oversight. To meet this GCP requirement, a small group will be responsible for the day-to-day management of the trial and will include at a minimum the Site PI and, project coordinator and statistician. The group will closely review all aspects of the conduct and progress of the trial, ensuring that there is a forum for identifying and addressing issues. Meetings must be minuted with attendees listed, pertinent emails retained and phone calls documented.

10.1.2 Trial Steering Committee (TSC)

A TSC will be established to provide expert advice and overall supervision, and ensure that the trial is conducted to the required standards. The SSC will meet at least annually, with more frequent meetings as needed, and will work to a Terms of Reference.

10.1.3 Safety Monitoring

Safety oversight will be under the direction of an Independent Safety Monitor, whose primary responsibility is to provide independent safety monitoring in a timely fashion. The Independent Safety Monitor will operate within agreed terms of reference / approved charter and will provide input to the Sponsor-Investigator.

10.2 Site Monitoring

Trial site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol and amendment(s), good clinical practice and applicable regulatory requirements.

Full details of trial site monitoring are documented in the Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will

be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Monitoring for this trial will be performed by Mr Richard Large, director of research at Frankston Public hospital. Monitoring will be on-site, occurring yearly, and will review consent forms, assess eligibility data and monitor for safety and withdrawals from treatment.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.3 Quality Control and Quality Assurance

Both the Sponsor-Investigator and Site Investigator have responsibilities in relation to quality management.

The Sponsor-Investigator will develop SOPs that identify, evaluate and control risk for all aspects of the trial, e.g. trial design, source data management, training, eligibility, informed consent and adverse event reporting. The Sponsor-Investigator will also implement quality control (QC) procedures, which will include the data entry system and data QC checks. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

As outlined in the previous section (Site Monitoring), the trial monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, good clinical practice and applicable regulatory requirements.

In the event of non-compliance that significantly affects human participant protection or reliability of results, the Sponsor-Investigator will perform a root cause analysis and corrective and preventative action plan (CAPA).

In addition, each clinical site will perform internal quality management of trial conduct, data and biological specimen collection, documentation and completion. An individualised quality management plan will be developed to describe a site's quality management.

11 STATISTICAL METHODS

11.1 Sample Size Estimation

Sample size is not formally determined a priori, as the aim of this randomised pilot study is to determine feasibility for a future definitive randomised trial. However, we deem a sample size of at least 50 participants per arm as reasonable for allowing estimation of key feasibility parameters.

11.2 Population to be analysed

The study sample will be analysed via the intention-to-treat principle. Therefore, all randomised participants will be included analysis, regardless of whether they received and/or adhere to their allocated trial drug.

11.2.1 Handling of missing data

All qualitative data will be analysed according to the intention-to-treat principle. No missing data will be imputed. There are no data substitutions for adverse events or adherence.

11.3 Methods of analysis

The two secondary aims of this feasibility study will be addressed statistically. For the first secondary aim, diagnosis of CRPS will be ascertained in the form of time-to-event data, and rate ratios will be calculated using univariate Cox proportional hazards regression to directly compare diagnosis rates between the treatment and control groups.

Given the small sample size of this feasibility study, we anticipate randomization may inadequately balance the baseline characteristics of participants in the two treatment groups (e.g, age, trauma vs elective surgery). If necessary, a secondary set of analyses will be performed to adjust for baseline characteristics found to be imbalanced between groups to the extent of a 0.25 standard deviation difference in means (quantitative measures) or an odds ratio of 1.5 (binary measures). These analyses will be conducted using multivariate Cox proportional hazards regression models.

In the survival analyses, loss to follow-up will be considered a censoring event. This equates to an assumption that data is missing at random given the participant's treatment group and the timing of their loss to follow-up. The adequacy of this assumption will be checked in sensitivity analyses that will include both a multiple imputation by chained equations (MICE) approach and adjustment for baseline covariates predictive of propensity for dropout.

A sensitivity analysis will repeat the proportional hazards regression to compare rates of CRPS as diagnosed by the presence of individual Budapest criteria, rather than 3 out of 4 patient-reported symptoms or 2 out of 4 clinician-observed symptoms as required for formal CRPS diagnosis.

For the second secondary aim, the incidence risk of CRPS 6 months post surgery for lower limb extremity trauma patients will be reported as a proportion of the study sample.

Adverse events will be coded as per the Medical Dictionary for Regulatory Activities. Adverse events will be calculated at each visit, and patients may have more than one adverse advent. Assessment of severity, frequency and relationship of adverse events to trial intervention will by presented by System Organ Class and information such as start date, stop date, severity, relationship expectedness, outcome and duration will be recorded. Adverse events leading to premature discontinuation from the trial intervention and serious treatment-emergent adverse events will be presented in a table.

12 ETHICS AND DISSEMINATION

12.1 Research Ethics Approval & Local Governance Authorisation

This protocol and the informed consent document and any subsequent amendments will be reviewed and approved by the human research ethics committee (HREC) prior to commencing the research. A letter of protocol approval by HREC will be obtained prior to the

commencement of the trial, as well as approval for other trial documents requiring HREC review.
Each participating institution will also obtain institutional governance authorisation for the research and associated HREC-approved documents. A letter of authorisation will be obtained from the RGO prior to the commencement of the research at that institution. Institutional governance authorisation for any subsequent HREC-approved amendments will be obtained prior to implementation at each site.

12.2 Amendments to the protocol

This trial will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, trial design, participant safety, or may affect a participants willingness to continue participation in the trial is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC, for approval prior to being implemented.

12.3 Protocol Deviations and Serious Breaches

All protocol deviations will be recorded in the participant record (source document) and on the CRF and must be reported to the Site Principal Investigator, who will assess for seriousness.

Those deviations deemed to affect to a significant degree rights of a trial participant or the reliability and robustness of the data generated in the clinical trial will be reported as serious breaches. Reporting will be done in a timely manner (Site Principal Investigator to report to the Sponsor-Investigator within 72 hours and to the Site RGO within 7 day; Sponsor-Investigator to review and submit to the approving HREC within 7 days).

Where non-compliance significantly affects human participant protection or reliability of results, a root cause analysis will be undertaken and a corrective and preventative action plan prepared.

Where protocol deviations or serious breaches identify protocol-related issues, the protocol will be reviewed and, where indicated, amended.

13 CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.

The trial protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical

records (office, clinic or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records.

All laboratory specimens, evaluation forms, reports and other records that leave the site will be identified only by the Participant Identification Number (SID) to maintain participant confidentiality.

Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC or regulatory agencies.

14 PARTICIPANT REIMBURSEMENT

Not applicable

15 FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

The funding will be provided by the Department of Surgery, Peninsula Health.

16 DISSEMINATION AND TRANSLATION PLAN

Trial results and participants randomisation arm will be communicated to participants in an email following the trial completion. A letter will also be written to the patient's general practitioner advising them of participation in the trial and treatment arm.
Dr Amy Touzell, principal investigator, will be responsible for publication of the trial.

17 ADDITIONAL CONSIDERATIONS

If a patient is diagnosed with CRPS, they will be referred to physiotherapy. The method for which they are referred will depend on whether the patient is referred in the public or private systems:

- Public: a written referral will be made to the Physiotherapy Department at Peninsula Health. This is standard practice for a patient diagnosed with CRPS in this institution.
- Private: a written referral will be made to the patient's regular physiotherapist. If the patient does not have a regular physiotherapist, a choice of local, experienced physiotherapists will be offered for a referral and a written referral will be made. This is standard practice for management of CRPS in this system.

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19 APPENDICES

19.1 Appendix 1: Division of sponsor responsibilities between sponsor and sponsor-investigator

Sponsor-Investigator:	Dr Amy Touzell	
Responsibility	**Sponsor**	**Sponsor-Investigator**
Ensure a peer review/independent expert review has demonstrated that the trial proposal is worthwhile and is of high scientific quality.	X	
Ensure the Sponsor-Investigator has adequate procedures in place for all key trial management activities	X	
Assign an overall risk category based on type of intervention	X	
Ensure that the Sponsor-Investigator has the necessary expertise and experience to conduct the trial	X	
Ensure that the Sponsor-Investigator has the resources needed to complete the trial successfully or that plans are in place to raise additional funds.	X	
Confirm provision of insurance and indemnity for the trial and trial related staff as well as measures for participant compensation for trial related injury	X	
Ensure all the roles and responsibilities for the clinical trial are delegated, agreed and documented appropriately	X	
Oversee/sign-off all contract negotiations with external providers (e.g. external lab facilities; pharmaceutical companies for supply of investigational product,)	X	
Ensure the protocol (or other document) details appropriate monitoring and management plans commensurate to the risk and complexity of the trial	X	
Maintain oversight to include audit, where applicable	X	
Ensure that the trial is based on a thorough review of scientific literature including whether any relevant systematic review exists.		X
Secure funding and/or confirm sufficient resources are available to conduct the trial (e.g. trial subjects, time, staff, facilities, finances) or put in place plans to raise additional funds.		X
Ensure that trials are registered on clinical.trials.gov, ANZCTR or other appropriate registry before first patient is enrolled and that appropriate plans for the dissemination of trial findings are in place		X
Unless delegated to a third party, undertake/oversee the design, conduct and reporting of the trial with support from all relevant specialist staff (e.g. statistician, research methodologist) including the development of a protocol that is compliant with international standards including the SPIRIT Statement. Where appropriate, prepare the regulatory dossier for trials aiming to commercialise a new investigational medicinal product/investigational medical device.		X
Ensure a trial risk assessment has been carried out and proportionate trial management and monitoring plans are in place		X
For investigational medicinal product trials, ensure (through the appointed pharmacist, medical engineering) that all requirements for IMP/IMD supplies are met (e.g. manufacture/ packaging/labelling).		X
Develop/endorse an appropriate strategy for independent trial oversight (e.g. Trial Management Group, Trial Steering Committee, Data Safety Monitoring Board) If a Data Safety Monitoring Board is not warranted, ensure alternative mechanisms for ongoing safety monitoring are in place		X

Document trial specific delegation of duty on a Staff Signature and Delegation Log		X
Confirm each member of the trial team are aware of their trial-related duties		X
Ensure the development of all relevant trial documentation (e.g. protocol, Participant Information and Consent Form and Case Report Form)		X
Develop/obtain the investigator's brochure or where appropriate, the Product Information to be used for the trial and ensure that the reference safety information for identifying expectedness of adverse events is clearly identified		X
Oversee the set-up of a clinical trial database		X
Ensure all trial approvals and notification are in place before the trial commences (e.g. HREC, SSA, TGA)		X
Ensure relevant agreements/signatories from service departments supporting the trial (e.g. pharmacy, laboratories, radiology) are obtained		X
Ensure arrangements are in place for the effective financial management of the trial		x
Prepare and submit amendments to the trial		X
Implement procedures to ensure the collection of high quality and accurate data		X
Oversee the set-up and maintenance of a Trial Master File		X
Ensure safety reporting and monitoring for the trial complies with the requirements of the NHMRC Guidance for Safety Monitoring and confirm and execute any sponsor reporting responsibilities that are delegated		X
Submit annual report(s) to the HREC and Research Office in accordance with Australian Guidance and local requirements		X
Report suspected serious breaches of GCP/protocol to the HREC and Research Office in accordance with the NHMRC Guidance		X
Notify HREC, Research Office, TGA and other relevant bodies of the completion of the trial		X
Produce all necessary reports to funders and others		X
Disseminate trial findings through publication/dissemination of trial results where applicable, following the CONSORT Statement		X
Fulfil commitments to trial participants, such as providing information about the outcome(s) of the trial, re-obtaining consent if required due to change in risk-benefit ratio (of investigational medicinal product) or change in protocol procedures		X
Ensure all trial data (including the Trial Master File) and materials, are archived appropriately and retrievable for audit purposes		X
Maintain trial registration record in accordance with the registry's requirements		X

19.2 APPENDIX 2: Significant Safety Issues (SSI) - some examples

Examples below have been extracted from the NHMRC's "Safety monitoring and reporting in clinical trials involving therapeutic goods" (November 2016)

- a serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial
- a hazard to the patient population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
- a major safety finding from a newly completed animal study (such as carcinogenicity)
- a temporary halt/termination of a trial for safety reasons

- recommendations of the Data Safety Monitoring Board, where relevant for the safety of participants, such as an increase in frequency or severity of an expected adverse reaction
- single case events (e.g. toxic epidermal necrolysis, agranulocytosis, hepatic failure) that lead to an urgent safety measure

Examples below have been extracted from the TGA's "Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements" Version 2.0, September 2017

- safety-related actions by comparable international regulatory agencies such as the:
  - withdrawal or suspension of the medicine's availability
  - addition or modification, for safety reasons, of a contraindication, warning or precaution statement to the product information or label
  - modification or removal, for safety reasons, of an indication.
- changes in the nature, severity or frequency of known serious adverse reactions which are medically significant
- detection of new risk factors for the development of a known adverse reaction or a new serious adverse reaction that may impact on the safety or benefit-risk balance of the medicine
- series of reports of similar or linked adverse reactions reported at the same time (that is, a cluster) assessed to suggest a quality defect issue that may have implications for public health
- an unusual and significant lack of efficacy occurring in or outside Australia that may have implications for public health
- major safety findings from a newly completed non-clinical study, post-registration study or clinical trial that may impact the benefit-risk balance of the medicine on the ARTG
- a signal of a possible teratogenic effect or of significant hazard to public health
- safety issues related to any raw materials used in the medicine that may impact the safety of the medicine and/or have implications for public health
- safety issues due to misinformation in the product information or label that may impact the safety of the medicine
- safety issues related to use outside the approved indication or intended use that may impact the safety or benefit-risk balance of the medicine

19.3 APPENDIX 3: Expedited Safety Report Form

EXPEDITED SAFETY REPORT FORM	
Reporting requirement: All sites to report to Sponsor-Investigator all *SAEs, SUSARs and USMs within 24 hours of **trial** staff becoming aware of the event. **Except those identified in the protocol as not needing immediate reporting*	
HREC Reference #	
Project title	Can Vitamin C prevent Complex Regional Pain Syndrome in lower limb trauma? A double-blinded randomised, controlled feasibility study.

Section A: To be completed by the Local Site	
Site:	Frankston Public Hospital Frankston Private Hospital Beleura Private Hospital Holmesglen Private Hospital Cabrini Brighton Private Hospital
Local Site Principal Investigator:	Dr Amy Touzell
Participant Enrolment OR Randomisation No.:	
Date the safety event occurred:	
Date Local Site Principal Investigator became aware of the safety event:	
Participant's date of birth, age and weight:	
Event description and management:	
Event outcome (synopsis):	
Trial phase *(amend to reflect protocol)*	☐ Screening ☐ Treatment ☐ Follow Up
Relationship to the trial drug	☐ Unrelated ☐ Unlikely to be related ☐ Possibly related ☐ Probably related
Expectedness (only complete for SAEs that are probably/possibly related):	☐ Not applicable ☐ Expected ☐ *Unexpected

	*Report SUSAR to local RGO within 72 hours of becoming aware of event
Was an Urgent Safety Measure (USM) instigated? *A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.*	* ☐ Yes ☐ No *Report to local RGO within 72 hours of becoming aware of event
Name and Signature (of local PI or delegate)	Date

Section B: To be completed by the Sponsor-Investigator only	
Is this event a Significant Safety Issue (SSI)? *A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability of the trial. Often SSIs do not fall within the definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR), thus are not reported as SUSARs but require other action such as the reporting of an urgent safety measure (USM), an amendment, a temporary halt or early termination of a trial.*	*☐ Yes ☐ No * Report to TGA, HREC and all site PIs within 15 days of becoming aware of event
Is this event an Urgent Safety Measure (USM)? *A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.*	* ☐ Yes ☐ No *Report to TGA, HREC and all site PIs within 72 hours of becoming aware of event
Is this event a SUSAR?	* ☐ Yes ☐ No *Report to TGA within 7 days of becoming aware of the event if fatal/life threatening, otherwise report within 15 calendar days
Does the <u>protocol</u> require amending as a result of this safety event? (If Yes, submit an amended protocol to approving HREC)	☐ Yes ☐ No
Do the <u>participant information statements</u> require amending as a result of this safety event? (If Yes, submit a**n amendment** request to approving HREC and RGOs with the amended forms)	☐ Yes ☐ No
Is a temporary halt or early termination of the trial required as a result of this safety event? (If Yes, ensure actions are taken within 15 days of decision to halt)	☐ Yes ☐ No
Name and Signature (of Sponsor-Investigator)	Date

Please email one signed copy to the Sponsor–Investigator <*insert name and email address***) and retain the signed original in the Site Investigator File**

19.4 APPENDIX 4: Specimens for biobanking - completed biobank registration form

Not applicable.