MONASH University

Exploring the use of Vitamin C in the prevention of Complex Regional Pain Syndrome: results of a systematic review, protocol design and randomised controlled feasibility study

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Abstract

Vitamin C has been demonstrated to reduce the incidence of Complex Regional Pain Syndrome in the upper limb. No randomized controlled trial has been performed to demonstrate this phenomenon in the foot and ankle. This thesis describes a local file audit, systematic review, protocol and randomized controlled feasibility study assessing the potential relationship between Vitamin C and prevention of Complex Regional Pain Syndrome in the foot and ankle. It provides evidence to support testing this in the future in an appropriately powered randomized control trial.

This thesis is structured with six chapters:

- Chapter 1 describes an overview of the role of Vitamin C in pain management, as well as the history of Complex Regional Pain Syndrome and rationale for development of the feasibility study.
- Chapter 2 reports the findings of a systematic review to determine if a gap in the literature was present in the utilization of Vitamin C to prevent Complex Regional Pain Syndrome following foot and ankle surgery.
- Chapter 3 describes a protocol for a randomized controlled feasibility study to develop a protocol and potential for a larger, randomized, appropriately powered study to determine whether Vitamin C reduces the incidence of Complex Regional Pain Syndrome following surgery to the foot and ankle.
- Chapter 4 describes the results of the feasibility study.
- Chapter 5 presents a discussion of the results, as well as a discussion of the unique complexities and challenges of running a randomized controlled trial during a pandemic.
- Chapter 6 concludes the findings of the research.

During the feasibility trial, patients who were scheduled for surgery to the foot and/or ankle in public and private hospitals were invited to participate in the study. Following informed consent, participants were randomized to receive Vitamin C 500mg daily or placebo, one tablet daily, for fifty days. The medication was commenced within 72 hours of their surgery. Participants were reviewed two weeks, six weeks, twelve weeks and twenty-six weeks following their surgery and assessed for signs and symptoms of Complex Regional Pain Syndrome according to the Budapest Criteria. Outcomes focused on recruitment capability, data collection procedures, suitability of intervention, resource availability and participant response.

20 participants consented to participate in the study, with 40 invited but declined to participate. All data for the 20 enrolled participants was collected in full. 19 of the participants adhered to the full doses of medication without reporting any side effects. One participant inadvertently was not given the medication as requested but elected to take Vitamin C anyway. One participant developed Complex Regional Pain Syndrome and three participants demonstrated signs and symptoms of two out of four criteria for Complex Regional Pain Syndrome without meeting the official criteria for diagnosis.

This is the first known randomized controlled trial assessing the safety and efficacy of Vitamin C in the prevention of Complex Regional Pain Syndrome following foot and ankle surgery. We have demonstrated that participants are willing to be consented into a trial of this design, are adherent with this medication over an appropriate length of time to adequately test effectiveness of medication to prevent Complex Regional Pain Syndrome, did not have any reported side effects or adverse events from either placebo or Vitamin C, and we have developed a protocol for a large-scale multi-centre trial where a sample size of 276 participants (138 in each group) will be appropriate powered to test the effectiveness of this medication to prevent Complex Regional Pain Syndrome.

Declaration

This thesis is an original work of my research and contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This work may demonstrate variation in structure, content and readability due to unprecedented impact of the global COVID-19 pandemic. The outbreak of this disease in 2019 resulted in unforeseen disruption to the normal course of academic research and thesis submission. Widespread lockdowns, cancellation of elective surgery and patient migration limited the physical capabilities of research, particularly a randomized controlled trial focusing on recruitment of patients undergoing elective surgery. Substantial efforts were made to access resources and follow up participants electronically but limitations imposed by the extraordinary situation may have affected the validity of results. The mental and physical well-being of participants, hospital staff and researchers were also impacted. Every effort has been made to ensure the quality and integrity of the research presented, despite the challenges presented by the pandemic.

Signature: Amy Touzell

Dr. Amy Touzell

20 August 2023

Presentations during enrolment

1. Touzell, A. Vitamin C and CRPS: what is the evidence? accepted for presentation at the Australasian Trauma Society meeting, June 2023. This meeting was subsequently cancelled.
2. Touzell, A. Can Vitamin C prevent Complex Regional Pain Syndrome in lower limb surgery? A double-blinded, randomized, multi-centre controlled feasibility study. Currently submitted for presentation (awaiting confirmation) at the Australian Orthopaedic Association Annual Scientific Meeting, November 2023.
3. Touzell, A. Vitamin C and Lower Limb Surgery. What is the evidence? A double-blinded, randomized, multi-centre controlled feasibility study. Currently submitted for presentation (awaiting confirmation) at the Australian Orthopaedic Association Annual Scientific Meeting, November 2023.

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This project was only possible with the support of Dr Taya Collyer from the Frankston Hospital Department of Medicine research team. Your ability to make sense of complex processes and experience with multicentre ethics applications and all things research have been invaluable.

Finally, to my husband, Adam. You have put up with every idea and project that I have started and still maintain unwavering support, enthusiasm and interest in everything I do. This project (and many others) would not have started or finished without you.

Chapter 1: Introduction

1.1 Outline of chapter

This chapter introduces the history of Complex Regional Pain Syndrome (CRPS), its diagnosis, classification and treatment. It also provides the history of Vitamin C and its prevention in CRPS. This provides the foundation for the thesis and subsequent research questions.

1.2 Background

1.2.1 What is CRPS?

Complex Regional Pain Syndrome (CRPS) is a debilitating condition, and also known as Reflex Sympathetic Dystrophy, Causalgia, Sudek Dystrophy or Algodystrophy (1). The condition normally has a stimulating event in the periphery, with common inciting pathology including an ankle sprain (2) or fracture to the distal radius (3). The rate of elective surgery as a precipitating event is as high as 12% (4), although rarely, the condition can also develop with no limb trauma history. Symptoms generally present within days after the inciting event(5), and the condition can take years to resolve. Symptoms include severe pain, swelling, skin discolouration, hypersensitivity and temperature changes in an injured limb. Symptoms and signs can sometimes spread proximally over the entire limb and even involve central areas such as the abdomen and thorax(6).

CRPS has been broadly classified into Type I and Type II. CRPS Type I is not associated with a major nerve injury. CRPS Type II is the development of pain after a nerve injury or an initial painful event(1). The clinical features of the two types are the same.

1.2.2 Natural history of CRPS

Traditionally, the clinical course of CRPS has been divided into three stages: acute, dystrophic and atrophic(7). Acute clinical features include a swollen, red and warm extremity, and patients complain of acute burning pain, an altered sweat pattern and joint stiffness(8). At this stage, there is no fixed joint contracture or muscle wasting. This acute phase lasts up to three months following a noxious event and typically starts within hours or days

after the initial injury. Intolerance to cold is one of the first signs of CRPS and can progress to intolerance to heat, wind and/or soft touch(9). The dystrophic phase occurs three to six months post-injury, and patients present with cool, cyanotic changes, shiny, hypersensitive skin, and fixed contractures(8). Fibrotic changes can occur on an MRI scan. In the atrophic phase, occurring six to twelve months after injury, there is loss of hair, nails and skin turgor. Muscle wasting is often present. Imaging suggests bone demineralisation and generalised osteopaenia. The resolution phase can take years(10).

1.2.3 Diagnostic challenges of CRPS

Ambroise Pare, a French barber surgeon, described what is most likely the first presentation of CRPS in 1594. His experience with gunshot wounds and other high-energy trauma resulted in the treatment of many amputees. He also described phantom limb pain, which has a close clinical correlation to CRPS(11). This was followed by a written description of CRPS by Denmark, a British navy surgeon who described lingering burning pain in the arm of a gunshot victim in 1812(12). CRPS was then described as 'Causalgia' by civil war surgeon, Silas Weir Mitchell, in 1864(1). His initial description was for soldiers who sustained a nerve injury, and by today's definition, would be CRPS Type II. In 1900, a student of German surgeon Paul Sudek (hence the term Sudek Dystrophy) described 'acute inflammatory bone atrophy', where bone atrophy occurred after an acute inflammation of the fingers, fracture or herpes zoster infection(12). His initial description was very accurate in comparison to today's modern definition: "*Irregular obliteration of the pattern of bony striation,... diffuse reduction in radiodensity of the bone image, with lacunae of spongiform bone,...the cortex is striated, especially in the digits, but does not show a reduction in thickness... It is likely that, in sites distant from the site of the illness, it takes the form of an inflammatory irritation, which involves nutritional problems... and, in consequence, resorption of bone. Evidently, it is not by nature a physiological resorption of in-active bone, but if I may so put it, an active atrophy*(13).

A formal description of the condition was first published by the International Association for the Study of Pain (IASP) in 1986(14). However, this description did not provide clear diagnostic criteria. Subsequently, research on the treatment and prevention of the condition was hindered by the difficulty in comparison and generalisability of published work(15). As a result, little valid research focusing on prevention and treatment of CRPS was conducted 1986 and 1993.

In 1993, the International Association for the Study of Pain (IASP) re-defined Complex Regional Pain Syndrome (CRPS) and the subsequent 'Orlando Criteria', named after the location of the meeting, was formed. This was the first attempt to clearly define CRPS Types 1 and 2, and were published in the IASP Classification of Chronic Pain Syndromes(16).

The Orlando Criteria(17) required the patient to meet the following definitions:

1) A noxious event or immobilisation able to start the process
2) Allodynia, hyperalgesia or anyway pain out of proportion compared to the precipitating event
3) Presence of oedema, changes in skin blood flow or abnormal sudomotor activity of the affected region in any stage of the disease process
4) The diagnosis cannot be excluded if the presence of this kind of pain and dysfunction could be related to other diseases

This definition was based solely on expert opinion, and never validated. Harden et al give the example that nearly 40% of patients with diabetic neuropathy also met the Orlando Criteria for CRPS(18). The main limitation was the lack of incorporation of motor and trophic features commonly associated with CRPS. Therefore, the IASP revised the criteria again at a meeting in Budapest, and the now commonly used 'Budapest Criteria' was developed in 2003. This criteria was validated in a study of 113 participants with CRPS Type I and 47 participants with non-CRPS neuropathic pain (18). The updated criteria is widely accepted in current literature and is currently the only standardised, internationally recognised definition of CRPS.

The 'Budapest Criteria'(12) uses four categories to describe symptoms and signs associated with CRPS:

- Sensory – hyperesthesia; allodynia
- Vasomotor – temperature asymmetry, changes in skin colour, skin colour asymmetry
- Sudumotor/oedema – oedema, sweating changes, sweating asymmetry
- Motor/trophic – decreased range of motion, motor dysfunction, trophic changes (hair, nails, skin)

The Budapest Criteria then further refines the definition of CRPS to include:

1) Continuing pain, disproportionate to any inciting event
2) Symptoms: must have at least one symptom in three of the four categories described above
3) Signs: at the time of evaluation, must have at least one sign in two or more of the four categories described above
4) No other diagnosis can better explain the patient's signs and symptoms(19)

Despite published validation, there are ongoing issues with the current diagnostic criteria. The Budapest Criteria do not include recommendations for diagnostic imaging assessment. This debate exists due to the early osteopaenic changes that can occur in this condition(20). Disuse osteopaenia can occur after prolonged weight bearing, and the radiographic findings are not dissimilar to CRPS. Therefore, close clinical correlation needs to be applied with consideration of radiographical data to CRPS diagnosis.

Vasomotor and sudomotor categories rely on comparison to the contralateral side, and in the setting of severe trauma (an inciting event for CRPS), both limbs can be injured. This can limit the clinician and patient's ability to assess for asymmetry. In addition, the diagnosis is one of exclusion where no other diagnosis can better explain the patient's signs and symptoms. This relies on the treating clinician's ability to correctly diagnose potential other causes of symptoms, for example, the non-union of a fracture or the presence of infection. Some authors comment that the current criteria are too strict for population-based studies, and it may be difficult to reliably apply a retrospective chart review(21).

1.2.4 Epidemiology of CRPS

Truly defining the incidence of CRPS has been difficult, given the evolving nature of its diagnostic criteria from 1987 until 2003. Subsequently, comparing epidemiological data from studies undertaken during that time is difficult. In the field of foot and ankle injury, the incidence has been reported to be as high as 4.36%(22). However, a prospective study of 306 participants presenting with a fracture to their foot or ankle demonstrated an incidence of 0.3% when strictly adhering to the Budapest Criteria(23). In this study, 110 participants reported symptoms from at least one category suggesting that some participants reported at least some signs and

symptoms of CRPS despite not strictly meeting the Budapest Criteria. The authors concluded that CRPS may be historically overdiagnosed and highlighted the importance of utilisation of validated diagnostic criteria.

Females are up to four times more likely than males to be diagnosed with CRPS(2,22). A 10-year population-based study observing CRPS also found that the upper limb was twice as commonly affected as the lower limb(2). It is commonly described as a condition in middle-aged adults but has been reported in children and the elderly(21). The majority of CRPS cases occur after orthopaedic surgical procedures(21).

1.2.5 Pathophysiology of CRPS

The understanding of the pathophysiology of CRPS is also evolving. Given the autonomic sensory changes associated with the condition, such as temperature changes, it was thought that autonomic nerve dysfunction could be the sole cause of the condition(24). However, it is now widely accepted that the condition has a multifactorial cause involving both the peripheral and central nervous systems. CRPS patients demonstrate changes in heat regulation and difficulty processing motor and noxious stimuli. In addition, bilateral sympathetic nervous system changes can be present even in patients with only one limb involved(25).

Pain pathways are complex, and there are subsequently multiple points for dysfunction. Bruehl and Warner have recently summarised the pathophysiology of CRPS and described nine mechanisms that may contribute to the development and severity of the condition(26):

Altered cutaneous innervation after injury - It is thought that even in CRPS Type I, some form of initial nerve trauma must be present to trigger the circumstances in which CRPS develops. CRPS has developed after excessively tight plaster casting, supporting a theory of ischaemic injury to small neurons(27). Skin biopsies of patients with CRPS have demonstrated lower densities of epidermal neurites in CRPS limbs in comparison to contralateral unaffected limbs. The changes primarily affected nociceptive fibres, and these changes were not present in patients with non-CRPS-related pain, such as pain from osteoarthritis. CPRS Type I, where there is no indication of peripheral nerve injury, still have significant loss of C-fibres and Aδ fibres in the affected

areas(28). However, it is unknown if the reduced density of nociceptive neurites in CRPS is the cause of, or simply related to, the condition.

Central sensitisation – persistent or severe noxious stimuli secondary to injury trigger increased excitability of nociceptive neurons in the spinal cord. Central sensitisation is mediated by the pain-associated release of neuropeptides such as Substance P and bradykinin. This results in an exaggerated pain response (hyperalgesia), resulting in normally non-painful stimuli such as light touch or temperature changes becoming painful via overactivation of nociceptive pathways(29). Wind-up is an objective measure where increased excitability of spinal cord neurons is evoked by repeated brief mechanical or thermal stimulation at a frequency similar to the natural firing rate of nociceptive fibres(30). Patients with CRPS demonstrate greater wind-up when repeated stimuli are applied to the affected limb in comparison to the contralateral limb. Again, it is unknown if central sensitisation causes the condition or is a result of prolonged, painful stimuli.

Peripheral sensitisation – like the spinal cord, primary afferent fibres in the injured limb also release nociceptive neuropeptides like Substance P and bradykinin. This increases the sensitivity of nociceptors and decreases the firing threshold for noxious stimuli (29), which is likely to be present from the initial trauma.

Altered sympathetic nervous system function – there is increased expression of adrenergic receptors on nociceptive fibres after injury, which may contribute to sympatho-afferent coupling where there is increased uptake of adrenergic neurotransmitters in normal nociceptive fibres. Development of CRPS following a fracture to the distal radius was predicted by early impairment in sympathetic nervous system function, measured by a reduced vasoconstrictor response(31).

Circulating catecholamines – patients with CRPS can display exaggerated vasoconstriction to cold challenge on the affected limb, but have lower noradrenaline levels (which causes vasoconstriction) compared to the contralateral side(32). These low noradrenaline levels suggest diminished local sympathetic nervous system outflow. This may be due to receptor up-regulation of peripheral adrenergic receptors and subsequent hypersensitivity to circulating catecholamines(33).

Inflammatory factors – an inflammatory mechanism hypothesis is supported by several papers suggesting improvement in CRPS symptoms with corticosteroid administration(34). Multiple inflammatory peptides have been implicated in CRPS development, including lymphocyte and mast cell release of interleukin and tumour necrosis factor(35). These peptides encourage oedema. Neurogenic inflammation can also occur with Substance P and bradykinin release described above. Increased inflammatory cytokines have been found in local tissue, circulating plasma and cerebrospinal fluid of patients with CRPS, as well as reduced anti-inflammatory cytokines such as interleukin-10(36). Inflammatory mediators may explain the initial features of CRPS, such as swelling, warmth and sensitivity.

Brain plasticity – neuroimaging does not support a consistent brain activation pattern associated with allodynia(37). However, there is evidence to support the reorganisation of somatotopic maps and reduction in the size of the representation of the CRPS-affected limb in the somatosensory cortex in comparison to the contralateral side, then return to normal when CRPS resolves(38). A similar reorganisation has been demonstrated in phantom limb pain(39).

Genetic factors – familial relationships between patients with CRPS have been described, and there is a threefold increase in the risk of a sibling developing CRPS(40). There is a suggestion that the genes of the major histocompatibility complex encoding human leukocyte antigen (HLA) may contribute to the development of the condition(41). Bruehl et al. suggested 'there is as yet no consistent and compelling evidence for specific genetic factors playing a role in the development of CRPS'(26) although the importance of genetic factors is an exciting future target for therapy.

Psychologic factors – given the association of CRPS with increased catecholamine sensitivity discussed above, it is reasonable to suggest that conditions such as a mentally stressful event associated with increased catecholamine could exacerbate or trigger the condition. CRPS is known to be associated with anxiety and depression(23). In addition, chronic psychological stress is associated with immune system dysfunction that may impact on the inflammatory mediators hypothesised in CRPS development(42). There is limited evidence to support this, although it may offer an area for further study.

1.2.6 Treatment of CRPS

Up to twenty-two treatment modalities have been proposed for CRPS (Table 1) (43). They can be broadly classified into intravenous regional blocks (IVRB), spinal cord blocks, topical therapy, rehabilitation, intravenous pharmacotherapy and oral pharmacotherapy:

Table 1. Common treatment modalities

Category	Types of interventions
Central blocks	o Spinal cord stimulation o Repetitive transcranial magnetic stimulation o Botulinum toxin to the lumbar sympathetic chain o Intrathecal glycine o Intrathecal methylprednisolone
Oral pharmacotherapy	o Oral gabapentin o Oral alendronate o Oral tadalafil o Iohexol
Intravenous pharmacotherapy	o Intravenous pamidronate o Intravenous mannitol o Low-dose intravenous ketamine o Low-dose intravenous immunoglobulin
Topical pharmacotherapy	o Topical transdermal isosorbide dinitrate
Intravenous regional blocks	o Intravenous regional block with methylprednisone o Intravenous regional block with parecoxib o Intravenous regional block with ketorolac, morphine with memantine
Rehabilitation	o Graded motor imagery o Electromagnetic field therapy o Splinting o Mirror therapy

Bisphosphonate, both IV pamidronate and oral alendronate, have been demonstrated to reduce pain in comparison to placebo in patients with early CPS and bone abnormalities on an x-ray or bone scan(44). Bisphosphonates are pyrophosphate analogues where the oxygen in P-O-P has been replaced by a carbon, resulting in a metabolically stable P-C-P structure resistant to enzymatic destruction(45). First-generation bisphosphonates inhibit bone formation and resorption equally and increase potency with each successive generation. Alendronate and pamidronate are second-generation bisphosphonates that stop osteoclast formation. They irreversibly bind to the hydroxyapatite of bone, inhibit the osteoclastic-reabsorbing surface, and block osteoclast function(45). This controls the bone demineralisation seen in CRPS(1), and is thought to

control pain associated with osteopaenia and disuse(7). Alendronate treatment given as a weekly dose of 70mg currently costs $212 per year, however, in Australia is only available as a restricted benefit. To receive treatment, patients must have corticosteroid-induced osteoporosis, osteoporosis (defined as patients aged 70 and over with a bone mineral density T-score of -2.5 or less) or established osteoporosis (defined as a fracture due to minimal trauma)(46). Alendronate is not currently available on the Pharmaceutical Benefits Scheme is Australia for CRPS treatment. Pamidronate, costing $565 a year, is given as a slow intravenous infusion of a single dose but is also only available for restricted conditions (hypercalcaemia of malignancy, multiple myeloma or bone metastases secondary to breast cancer) in Australia(46) and is not available for the treatment of CRPS. Side effects of more potent, late generation bisphosphonates can include osteonecrosis of the jaw, atypical femoral fractures, renal failure and electrolyte disturbance(45). Therefore, bisphosphonate therapy in CRPS should be limited to when osteopaenia is also present, and risk of side effects need to be carefully discussed with the patient and health practitioners involved in their care.

In the upper limb, stellate blocks with lignocaine/clonidine and parecoxib and lidocaine/clonidine were given weekly for three weeks for participants with severe, chronic CRPS. This study demonstrated improvement in pain and quality of life but did not improve function(47).

Physical therapy includes graded motor imagery and mirror therapy. This involves left/right discrimination and explicit motor imagery where the patient imagines moving their affected body part without actually moving it. Mirror therapy involves using a mirror to reflect the movement of the unaffected limb while visualising using the CRPS-affected limb. The goal is to create an illusion of normality in the affected limb and was initially used to treat phantom limb pain(48). Both treatment modalities *'may provide clinically meaningful improvements in people with CPRS Type I, although the quality of the supporting evidence is very low'*(49).

Chapter 2: Vitamin C and prevention of Complex Regional Pain Syndrome – a literature review

2.1 Presentations during enrolment

1. Touzell, A. Does Vitamin C reduce the incidence of Complex Regional Pain Syndrome in patients with trauma to the lower limb? A Systematic Review of the literature. Presented at the 2019 Combined Australian and New Zealand Orthopaedic Foot and Ankle Societies Conference, Gold Coast, QLD. August 2019.

2.2 Outline of chapter

This chapter describes a systematic review aiming to examine the contemporary literature examining the effectiveness of Vitamin C in preventing Complex Regional Pain Syndrome (CRPS) following surgery on the foot and ankle.

2.3 Focused Question

In patients undergoing elective and trauma surgery to the foot and ankle, will Vitamin C, when compared with placebo, reduce the incidence of CRPS?

2.4 Background

CRPS can be debilitating for patients. It is described as a sustained sympathetic activity in a perpetuated reflex arc, characterised by pain out of proportion to examination findings. 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. Early diagnosis and treatment is generally associated with better outcomes, but diagnosis is often delayed. Preventative treatment would be the mainstay of therapy due to the poor clinical response of the condition following diagnosis.

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

The pathophysiology of the condition is still poorly understood. Standard homeostasis can be inundated in patients who have sustained major trauma, resulting in a massive systemic inflammatory response. CRPS 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(1). An increase in inflammatory markers such as TNF-alpha and calcitonin are present locally and systemically.

CRPS can affect patients of all ages with a 4:1 female to male ratio and median age of 46 years at onset(50). The incidence has been described as up to 37% following distal radius fractures and 30% following tibial shaft fractures(50). However, it is worth noting that only a small proportion of patients develop a more severe form of CRPS, and the definition and consequences of this condition can vary from mild to severe. Trauma is the commonest precipitating event(51).

Current treatment is generally via a multidisciplinary team. At many institutions, and in the experience of the lead author, this involves a physiotherapist, podiatrist (in the setting of foot and ankle pathology) or hand therapist (in upper limb pathology) and a pain specialist. In addition, other disciplines such as social work, psychology and occupational therapy can also be involved in the treatment of patients with CRPS. There is an increase in the incidence of CRPS in patients whose have a workers' compensation injury(52) and often a return-to-work occupational therapist, exercise physiologist or other rehabilitation provider are also involved in patient care.

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 a reduction of symptoms(50). Antidepressants 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 and spinal cord stimulation have also been described. Physiotherapy and occupational therapy are the mainstay of treatment and aim to

control oedema, and stretch the affected limb to prevent contraction. Massage, contrast baths and transcutaneous electrical stimulation can be used to desensitize the affected limb. Good-quality evidence supports physiotherapy management in CRPS patients(1).

Vitamin C given in high doses during the first twenty-four hours of burn resuscitation reduced resuscitation fluid requirements and wound oedema has demonstrated effectiveness in preventing CRPS(53). Vitamin C works through scavenging hydroxyl free radicals, protecting the delicate vascular epithelium, inhibiting vascular permeability, and in turn reduces oedema(53). 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(54). Besse et al. performed a quasi-randomised prospective trial that also demonstrated a dose-response relationship between vitamin C and the prevention of CRPS(55). Zollinger also described a statistically significant reduction in the diagnosis of CRPS in participants taking 500mg of Vitamin C with no statistically significant difference between participants taking 500mg and 1500mg but a difference between placebo and 200mg. This highlights a dose response for future study designs(54).

To date, it remains unknown if these results would be replicated in injuries to the foot and ankle. Therefore, the primary aim of this systematic review was to assess the effects of vitamin C in a dose-response relationship for patients who sustained trauma (including elective surgery) to the foot and ankle, in the prevention of Complex Regional Pain Syndrome. Secondary aims were to to describe the measurement methodology of assessing CRPS and contexualise this to the lower limb, determine the incidence of CRPS in the foot and ankle and assess the morbidity associated with CRPS following foot and ankle trauma.

2.5 Methodology

This systematic review was reported and performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (ref). The PICO (Population, Intervention Comparison and Outcomes) model was used to establish the search terms.

2.5.1 Search strategy

The search engines EMBASE, MEDLINE, SCOPUS, SCIENCE DIRECT, PUBMED and The Cochrane Library of Systematic Reviews were accessed. A PIO (Population, Intervention, and Outcome) question was generated to develop the search terms(56), and Boolean operators were utilised as outlined in Table 2.

Table 2. Search terms and Boolean operators

P		**I**		**O**
Lower limb trauma		Vitamin C		Complex regional pain syndrome type I
OR		OR		OR
Lower limb surgery		Ascorbic acid		Complex regional pain syndrome type II
OR				OR
Ankle fracture				Reflex sympathetic dystrophy
OR				OR
Foot fracture				Complex regional pain syndromes
OR				OR
Foot surgery				Chronic pain
OR				OR
Ankle surgery				Chronic pain syndromes
OR				
Tibiotalar	AND		AND	
OR				
Forefoot				
OR				
Ankle injuries				
OR				
Lateral ligament, ankle				
OR				
Arthroplasty, ankle, replacement				
OR				
Ankle				
OR				
Lower extremity trauma				
OR				
Foot injuries				
OR				
foot				

Study designs were included if they were published in peer reviewed journals in English language. Studies were excluded if they described paediatric patients (defined as under 18 years of age), patients who underwent

surgery for malignancy and animal only studies. Qualitative or ecological studies were also excluded as they were not relevant to the research question.

Titles and abstracts were independently screened by three authors (AT, BB and SG) using Covidence software. Full text records were independently screened by two authors (AT and BB) with inclusion based on aforementioned criterial. Inclusion was only through agreement by both raters and conflicting decisions discussed until consensus reached.

2.5.2 Planned Quality Assessment

Critical appraisal checklists were used to assess the quality of included studies, related to the type of study design best suited to answering the review question. The primary aim of this systematic review was focused on the outcome of an intervention. Therefore the PEDro appraisal checklist was utilised for intervention studies. The PEDro appraisal checklist is a validated quality appraisal checklist for randomised control trials (57) with clear checkpoints help determine that any source of bias is unambiguous. Key bias criteria using this checklist identifies:

- Selection bias
- Allocation bias
- Concealment
- Participant blinding
- Therapist/interventionist blinding
- Outcome assessor blinding
- Attrition bias
- Method of statistical analysis.

In order to address the secondary aims, where appropriate, studies were assessed for:

- Internal validity: the likelihood that the work was conducted so potential bias is unlikely to affect the outcomes
- External validity: the extent to which the study findings can be generalised beyond the study to other situations.

It was predicted that a systematic review of the literature could already be discovered as part of the literature search. Whilst this was not the case, it was planned that in this event a 'review of a review' would include the same strict criteria applied in this systematic review:

- Utilisation of PRISMA guidelines
- AMSTAR checklist(58)

2.5.3 Data Extraction

The following information was included in the planned data extraction:

1. Author
2. Title
3. Design
4. Country
5. Total sample size
6. Total feet
7. Sex
8. Age (mean and standard deviation) in control groups
9. Age (mean and standard deviation) in intervention groups
10. CRPS diagnostic criteria used
11. CRPS prevalence in control groups
12. CRPS prevalence in intervention groups
13. Treatment method
14. Control sample size
15. CRPS numbers
16. Comment

2.5.4 Data Synthesis

A meta-analysis was initially proposed. However, due to limited studies and data heterogeneity, we have presented the results narratively.

2.6 Results

2.6.1 Search yield

The initial search yielded 487 studies, of which 187 were duplicates and therefore removed. Figure 1 displays the process of study retrieval and selection, with 18 studies included. Of these 18 studies, only one study met the criteria of being a clinical trial assessing the outcome of Vitamin C following surgery to the foot and ankle. The most common reasons for elimination of a study following full text inclusion were:

- Not related specifically to surgery or injury of the lower limb (n=180)
- Study participants not assessed according to the standardised Budapest Criteria (n=20)
- Did not specify prevention of CRPS using vitamin C (n=10)

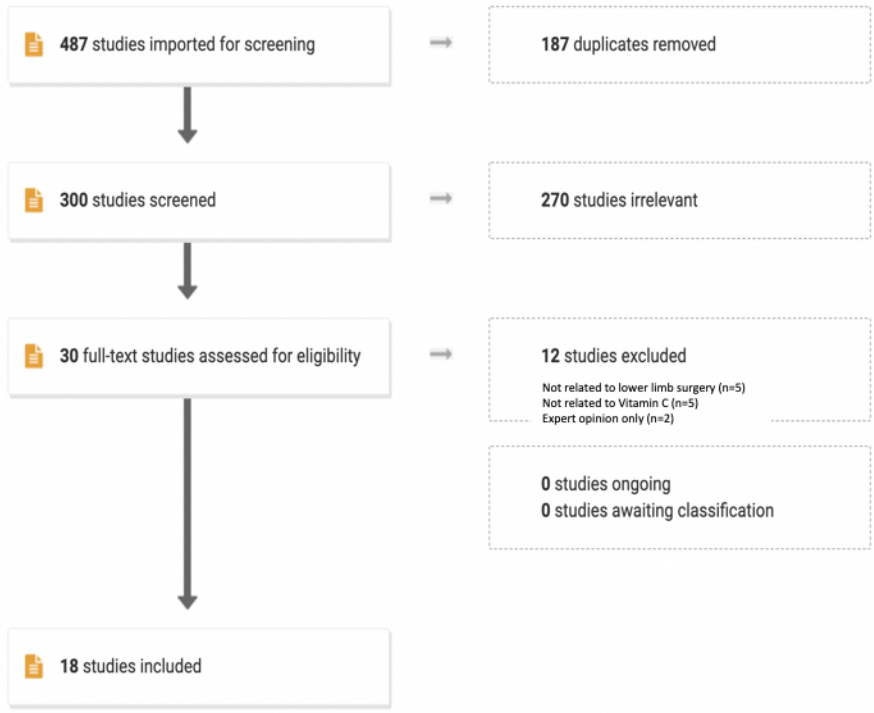

Figure 1. PRISMA flow chart:

Only one paper met criteria for review (55), a French quasi-randomised trial. Participants in the study were all patients having scheduled surgery performed by the primary author. From July 2002 – June 2003, participants had surgery without prescribed Vitamin C post-surgery ('group I'). From July 2003 – June 2004, all participants were prescribed Vitamin C post-operatively ('group II'). Diagnosis of CRPS was made from clinical data as proposed by the IASP criteria(16). Two categories of classical reflex sympathetic dystrophy signs were distinguished, and diagnosis was made in the presence of the set A criterion or at least two set B criteria. This

criteria was outlined within this thesis in Chapter 1. The treatment protocol was 1g of Vitamin C was received orally on the first post-operative day, then each morning for 45 days. In group I authors reported left sided surgery in 45.4% of participants (n=84), and right sided surgery in 54.6% of participants (n=101). In group II, authors reported left sided surgery in 53.2% of participants (n=125) and right sided surgery in 46.8% of participants (n=110). In both groups combined, there were 4.8% (n=20) participants with a prior history of CRPS. Key features of the operation were also described including type of anaesthesia provided, mean tourniquet time and psychological context. Specifically, the type of surgery was reported including forefoot, hindfoot, ankle bone, ankle tendon, neurological, specific hardware removal and other. Authors report there were no statistical differences between the two groups at baseline.

The data within the included study were extracted into Table 3:

Table 3. Data extraction from 'Effect of vitamin C on prevention of complex regional pain syndrome type I in foot and ankle surgery' (58)

Variable	All participants N (% of total population), mean (standard deviation) range	Participants not prescribed Vitamin C: Group I N (% of total population), mean (standard deviation) range	Participants prescribed Vitamin C: Group II N (% of total population), mean (standard deviation) range
Sample size (per person)	392 participants	177 participants	215 participants
Feet operated on	420 feet	185 feet	235 feet
Sex (female)	299 females (76.3%)	133 females (75.1%)	166 females (77.2%)
Age (years)	51 (16) years, 15-87 years	47.1 years (17) years, 16-78 years	51 (16) years, 15-87 years
CRPS Prevalence	22, (5.2%)	18, (9.6%)	4, (1.7%) (n=4)

2.6.2 Quality assessment of included studies

The PEDro (Physiotherapy Evidence Database) scale(57) was used to assess the included quasi-experimental' study. The appraisal is outlines in Table 4:

Table 4. PEDro scale assessment of included study

	Criterion	Yes/No	Where
1.	Eligibility criteria were specified	Yes	2.2: inclusion criteria
2.	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	No	2.1: study design (quasi-experimental study with chronologically successive surgical groups)
3.	Allocation was concealed	No	2.1: study design – patients were not blinded, although the statistical analysis was
4.	The groups were similar at baseline regarding the most important prognostic indicators	Yes	3.1: Results. There were no significant inter-group differences on general characteristics
5.	There was blinding to all subjects	No	2.1: study design – only statistical analysis was blinded
6.	There was blinding of all therapists who administered the therapy	No	2.1: study design – only statistical analysis was blinded
7.	There was blinding of all assessors who measured at least one key outcome	No	2.1: study design – only statistical analysis was blinded
8.	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Unsure	2.4: methodology – it appears all patients were followed up by the same physician but there is no direct mention of all patients being followed up
9.	All subjects for whom outcome measures were available received the treatment or controlled condition as allocated or, when this was not the case, data for at least one key outcome was analysed by 'intention to treat'	No	3.2: effect of vitamin C. One Group II patient stopped Vitamin C after one day's treatment, and went on to develop post-operative CRPS I; he was excluded from the analysis.
10.	The results of between-group statistical comparisons were reported for at least one key outcome	Yes	3.2: effect of vitamin C
11.	The study provides both point measures and measures of variability for at least one key outcome	Yes	3.2: effect of vitamin C - CRPS I occurred in 9.6% of Group I patients (n = 18), as against 1.7% (n = 4) in Group II ($p < 0.0001$).

2.7 Discussion

There is an obvious paucity of quality evidence on this topic in the literature. Out of a review of 487 studies, only one met our inclusion criteria and specifically addressed CRPS following foot and ankle surgery. This single study

had high levels of bias such as an absence of random group allocation and blinding. There is a clear need for a well designed, randomised controlled trial to answer our research question.

A previous systematic review discussing the effect of perioperative Vitamin C supplementation on post-operative pain and the incidence of chronic regional pain syndrome observed in a variety of surgical procedures(59). Surgical procedures included abdominal surgery, head and neck surgery, dental surgery, and upper limb surgery. Our single identified study (60) was also included in the analysis. The authors concluded that there was moderate level evidence for Vitamin C use post-operatively for reducing both post-operative pain and CRPS, although called for further trials to identify optimum dosage and route of administration(59).

Specific to CRPS and limb trauma or surgery, one of the largest, randomised control trials assessed the effect of post-operative Vitamin C on CRPS prevention (61). This trial randomised 317 participants in a double-blinded, prospective, multicentre trial. Two treatment arms were established, with one group administered placebo or a dosage of 200mg, 500mg or 1500mg of Vitamin C daily following a wrist fracture. However, the outcomes of this trial were impacted by their non-routinely accepted method of CRPS diagnosis, and unvalidated method of diagnosis. This study employed a simpler criterion in comparison to the validated Budapest Criteria by describing the diagnosis of CRPS if four of the five symptoms were present:

1. Unexplained diffuse pain that was not normal in relation to the stage of fracture treatment
2. A difference in skin colour relative to the other hand or wrist
3. Diffuse oedema
4. A difference in skin temperature relative to the other hand and wrist
5. Limited active range of motion of the wrist and fingers that was unrelated to the stage of fracture treatment.

The authors used these unvalidated methods to address the difficulty in CRPS diagnosis, highlighted by Bullen et al(23). Whilst this paper is the largest randomised controlled trial to date assessing whether Vitamin C prevents CRPS following extremity surgery, the lack of validated criteria to assess CRPS makes comparison to other studies difficult. This study demonstrated a need for further, high-quality evidence utilising validated, current outcome criteria for the diagnosis of CRPS.

The single peer-reviewed study identified in this systematic review is a substantial limitation when presenting the findings of this literature search. This highlighted a clear gap in the literature to determine whether Vitamin C could prevent CRPS following surgery to the foot and ankle.

2.8 Conclusion

CRPS is a disabling condition associated with significant morbidity and loss of quality of life. It is established that early detection and prevention of this syndrome would be of benefit, particularly in high risk patients. Post-operative administration of Vitamin C may offer a cost-effective preventative strategy with minimal side effects and should be explored further following elective and emergency foot and ankle surgery. There is a clear gap in the literature for high quality studies to determine the effectiveness of Vitamin C in the prevention of CRPS in extremity surgery.

Chapter 3: A protocol of a double-blinded, randomized, multi-centre, controlled feasibility study to understand if Vitamin C prevent Complex Regional Pain Syndrome in foot and ankle surgery?

3.1 Research outputs:

Submitted for publication to Open Science Framework

3.2 Outline of chapter

This chapter reports the approved protocol for the proposed study, 'Can Vitamin C prevent Complex Regional Pain Syndrome in foot and ankle surgery? A double-blinded, randomized, multi-centre controlled feasibility study'. The results of this study protocol are outlines in Chapter 4.

3.2.1 Statement of Compliance

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

3.2.2. Protocol synopsis

Table 5 describes the protocol synopsis and summarises relevant components of the protocol.

Table 5 Summary of trial protocol

TITLE	Can Vitamin C prevent Complex Regional Pain Syndrome in foot and ankle trauma? A double-blinded randomised, controlled feasibility study.
TRIAL DESCRIPTION	This is a randomised controlled feasibility trial conducted at approved sites: • Peninsula Health • Peninsula Private Hospital • The Bays Private Hospital • Beleura Private Hospital The trial recruited patients who presented for elective and emergency surgery of the foot and ankle. Participants were randomised into two groups – placebo and 500mg vitamin C. Participants were then 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 participants with foot and ankle extremity trauma in a dose-response manner 2. to determine the incidence of CRPS in foot and ankle extremity trauma and elective surgery. 3. To determine the demographics and characteristics of participants who develop CRPS of the foot and ankle
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'(18).
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 • Peninsula Private Hospital • The Bays 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) • Peninsula Private Hospital • The Bays Private Hospital • Beleura Private Hospital
DESCRIPTION OF INTERVENTIONS	Participants were allocated to one of two groups: • Placebo • Vitamin C 500mg daily 50 capsules were given to a patient in a box and participants were asked to take one capsule daily for fifty days.
TRIAL DURATION	The trial took approximately eight months to complete. Participants were enrolled for six months and the trial took approximately three months to recruit appropriate numbers. Data analysis took approximately three months.
PARTICIPANT DURATION	Participants were enrolled in the study for six months from the date of their index surgery and were 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 procedure

3.2.3 Glossary of abbreviations

Table 6 provides a glossary of abbreviations used in the protocol.

Table 6 Abbreviation glossary

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

3.3.4 Investigator Agreements

The following Investigator Agreement was included for researchers, including senior investigators, who participated in the study and this will be approved through the ethical governance processes:

"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."

3.4 Trial registration

The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR). The protocol number was ACTRN12621000812897p.

3.4.1 Expected duration of study

The recruitment period was three months. The length of the treatment period was fifty days and the follow-up period was six months. The study was completed within approximately eight months.

3.4.2 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
    - Peninsula Private Hospital
    - The Bays Private Hospital

The investigators have discussed the nature of the trial with these key stakeholders and incorporated preliminary feedback.

3.5 Introduction and background

3.5.1 Trial rationale and aims

This study was planned as a feasibility trial to inform a future trial.

The primary objective – to determine if the proposed protocol was feasible with regards to:

- Recruitment capability
- Data collection procedure

- Suitability of intervention
- Resource availability
- Participant response

Secondary objectives:

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

The role of Vitamin C and the prevention of CRPS has been demonstrated in upper limb trauma(61) but not clearly proven in foot and ankle 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(60)(62).

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 foot and ankle trauma.

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

3.6 Risk/Benefit assessment

3.6.1 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(63). Neither Zollinger nor Besse described any complications from their vitamin C dosing (maximum 1000mg) in their published trials (61)(60).

3.6.2 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(59). It is therefore reasonable that the potential analgesic benefits of vitamin C are considered.

3.6.3 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)(1). 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(64).

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.

3.7 Trial outcomes

3.7.1 Outcome alignment with objectives

Table 7 outlines each of the study objectives and links it to its relevant outcome measures.

Table 7. Study objectives and outcome measures

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 participant 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 foot and ankle extremity trauma in a dose-response manner 2. to determine the incidence of CRPS in foot and ankle extremity trauma	To determine if vitamin C prevents CRPS in patients with foot and ankle extremity trauma in a dose-response manner: Participants were 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 participant meets the 'Budapest criteria' at any of their four post-operative review appointments. This is a combination of asking participants about their symptoms and examining them for positive signs as per the below criteria: A: continuing pain, which is disproportional to any inciting event B: The participant 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

OBJECTIVE	OUTCOME & OUTCOME MEASURE
	(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(18).
To describe the demographics and characteristics of patients who develop CRPS of the foot and ankle	Participant demographics will be collected: • Age • Gender • Mechanism of injury (high energy/low energy) • Workers compensation injury • Smoking status • Diabetes • Pre-existing history of CRPS This information will be used to comment on the demographic of participants who do develop complex regional pain syndrome with the aim of predicting and preventing the condition in this population.

3.8 Study Design

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

- Placebo
- Vitamin C 500mg

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

The trial was conducted at four sites in Victoria, Australia:

- Frankston public hospital
- Beleura Private Hospital
- Peninsula Private Hospital
- The Bays Private Hospital

3.8.1 Justification for dose

Participants were given an oral dose of vitamin C or a placebo. Participants received 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 participants taking 500mg vitamin C. It has been demonstrated that 250mg is less effective than 500mg dosing in preventing CRPS(61). There has also been a very small complication rate in dosing greater than 1000mg/day(65). Therefore, 500mg was determined as most appropriate for this feasibility study.

3.8.2 Trial population

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

Patients who were unable to provide informed consent to participate in the trial were excluded.

3.8.3 Eligibility criteria

Participants were assigned to a randomised trial treatment only if they met all of the inclusion criteria and none of the exclusion criteria.

3.8.4 Inclusion criteria

Each patient met 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 foot and ankle in children are treated non-operatively. In addition, most sites have limited numbers of younger patients who have surgery for foot or ankle problems, so recruitment of people under 18 was unfeasible.
- Patients were required to be able to provide informed consent for the trial via a signed and dated consent form. Patients who were unable to provide informed consent because of (for example) cognitive impairment were excluded.

- Patients who presented to Peninsula Health, Peninsula Private Hospital, The Bays Private Hospital or Beleura Private Hospital for surgery of the foot and ankle, either elective or emergency, were eligible to participate.

3.8.5 Exclusion criteria

Patients meeting the following criteria were excluded from the trial:

- Current or recent (ie less than three months prior to randomisation) use of vitamin C, either as an isolated substance or as part of a multi-vitamin tablet. This is because the vitamin C dosing could 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 were pregnant or breastfeeding will be excluded due to the unknown safety risks in this patient population.
- Patients who were unable to commence taking the placebo/vitamin C medication within 72 hours after their surgery were excluded from the trial
- Patients unable or unwilling to take oral medications.
- Patients who are vegan (as the placebo acidophilus is diary based)

3.8.6 Lifestyle considerations

Patients were required to take one capsule once per day for fifty days. It was noted that this did not inconvenience patients, similar to compliance in other trials.

3.8.7 Screen failures

Eligibility information was 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

Participants had their willingness to participate recorded in the electronic medical record.

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

3.8.8 Recruitment and identification of potential participants

Participants were recruited in the following ways:

- Following HREC approval, elective and trauma theatre lists were screened and potential patients with elective and trauma foot and ankle surgery were identified and asked to participate in the trial. They were contacted by a member of the research team.
- Clinicians in the fracture and elective clinics invited eligible patients to participate in the trial.

Contact details for the patients, including an email address and mobile phone number, were 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 was 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 25 participants were needed to assess the feasibility of the trial.

The recruitment period was approximately three months.

Recruitment was done at the following sites:

- Peninsula Health – Frankston Hospital
- Peninsula Private Hospital
- Beleura Private Hospital
- The Bays Private Hospital

Recruitment occurred in the outpatient setting. There was policy in place for patients who presented with inpatient trauma who were admitted via the Emergency Department, although this did not occur during the recruitment period of this study.

Prior to performing any trial-specific intervention, a signed consent form was obtained for each participant. The investigator or delegated member of the trial team discussed the trial with the potential participant. The investigator provided the Participant Information and Consent Form to the patient which described the purpose of the trial, the procedures to be followed, and the risks and benefits of participation.

The investigator conducted the informed consent discussion and confirmed that the participant understood the information provided. The investigator answered any questions about the trial. The patient was invited to provide written consent. Consent was voluntary and free from coercion. The investigator who conducted the consent discussion also signed the informed consent form. A copy of the consent form was given to the participant where the participant has signed.

It was documented in the participant's record that consent was provided. When the all the inclusion/exclusion criteria were addressed and the eligibility of the participant confirmed, the participant was assigned to a trial arm/intervention.

3.8.9 Consent

Patients were 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 was 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 received written and verbal information about the trial, the risks involved and the follow up required for the study.

Consent from minors was not sought as only patients aged 18 and over are eligible for the trial. A member of the research team obtained informed consent. Patients verbally consented to participating in the trial and this was confirmed in writing and also documented in the patient's Electronic Medical Record.

Patients deemed ineligible for participation, or who declined to participate, was recorded anonymously with reason as to why they did not participate in the trial.

Recruitment and consent was performed by the investigators as well as other members of the investigative team. Patients were given opportunity to consider their involvement in the study, and to discuss their involvement with family members or support persons. It was made clear that participation is voluntary, and the patient's decision to participate would not affect their relationship with any of the treating practitioners including Dr Amy Touzell. It was 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.

3.9 Intervention

3.9.1 Treatment arms

There were two treatment arms: placebo and vitamin C 500mg. Participants were randomised to one of the two arms. Placebo and Vitamin C 500mg capsules were sourced from Peninsula Health pharmacy and kept in a locked office in all sites. Boxes were labelled with a randomised number only. Pharmacy had access to the randomised number and its allocation to placebo or vitamin C 500mg. The participants, clinicians and researchers were not privy to the randomised group. Other labelling of the intervention was as applicable on the vitamin C packet. This included:

- 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 were of similar size and taste. Participants took one capsule orally once per day for fifty days. Capsules were stored in a cool, dry place and prepared by pharmacy.

3.10 Description of trial investigational products

3.10.1 Placebo

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

3.10.2 Vitamin C 500mg

Active substance	Ascorbic Acid (Vitamin C) 500mg Citrus bioflavonoids extract 50mg
Trade or Generic name	Go Healthy Vitamin C 500mg vege capsules

Dosage form	Capsule
Route of administration	Oral one capsule daily for fifty days

3.10.3 Dosage

Participants were randomised to placebo or vitamin C 500mg. They were blinded to their intervention arm until the end of the study.

Participants were told to take one capsule once per day, for fifty days. There was no restriction on the timing of the capsule and could be taken with or without food.

3.10.4 Dose modification

In the very rare event that participants developed 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 were advised to cease taking the medication altogether. They would still be analysed using the intention to treat principle. This did not occur during the trial.

3.10.5 Storage, preparation, dispensing and administration of trial drug

The trial medication was kept in a locked office, and the box of medication was distributed to the participant at either at the time of their surgery or just prior to their procedure, and participants were advised to commence the medication within 72 hours of their surgery. The medication was kept in a locked office with access only by the primary researcher.

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

In the setting of delayed or missed doses, participants were told not to “make up” the dose but instead continue their normal daily dosing.

Participants were 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.

3.10.6. Product accountability

The trial medication was sourced through pharmacy at Peninsula Health. The pharmacist was responsible for randomising the medication and only the pharmacist had access to the randomisation results. The participant

and investigators were blinded to the intervention. The pharmacist maintained accurate records of the receipt of all trial medication including dates of receipt.

Participants were instructed to return leftover medication at the end of the fifty days, but no leftover product was present as only fifty days' supply was provided. Policy was in place to document reasons for departure from the expected dispensing regimen, but this was not necessary. At the end of the trial, final reconciliation of the trial drug received, dispensed, consumed and returned was performed. Any discrepancies were investigated, resolved and documented by the trial team. Unused trial drug was destroyed in compliance with applicable regulations.

3.10.7 Measurement of participant adherence

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

3.10.8 Excluded medications and treatments

Participants were 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.

3.10.9 Concomitant therapy

Participants were 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.

Participants were advised to inform the researchers if they are to commence chemotherapy during their fifty days of treatment. Policy was in place to manage this rare instance, and it was planned for the researcher to liaise with the treating oncologist to determine that 500mg vitamin C is appropriate during their chemotherapy regime and the trial treatment will be stopped immediately if deemed unsuitable. This did not occur during the study.

3.11 Discontinuation from trial intervention

Participants who discontinued trial treatment remained in the trial. The remaining trial procedures were completed as indicated by the trial protocol.

Potential reasons for discontinuing the trial were identified as:

- 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 could also withdraw all trial participants from the trial treatment in the event the trial was terminated.

The procedure for transitioning a participant off the trial drug and/or onto alternate therapy was 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 were undertaken to capture new safety events and to assess existing, unresolved safety events. All scheduled follow-ups of trial participants was planned to occur following treatment discontinuation, where possible.

In addition to the safety evaluations, in the event of intervention discontinuation, the data to be collected at the time of discontinuation included 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 was planned to capture the date and the specific underlying reason for discontinuation of the trial intervention.

It was proposed that participant should remain in the trial for scheduled visits for trial assessments (follow-up) per protocol.

3.12 Randomisation and blinding

An investigator not directly involved in the analysis of the trial results prepared the randomisation schedule using block randomisation to maintain balance between treatment arms. This was done by the Clinical Trials Pharmacist at Peninsula Health, Shu Min. The Pharmacist generated sealed envelopes containing the treatment allocation of each randomisation code and could be provided to the investigator in case of emergency.

3.12.1 Concealment mechanism

Table 8 outlines the methods and reasons for concealment.

Table 8. Concealment

	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

	Allocation concealment	Blinding (masking)
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

3.12.2 Breaking of the trial blind

3.12.2.1. On trial

The randomisation code for an individual participant was proposed to only be unblinded in emergency situations, where the Investigator decided a participant could not be adequately treated without knowing the identity of their treatment allocation. Specifically, if the participant reported symptoms of vitamin C toxicity such as severe gastrointestinal upset or kidney stones, the randomisation code was planned to be broken in order to communicate to the participant's treating physician(s) the vitamin C dosing. To break the randomisation code the Investigator needed to open the emergency unblinding envelopes provided, or contact the randomisation facility/personnel. It was proposed that in the event of any unblinding envelope required opening, the time, date, participant number and reason for opening was to be documented. This was not required during the study. Blinding was imperative in this trial to avoid bias and answer the specific research question and all researchers were aware of the importance of this.

Inadvertent unblinding did not occur, due to our strict randomisation and blinding protocols.

3.12.2.2 On completion of the trial

Trial drug codes and dosing was available once all data collected has was entered into the trial database for every participant and the database was finalized. There were no emergencies that may result in deviation of this protocol on completion of the trial.

Participants received a written letter or email informing them of their treatment arm allocation as well as preliminary trial results at the end of the trial. Participants were also contacted by the researcher over the phone following written communication.

3.13 TRIAL VISITS AND PROCEDURES

3.13.1 Trial timeline

To obtain appropriate feedback for the trial, it was deemed 25 participants would be appropriate for a feasibility study. Figure 2 describes the recruitment process and follow up protocol.

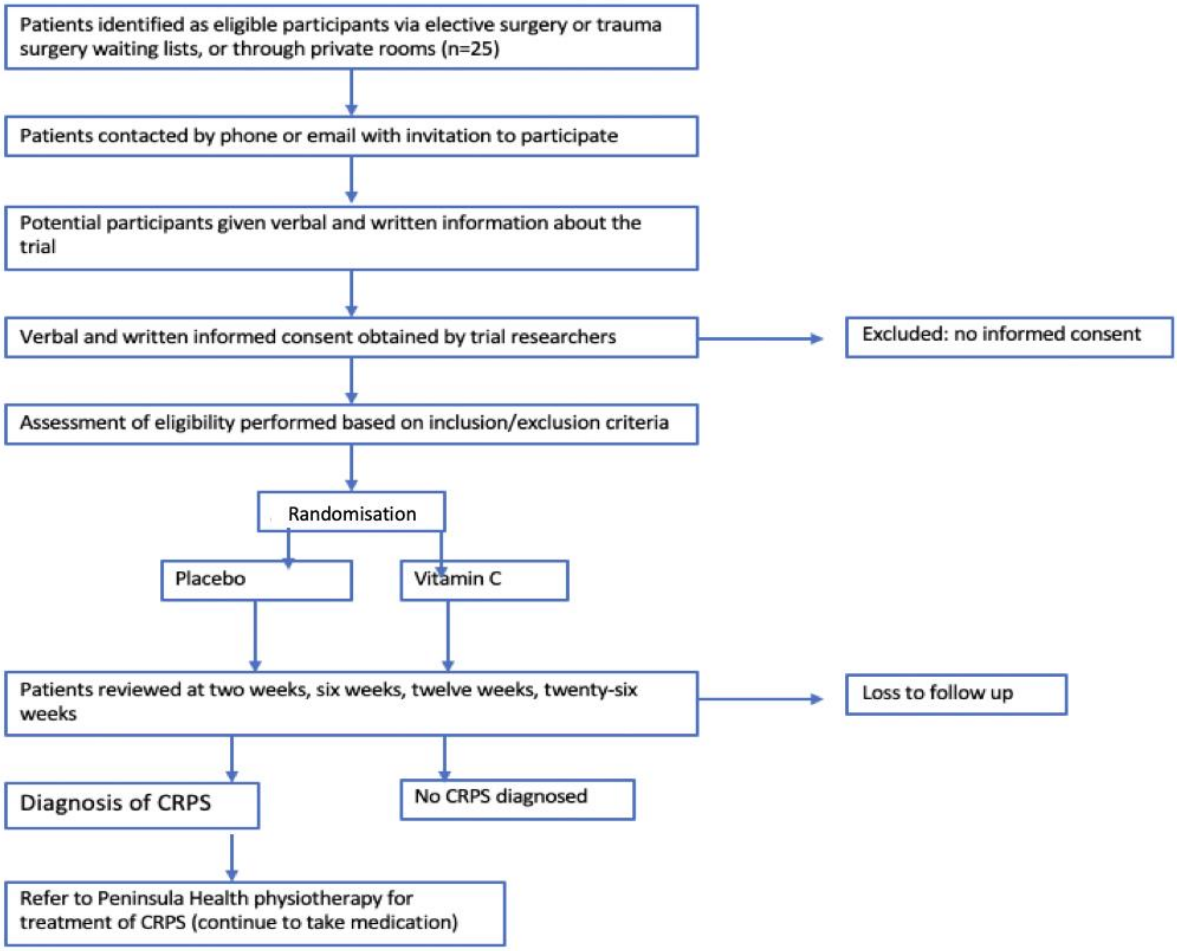

Figure 2. Trial recruitment and follow up

3.13.2 Schedule of assessments

Participants were assessed prior to surgery as well as two, six, twelve, and twenty-six weeks post surgery. This is described in Table 9:

Table 9. Timeline and schedule of assessment.

	TRIAL PERIOD							
	Enrolment	**Allocation to intervention**	**Post-surgery**					**Close-out**
TIME POINT**	**$-t_1$**	**0**	***Two weeks***	***Six weeks***	***Twelve weeks***	***26 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

3.13.3 Description of procedures

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

To determine suitability for inclusion, all elective and trauma orthopaedic theatre lists were 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,

were deemed a potential participant. Patients were contacted by a researcher prior to their surgery via telephone or email if unable to be contacted via phone. If patients were admitted as an inpatient, seen in an outpatient clinic or after hours, they were contacted by a researcher within 72 hours following their surgery. They were randomised and commenced on their treatment within 72 hours of injury or surgery. If patients were unable to commence their vitamin C/placebo treatment within 72 hours of injury or surgery they were deemed ineligible to participate as comparative studies have commenced vitamin C supplementation the following day after surgery or injury.

As patients consented to their own surgical procedure, they were 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 was collected during the initial contact with the participant following 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 was administered by a researcher and commenced within 72 hours of surgery or injury. In the event that a patient sustained an injury the subsequently had surgery, their 72 hour 'clock' commenced immediately following their surgery.

At each trial visit, participants were assessed as per the outcome criteria. Participants were asked about their symptoms and examination documented by the clinician to specifically address the Budapest Criteria for CRPS diagnosis, as described in Figure 3 and entered into the REDCaps database.

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

Figure 3. Outcome assessment criteria as per RedCap database

Participants were 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

When participants were unable to attend their appointment in person, a Telehealth appointment and videoconference examination where possible was utilised instead of a face-to-face appointment.

This data was recorded in RedCap database managed by Monash University.

Participants who met the above criteria were diagnosed with complex regional pain syndrome and referred to physiotherapy for management of this condition. They were told to continue their treatment medication. Participants were then be removed from the trial follow-up (as you cannot have CRPS twice from the same event).

Participants diagnosed with CRPS were communicated to the lead researcher via email and subsequently entered into the trial database as meeting the outcome.

All hospital registrars and orthopaedic consultants were given a verbal presentation to introduce the research project and the study investigators involved in the trial. This was done at an orthopaedic weekly business meeting for approximately one hour. Education on trial design and CRPS examination and history was provided.

Study researchers conducted 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 participant was diagnosed with CRPS, they were referred to physiotherapy as per usual care. The method for which they are referred will depend on whether the participant is referred in the public or private systems:

- Public: a written referral was 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 was 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.

Participants were also asked at each review appointment if they have adhered with the medication and if they are experienced any side effects as per Figure 4 below.

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

Figure 4 Outcome assessment of adherence

If participants skipped up to three consecutive doses of their medication, they were deemed 'non adherent' and a note made on their Electronic Medical Record but was still analysed to where they were randomised. If participants skipped one dose they were advised to simply continue the medication and not 'make up' a dose.

3.14 Notes on specific trial visits

3.14.1 Screening

Participants will be recruited via two methods:

- Elective surgery theatre lists
- Trauma surgery theatre lists

In the event of trauma and elective surgery, patients were 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 were reviewed and patients 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 were deemed eligible.

Patients were consented and enrolled in the trial prior to surgery and randomisation and commencement of treatment occurred afterwards. If patients were unable to commence their treatment within 72 hours of injury they will not be deemed eligible to participate.

3.14.2 Final trial visit

The final trial visit occurred approximately six months following surgery. There were no special procedures or evaluations at this time except the standard questions. Trial results and randomisation results were shared with participants via email and subsequent follow up phone call at the conclusion of the trial. It is not expected participants will need to be contacted in the future.

Any adverse events as a result of the medication were planned to be followed until resolution.

3.14.3 Final trial visit

Participants were 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. Participants were asked at each review whether they had presented to another centre for their injury or side effect at any stage.

3.14.4 Telehealth consultations

In light of the recent coronavirus pandemic and shift to telehealth consultations, the need for potential telehealth follow up was made. It was expected that participants were followed up by standard face-to-face appointments but, if required, follow up could be via videoconference using secure videoconference programs as recommended by the Department of Health – these are Health Direct (Peninsula Health) or Coviu. These videoconferencing systems are secure and recommended by the federal Department of Health for telehealth consultations.

3.15 Treatment discontinuation, participant withdrawals and losses to follow up

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

Participants who discontinued trial treatment remained in the trial. The remaining trial procedures were completed as indicated by the trial protocol.

It was anticipated that participants may have discontinued 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 could 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 was as follows – immediate cessation of the intervention medication and opening of randomisation envelope so treating clinicians are aware of the dosage.

For the safety of all participants ceasing trial treatment, the protocol-specified safety evaluations were 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 would include the following:

- Reason for discontinuation
- Assessment for CRPS

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

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

3.15.2 Withdrawal of consent - participant withdraws from all trial participation

Participants were free to withdraw from the trial at any time upon their request or the request of their legally acceptable representative. Withdrawing from the trial was 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, if this occurred it was planned that reasonable efforts would be made to undertake protocol-specified safety evaluations to capture new safety events and to assess existing, unresolved safety events following withdrawal. This was not required.

If participants had severe symptoms they were referred to the most appropriate treating clinician (for example, urology in the setting of kidney stones). Participants were advised to cease treatment and randomisation treatment arm will be made known to participant and clinician.

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

3.15.3 Losses to follow-up

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

- The site attempted 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 wished to and/or should continue in the trial.
- Before a participant was deemed lost to follow-up, the investigator or designee made 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 participant's general practitioner and also an email to the participant). These contact attempts were documented in the participant's medical record or trial file.
- Should the participant continue to be unreachable, he or she were considered to have withdrawn from the trial with a primary reason of lost to follow-up.

3.15.4 Replacements

Participants who signed the informed consent form but were not randomised or assigned trial intervention were replaced.

Participants who have been randomised / assigned trial intervention were not replaced.

3.15.5 Trial Closure

A participant was considered to have completed the trial if he or she had 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 was defined as completion of the last visit in the Schedule of Assessments in the trial at all sites. At this stage, the Sponsor-Investigator ensured that all HRECs and RGOs as well as all regulatory and funding bodies have been notified.

It was planned that this trial could be temporarily suspended or prematurely terminated if there was sufficient reasonable cause. In this event, it was proposed that the trial was prematurely terminated or suspended, the Sponsor-Investigator would 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 could have included (but 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 could then resume once the concerns have been addressed to the satisfaction of the sponsor, HREC, RGO, funding and/or regulatory bodies. This was not required.

3.15.6 Continuation of therapy

Participants were only be given a 50 day supply of treatment medication. Participants ceased this medication before the trial finished so no continuation of medication was required.

3.16 Safety events and risks

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 were proposing.

3.16.1. Definitions of events 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.

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.

3.16.2 Capturing and eliciting adverse event/reaction information

It was planned that all adverse events and adverse reactions (non-serious and serious) would 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 followed until resolution or stabilisation.

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

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

3.16.3 Documentation of AEs

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

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

In the event of an Adverse Event, the AE was planned to be described in the source documents (e.g. medical record or trial shadow file) and captured on the CRF and would 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 would have been reported in the setting of an AE. AEs characterised as intermittent would be documented for each episode. All AEs would be followed to adequate resolution, where possible.

3.16.4 Assessing the seriousness of a participant's AE

The seriousness of an AE was to 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.

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

All adverse events were to have their relationship to trial intervention assessed by the investigator who evaluated the adverse event based on temporal relationship and their clinical judgment. The degree of certainty about causality would 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.

3.16.6 Assessing the expectedness of a participant's AE

The investigator was responsible for determining whether an adverse event (AE) was expected or unexpected. An AE was considered unexpected if the nature, severity, or frequency of the event was 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.

3.16.7 Reporting of safety events

Site Principal Investigator Reporting Procedures

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

The Investigator was 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 was 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. If required, it was proposed that these reports would be submitted using the trial Expedited Safety Report Form (see Appendix 3).

The Site Principal Investigator was 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

It was proposed that the Sponsor-Investigator was to 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 were planned to clarify the impact of the safety event on participant safety, trial conduct and trial documentation.

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

3.17. Data management

3.17.1 Overview

The investigators were responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents were completed in a neat, legible manner to ensure accurate interpretation of data. The investigators maintained adequate case histories of trial participants, including accurate case report forms (CRFs), and source documentation. The Investigators used a record that detailed the location of essential documents, including those documents stored outside the Investigator Site File.

3.18 Data Collection, processing and storage

3.18.1 Source Data

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

Participant consent forms were stored in a locked office in the department of surgery, Frankston Hospital as well as the patient's electronic medical record.

Study investigators entered the data directly into RedCap and notes made in the participant's electronic medical record that this was performed.

3.18.2 Data Capture Methods and Storage

Study investigators were 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 was provided by the Principal Investigator.

Clinicians documented the following assessment criteria in RedCap at each two week, six week, twelve week and twenty-six week follow up point as per the protocol.

The diagnosis of CRPS was made if the participant met the Budapest criteria, and participants were referred to physiotherapy for pain management. The investigator then recorded whether the participant was diagnosed with CRPS in the EMR, and this was communicated back to the participant's General Practitioner via a clinical letter (this is standard practice in the event of a post-operative complication).

Randomisation data was stored on a locked computer in the Department of Pharmacy.

Data analysis was 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.

3.18.3 Record Retention

Data will be kept for 15 years after the completion of the trial. Hard-copy consent forms were stored in a locked office in the department of surgery. Electronic data was stored on a locked laptop using a password protected file. Records were not destroyed without the written consent of the primary investigator. Dr Amy Touzell, primary researcher, had access to the stored data and will be responsible for deleting data at the end of the archival period. Hard-copy consent forms were shredded.

3.19 Study oversight and governance structure

3.19.1 Trial Management Group (TMG)

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

3.19.2 Trial Steering Committee (TSC)

A TSC was established to provide expert advice and overall supervision, and ensure that the trial was conducted to the required standards. The SSC met twice during the trial, with more frequent meetings planned if required, and worked to a Terms of Reference.

3.19.3 Safety Monitoring

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

3.19.4 Site Monitoring

Trial site monitoring was conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data were accurate, complete, and verifiable, and that the conduct of the trial was in

compliance with the currently approved protocol and amendment(s), good clinical practice and applicable regulatory requirements.

Full details of trial site monitoring were 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 was performed by Mr Richard Large, director of research at Frankston Public hospital. Monitoring was on-site and reviewed consent forms, assessed eligibility data and monitored for safety and withdrawals from treatment.

The investigational site provided 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.

3.19.5 Quality Control and Quality Assurance

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

The Sponsor-Investigator developed SOPs that identified, evaluated and controlled 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 also implemented any quality control (QC) procedures, which included the data entry system and data QC checks. Any missing data or data anomalies were planned to be communicated to the site(s) for clarification/resolution.

As outlined in the previous section (Site Monitoring), the trial monitors verified that the clinical trial was 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 would perform a root cause analysis and corrective and preventative action plan (CAPA). This was not required.

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

3.20. STATISTICAL METHODS

3.20.1 Sample Size Estimation

Sample size was not formally determined a priori, as the aim of this randomised pilot study was to determine feasibility for a future definitive randomised trial. However, we deemed a sample size of at least 20 participants per arm as reasonable for allowing estimation of key feasibility parameters.

3.21 Population to be analysed

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

3.21.1 Handling of missing data

All data was analysed according to the intention-to-treat principle. No missing data was imputed. There were no data substitutions for adverse events or adherence.

3.21.2 Methods of analysis

The two secondary aims of this feasibility study was addressed statistically. For the first secondary aim, diagnosis of CRPS was ascertained in the form of time-to-event data, and rate ratios were 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, it was anticipated that randomisation 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 could 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 were conducted using multivariate Cox proportional hazards regression models.

In the survival analyses, loss to follow-up was 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 was 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 repeated 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 foot and ankle extremity trauma patients will be reported as a proportion of the study sample.

Adverse events were planned to be coded as per the Medical Dictionary for Regulatory Activities. Adverse events were planned to be calculated at each visit, and participants could have had 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.

3.22 Ethics and dissemination

3.22.1 Research Ethics Approval & Local Governance Authorisation

This protocol and the informed consent document and any subsequent amendments were reviewed and approved by the human research ethics committee (HREC) prior to commencing the research. A letter of protocol approval by HREC was obtained prior to the commencement of the trial, as well as approval for other trial documents requiring HREC review.

Each participating institution also obtained institutional governance authorisation for the research and associated HREC-approved documents. A letter of authorisation was obtained from the RGO prior to the commencement of the research at that institution. Institutional governance authorisation for any subsequent HREC-approved amendments was obtained prior to implementation at each site.

3.22.2 Amendments to the protocol

This trial was conducted in compliance with the current version of the protocol. Any changes 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 was considered an amendment, and therefore was written and filed as an amendment to this protocol and/or informed consent form. All such amendments were submitted to the HREC, for approval prior to being implemented.

3.22.3 Protocol Deviations and Serious Breaches

All protocol deviations were recorded in the participant record (source document) and on the CRF and were 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 were planned to be reported as serious breaches. Reporting was 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 affected human participant protection or reliability of results, a root cause analysis was planned to be undertaken and a corrective and preventative action plan prepared.

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

3.23 Confidentiality

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

The trial protocol, documentation, data and all other information generated was held in strict confidence. No information concerning the trial or the data was released to any unauthorised third party, without prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution were permitted to 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 permitted access to such records if required.

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

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

3.24 Participant reimbursement

No participant reimbursement was provided for inclusion within this trial

3.25 Financial disclosure and conflicts of interest.

Dr Amy Touzell was supported by an Australian Government Research Training Program Scholarship. Peninsula Health provided in-kind funding through support with health professionals involved within this research. Placebo and Vitamin C drugs were supplied by Dr Amy Touzell.

There were no conflicts of interest to declare for this research.

3.26. Dissemination and translation plan

Trial results and participants randomisation arm were communicated to participants in an email following the trial completion. A letter was also written to the participant'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.

3.27 Additional considerations

If a participant was diagnosed with CRPS, they were referred to physiotherapy. The method for which they were referred will depend on whether the participant was referred in the public or private systems:

- Public: a written referral was 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 was made to the participant's regular physiotherapist. If the participant 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.

Chapter 4: Can Vitamin C prevent Complex Regional Pain Syndrome in foot and ankle surgery? A double-blinded, randomized, multi-centre, controlled feasibility study. Results and discussion.

4.1 Outline of chapter

This chapter describes the outcomes of the study, "Can Vitamin C prevent Complex Regional Pain Syndrome in lower limb surgery? A double-blinded, randomized, multi-centre controlled feasibility study". It also discusses the challenges associated with running a clinical trial during the COVID-19 pandemic in Melbourne, Australia.

Research outputs: Presentation: Can Vitamin C prevent Complex Regional Pain Syndrome in lower limb surgery? Outcomes of a double-blinded, randomized, multi-centre controlled feasibility study

Submitted: Currently awaiting acceptance for presentation at the Australian Orthopaedic Association Annual Scientific Meeting

4. 2. Results

The trial attempted to commence in 2020 and again in 2021 and 2022. During this time there were six lockdowns in Victoria, Australia and elective surgery was ceased or limited at varying stages between 2020 and 2022. This dramatically impacted the recruitment process as well as the timeframe of the study. Participants were formally recruited at the end of 2022 and during 2023.

4.2.1. Participant recruitment

There were 46 participants identified for potential trial eligibility with 21 participants excluded based on current medication and potential interactions or ethical concerns relating to the placebo. This resulted in 25 participants consent and commence the study.

4.2.2 Follow up

Three participants were completely uncontactable following initial recruitment into the study and did not present for follow up appointments. These participants all had their surgery through the public system. One participant was advised by ward nurses not to take the medication as they were unaware of the study, and the trial

medication was removed from the participant without contacting the researchers. The participant contacted the researchers to advise of the advice given but the medication had already been removed, the participant was unable to continue the trial. However, this participant continued to take Vitamin C of his own accord as he felt that it may be beneficial for his recovery. Outcome data was collected due to an 'intention to treat' principle. One bottle of medication was damaged prior to study commencement and unable to be used at all. See Figure 5 below for a flowchart summary of patient recruitment and flow:

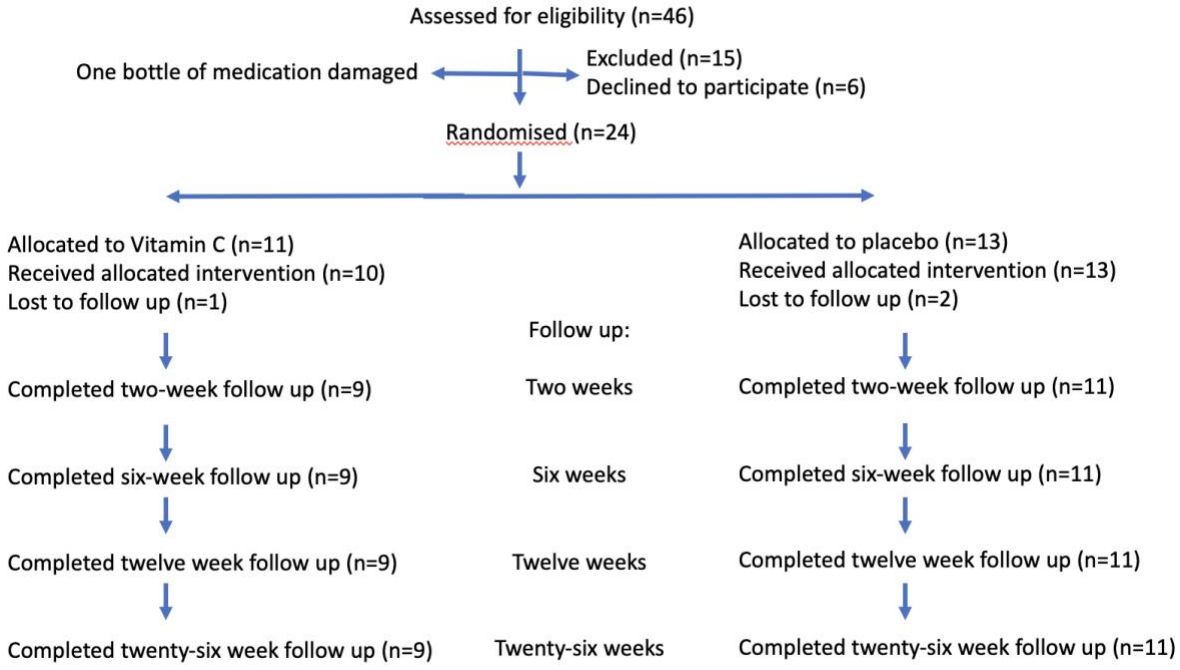

Figure 5 Participant recruitment and study flow

Overall, there were 8 male and 12 female participants who completed the trial to the full twenty-six weeks. 6 participants were recruited through Frankston public hospital with the remainder recruited through South East Orthopaedic Surgery. Table 10 provides the baselines information for participants within each group.

Table 10 Baseline data for each group

Demographics	Vitamin C (n=9)	Placebo (n=11)
Sex (%)		
Female	67% (n=6)	55% (n=6)
Male	33% (n=3)	45% (n=5)
Mean Age (years)	53 years	62 years
Anatomical location of surgery (%)		
Forefoot	33% (n=3)	27% (n=3)
Midfoot	11% (n=1)	0% (n=0)
Hindfoot	55% (n=5)	72% (n=8)

Compensation status (%)		
Public	44% (n=4)	18% (n=2)
Private	22% (n=2)	72% (n=8)
Workers compensation	33% (n=3)	9% (n=1)
Hospital surgery performed		
Frankston public hospital	44% (n=4)	18% (n=2)
Beleura Private Hospital	22% (n=2)	45% (n=5)
Peninsula Private Hospital	11% (n=1)	11% (n=1)
The Bays Private Hospital	22% (n=2)	27% (n=3)

4.3 Outcomes

4.3.1 Recruitment capability

This study demonstrated appropriate recruitment capability with the majority of patients eligible to participate subsequently consent to participate in the trial. There was substantial impact on recruitment capability due to the COVID 19 pandemic. It was initially estimated that 100 patients could be recruited for this feasibility trial based on the average foot and ankle trauma or elective surgeries at the trial sites. This trial timeline was initiated prior to suspension and cessation of elective surgery. Upon resumption of elective surgery in 2022, there were drug availability changes and Peninsula Health pharmacy was unable to source or fund either the placebo or Vitamin C medication. It therefore became the responsibility of the single clinician-researcher to privately source placebo and Vitamin C medication. This medication was given to Peninsula Health pharmacy who then bottled and randomized the medication according to the protocol. There was a world-wide shortage of the placebo medication which made sourcing enough medication for 100 participants impossible, therefore the trial was limited to 25 participants. It is worth noting that should the trial expand in the future, this shortage has now resolved.

An additional and unexpected recruitment impact was higher than expected potential participant use of the oral contraceptive pill. There is historical evidence that Vitamin C may result in increased oestrogen levels in women undergoing hormone replacement therapy (HRT) or who take the oral contraceptive pill(66). Even though some evidence has suggested this interaction is incorrect(67), manufacturer guidelines still recommend avoiding Vitamin C supplementation if HRT is prescribed, and patients taking HRT were therefore not invited to participate. There were four patients ineligible to participate due to HRT treatment at time of data analysis.

There is also limited evidence that Vitamin C may induce warfarin resistance(68)(69). This is a very rare complication of Vitamin C supplementation, but manufacturers of Vitamin C and warfarin recommend that these two medications should not be taken together. Warfarin is becoming less favourable in comparison to the more

modern non-vitamin K antagonist oral anticoagulant (NOAC) and direct oral anticoagulant drugs (DOAC) due to the improved safety and less invasive monitoring of these medications compared to warfarin(70). There is no known contraindication between DOACs and NOACs and Vitamin C, but two patients were excluded from participation invitation due to warfarin use.

Surprisingly, we also found that some patients already took a vitamin supplement which contained Vitamin C. There is potentially as a result of community focus on 'health and wellness' and ongoing advertising for vitamin supplementation (71), often with little to no benefit(72). Thirteen patients advised that they already took a vitamin supplement that contained Vitamin C and were therefore ineligible to participate in the trial.

Lastly, the placebo tablet contains, Blackmores Probiotic Health +, contained lactobacillus acidophilus, lactobacillus paracasei, Bifidobacterium lactis, Bifidobacterium lactis Bi-07, Bifidobacterius lactis Bi-04 and bifidobacterioum lactis HN019. All these products contain lactose in small amounts and are therefore not suitable for patients with lactose intolerance. No patients declined to participate due to lactose intolerance. In addition, this medication is derived from animal products therefore not suitable for vegans. Whilst veganism is slowly increasing in Australia with up to one million people identifying as vegan(73), two patients declined to participate in this study because of their veganism.

4.3.2 Data collection procedure

The time taken to follow up these partiicipants by a single clinician researcher was underestimated. Whilst recruitment of 100 participants was likely to have been possible, it was noted that follow-up was more intensive than expected and it would have been impossible for a single clinician-researcher to manage the extensive follow up required for these participants with the competing post-covid health care demands.

The data collection procedure involved utilising the cloud-based data storage software RedCap. This also contains a mobile phone application, but this was not utilised as the study protocol required face to face assessment where possible to assess for colour changes, swelling and range of motion. Cloud-based data storage supported the multi-site nature of the project and made data entry uncomplicated. Cloud based storage required a stable and secure internet connection. This connection was sometimes difficult in a public hospital with limited WIFI

capabilities, particularly during business hours when the hospital internet usage was at a peak. However, this cloud-based data collection and storage method was still preferable to alternative data storage mechanisms such as a single computer or local server. There were no noted errors in data entry during the course of the tria during audit and analysis.

4.3.3 Suitability of the intervention

No participants reported an adverse event related to the medication prescribed and all participants who were contactable advised they were adherent with the medication regime. Some participants advised that the capsule was bulky but not difficult to swallow. Both the trial Vitamin C and placebo tablets were chosen based on their similarity in size. Participants reported that the single dose tablet was easy to remember and often taken at times when other medication is taken and has formed part of their daily routine. Some participants (4 in control group, 3 in placebo group) described feeling 'better overall' during the blinded phase of the trial. One participant in the placebo group reported complete resolution of pre-existing gastrointestinal symptoms.

4.3.4 Resource availability

Clinical trials require an increase in staffing and infrastructure resourcing, particularly to collect outcome measures. Good trial design results in multiple accesses who are blinded and separate to the participant's treating practitioner. Whilst this was impossible due to the nature of this study design due to the lack of funding for this trial, utilisation of a clinician-researcher was also difficult. We found participants wanted to discuss their surgery and surgical outcomes, rather than their participation in the trial. This resulted in time consuming follow up appointments. A trial coordinator and additional staff to collect data from patients would be required for a larger-scale trial.

It was possible to manage approximately 25 patients at one time over a six month period, but without further resource allocation it is logistically difficult to maintain a cohort of more participants, who are also patients of the clinician-researcher. It may be more practical for students undergoing a full-time masters degree but this would lack the capability to recruit participants if clinical work was suspended. We recommend integrating a research nurse or other practitioner into the study to assist with recruitment, data entry and assessment would be required if more participants were to become involved at one time.

It was noted that is was more difficult to follow up participants in the public system in comparison to the private system. All participants lost to follow up were through the public system. Three participants were completely uncontactable and failed to attend any of their post-operative follow up appointments. One participant was advised by the nursing staff on the ward not to take their trial medication as prescribed due to lack of knowledge on the ward about the trial (this participant was sent to a non-orthopaedic ward post-operatively due to lack of bed availability). All participants who had private health insurance attended their post-operative appointments and were followed up at their standard two, six, twelve and twenty-six week follow up appointments.

4.3.5 Participant response

Participant response to this project was mostly positive. On recommencement of elective surgery, patients were keen to participate in clinical trials if able with some patients stating they felt a need to 'help the medical community' by participating in clinical trials. Participants were contacted via phone and email at the end of the trial, defined when all participants had their 26-week follow up appointment, to inform them of their randomisation group. Some participants were also of the impression that Vitamin C may help their overall health and, (whilst not encouraged by the researchers), continued to take Vitamin C even after cessation of the trial as they noted some improvement in their overall well being. This was prior to notification of their randomisation group. One participant had no pain following her surgery at all and attributed this to her participation in the trial. One participant underwent sequential, bilateral surgery during the trial. He was randomised to placebo for his initial right sided surgery, and took Vitamin C of his own accord for his sequential left sided surgery (not included in the trial). He reported substantial improvement in pain and swelling despite not being informed of his placebo randomisation until after both procedures.

4.4 Secondary outcomes

Our secondary outcomes included to determine if vitamin C prevents CRPS in patients with foot and ankle extremity trauma in a dose-response manner and to determine the incidence of CRPS in foot and ankle extremity trauma. This feasibility study is underpowered, therefore unlikely that the small sample size will demonstrate a statistically significant effect of Vitamin C on CRPS prevention. The incidence may help guide sample sizes for a larger study.

One participant developed CRPS, as defined by the Budapest criteria, following their surgical procedure. This patient was randomised to the placebo group. Three participants met two of the four criteria for CRPS and were noted to have increased pain following their surgery, not explained by other post-operative complication (such as a wound infection). Two participants with increased pain were randomized to the placebo group, and one participant with increased pain was randomized to the Vitamin C group.

Chapter 5: Discussion

5.1 Recommendations for a larger, appropriately powered randomized controlled trial

This feasibility study has demonstrated a number of challenges but also learning points to make several recommendations for the conduction of a larger, appropriately powered trial in the future.

5.1.1 Personnel Resources

The utilization of a single surgeon-researcher to conduct the trial was the only option for this project due to the funding constraints and availability of resources at the time of the trial conduction. Whilst managing approximately twenty participants in the trial by a single surgeon researcher conducting a part-time Master of Surgery was possible, it was found that twenty participants would be the maximum number to safely recruit and consent participants, update records, contact participants for follow up and maintain an accurate database. In addition to surgeon involvement, a full-time trial coordinator would be required should the trial expand in the future.

5.1.2 Statistical analysis for an appropriately powered, randomized controlled trial

Three participants were lost to follow up. One participant was not given his medication on the ward despite education from the nursing staff. One participant initially consented to participate in the trial but later withdrew their consent and did not take the medication as prescribed. They were not included in the trial. It is therefore estimated that in larger-scale trial, approximately 20% of participants would be lost to follow up or unable to continue in the trial.

One participant developed Complex Regional Pain Syndrome which resolved after six months of treatment. Three participants demonstrated 2/4 criteria for the diagnosis of Complex Regional Pain Syndrome but did not formally meet the Budapest criteria.

Assuming an incidence of 9% in the control group and 1% in the intervention group, based on the findings of Besse et al(74), probability of type I (alpha) error of 0.05, probability of type II (beta) error of 0.2 and power of 0.8, 115 participants would need to be recruited into each group. This assumes two independent study groups and the dichotomous outcome of CRPS or no CRPS. Given a 20% estimate of loss to follow up, it is recommended that 138 participants would be recruited into each group (276 patients in total) to conduct an appropriately powered randomized controlled trial.

5.1.3 Cost

The medication was purchased by a single-surgeon researcher which limited the amount available for randomisation. Initially Peninsula Health agreed to cover the cost of the medication, but following changes in the supply chain after and during the pandemic, this offer was withdrawn prior to study commencement but after initial costings had been made and the protocol had been written. The medication costs are, at time of writing:

- GoHealthy Vitamin C capsules - $47.00 per bottle of 120
- Blackmores Probiotic capsules - $39.00 per bottle of 90

To provide enough medication for 138 participants in each group (one capsule per day for fifty days), 58 bottles of Vitamin C medication would be required and 77 bottles of Probiotic capsules would be required to meet the minimum 6900 individual capsules in each group. The cost of the vitamin C medication would be $2726 and the cost of the placebo medication would be $3003, requiring a minimum of $5429 for medication costs.

Randomisation was performed by a clinical trials pharmacist at Peninsula Health.

5.1.4 Follow up data points

Similar to the follow up points of Zollinger et al(54), we used evaluation points of two, six, twelve and twenty-six weeks following surgery to assess for development of CRPS. It was our experience that fewer follow up points would be required for a larger trial, which would improve efficiency of data collection. The participant in this feasibility study who developed CRPS demonstrated CRPS at two, six and twelve weeks post-operatively but had responded to treatment by twenty-six weeks. Three participants who almost met the criteria also demonstrated some signs and symptoms of CRPS at two, six and twelve weeks post-operatively.

It is therefore recommended that a single assessment for CRPS at six weeks post-operatively, which would coincide with routine six-week post-operative review (which is industry standard following extremity surgery) would be sufficient to detect whether CRPS had developed, as well as provide an opportunity to refer patients on for treatment of CRPS if required.

As all patients were compliant with their medication and did not report any side effects, further assessment to determine compliance would not be required in a larger trial.

5.2 Experience running a clinical trial during a pandemic

5.2.1 Challenges of running a clinical trial during a pandemic

The coronavirus pandemic, and subsequent suspension of elective surgery, resulting in several challenges to recruitment and patient participation in this study. In Victoria, Australia, elective surgery was halted with less than one day's notice six times over a two-year period due to government concern about increased hospitalisation and resource allocation due to the pandemic. This made patient participation and consent for the trial difficult to facilitate and predict. A rapid pivot to online and telephone consenting was made but patient recruitment was impossible when surgeries were cancelled with little to no notice. This project was therefore placed on hold for six months to allow for more predictable elective surgery bookings and subsequent recruitment of patients.

On recommencement of elective surgery, it was noted by the authors that some patients were hesitant about participating in clinical trials. Reasons given included a lack of faith in medical practitioners and vaccine hesitancy, with a small number of patients suggesting this clinical trial was part of a mandatory vaccination program. It was noted that predictive factors for vaccine hesitancy included women, younger age groups and people with no tertiary qualifications(75). Whilst not a formal outcome for this study, it was noted by the authors that patients who were concerned about participation in this clinical trial were of similar demographics to those who described vaccine hesitancy for the COVID-19 vaccination.

Several authors have reported similar challenges to conduct research during the coronavirus pandemic(76). Lack of access to patients, families and institutional resources has limited the ability of researchers to safely conduct their projects. Ethics committees, trial registration committees and local governance committees often retreated to remote working making face-to-face meetings to engage and facilitate research difficult. A reliance on email, phone and videoconference was, at times, difficult to gain rapport and develop relationships with both patients and governance bodies and relevant institutions.

5.2.2 Benefits of running a clinical trial during a pandemic:

However, remote working also improved the facilitation of research for many researchers. Standardisation of protocols for telehealth and face-to-face assessments have been made to allow for remote assessment and adaptation of research protocols (77). Improved access to remote conduction of research allows for a more

diverse population of researchers as well as patients participating in clinical trials. For example, those with parenting responsibilities, and disabilities and who live in rural and regional locations that may not have access to a tertiary education centre may have, pre-COVID, had difficulty participating or coordinating clinical trials due to a need for an on-site presence. Much work can now be performed remotely which has made certain types of research more simplified.

The utilisation of telehealth and online databases has also simplified the research process for some researchers, and in particular, allowed remote working protocols and procedures. Online databases such as RedCap have revolutionised database storage and the addition of a patient mobile phone app for patient-reported data outcome measures has also changed how data is collected and collated.

5.3 Conclusion

We present a unique protocol to facilitate research on the efficacy of Vitamin C and the prevention of CRPS following surgery on the foot and/or ankle. The coronavirus pandemic produced several challenges to conducting research, and it was noticed that patient attitudes and behaviours changed considerably following the coronavirus pandemic.

Positive outcomes as a result of the pandemic included increased ease of remote working and conducting research via telehealth or videoconference and less reliance on face-to-face attendance at university. The consequences of changes to research methodology, patient attitudes and remote working for universities will continue to evolve and the outcomes not be apparent for several years.

Chapter 6: Summary and recommendations

Complex regional pain syndrome is debilitating for patients. Due to the complexities of diagnosis, cost of treatment and access to appropriately trained clinicians, treatment can be delayed resulting in preventable morbidity for patients and the health care system. Focus should be on prevention of this condition, and this feasibility study has demonstrated that Vitamin C, 500mg daily for fifty days following foot and ankle surgery, is well tolerated by patients and easily accessible by patients.

A comprehensive literature search demonstrated the possibility of some benefit of Vitamin C following extremity surgery in the prevention of CRPS and our feasibility study did not demonstrate any harm in taking either Vitamin C or the placebo medication.

A study protocol, approved by Monash Ethics Committee, demonstrated that a randomized controlled feasibility study was possible and this was undertaken by a single surgeon clinician/researcher. A loss to follow up of 20% was demonstrated, but 20 participants were successfully recruited and followed up in the trial demonstrating important insights and learning points should a larger randomized controlled trial be conducted in the future.

It is our recommendation that, based on this work, a larger trial with 138 participants in each group be undertaken to appropriately power a future study. An individual surgeon would reasonably be able to manage approximately twenty patients so additional resources, such as a full-time trial coordinator, would be required in addition to the engagement of practicing clinicians. A single follow-up point six weeks following surgery would be appropriate and demonstrate whether CRPS had developed, and would improve efficiency of this project as most participants are reviewed six weeks following surgery.

This project has had an impact on my patient management. Based on the literature review, investigation into Vitamin C and feedback from patients who participated in the trial, I now recommend Vitamin C 500mg daily for fifty days for patients who are at risk of development of Complex Regional Pain Syndrome following injury or surgery to foot and ankle. In particular, this includes crush injuries, patients who present with increased sensitivity, swelling or colour changes that could meet some of the criteria of CRPS at their two week post-operative or follow up appointment or patients who have been diagnosed with CRPS in the past.

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Appendix 1

Patient consent and information forms

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Peninsula Health

Title	Can Vitamin C prevent Complex Regional Pain Syndrome in lower limb trauma? A double-blinded randomised, controlled feasibility study.
Short Title	V-CRILL study
Protocol Number	1.0
Coordinating Principle Investigator/Principle Investigator	Professor David Hunter Smith
Associate Investigator(s)	Associate Professor Cylie Williams Dr Amy Touzell Dr Taya Collier Dr Tim Darby
Location	Frankston Public Hospital

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. You are invited because you are undergoing foot and/or ankle surgery. The research project is testing a treatment for the prevention of complex regional pain syndrome or CRPS. CRPS is a rare but severe, unrelenting pain that can occur after a surgical procedure without a specific cause. The new treatment is vitamin C, 500mg daily.

This Participant Information Sheet tells you about the research project. It explains the treatment involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part. Your decision to participate in the study, or not to participate in the study, will not affect your relationship with your surgeon. Your decision to participate in the study, or not to participate in the study, will not affect factors regarding your surgery including your waiting time, follow up or involvement of your surgeon.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Vitamin C is an over-the-counter medication that does not require a prescription. It is used to treat inflammation, and is approved in Australia to treat, and prevent complex regional pain syndrome.

The results of this research project will be used by the study doctor, Dr Amy Touzell, to obtain a Masters of Surgery degree.

This research has been funded by Peninsula Health.

This research is being conducted at the following locations:
Frankston Public Hospital
Frankston Private Hospital
Holmesglen Private Hospital
Cabrini Brighton Private Hospital
Beleura Private Hospital

3 What does participation in this research involve?

You will be participating in a double-blind randomised controlled trial. This is a type of research where you may or may not get the medicine and neither you, nor your surgeon will know which type of medicine you receive. Vitamin C has been demonstrated to prevent CRPS in upper limb fractures (broken bones), but we do not know if vitamin C can prevent CRPS after surgery to the lower limb (foot and ankle). To find out we need to compare different treatments.

A randomised trial is where we put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random). One group will receive vitamin C (Amplio Vitamins GMO Free Vitamin C), and the other group a placebo tablet (Blackmores Acidophilus Bifidus). A placebo is a medication with no active ingredients. It looks like the real thing but is not. You have a 50% chance of receiving the vitamin C tablet.

If you get the placebo tablet, it is an ‘acidophilus’ tablet, or a very small amount of probiotic (an over-the-counter tablet for gut health). This probiotic contains a small protein that is a derivative of the milk-based substance, lactose. It is therefore NOT suitable for vegans but is suitable for those with lactose intolerance. There are no known side effects to this medication when taken in the very small doses for this placebo tablet.

If you are a vegan or do not eat animal products you cannot participate in this study.

A double-blind study means that neither you nor your study doctor will know which treatment you are receiving. However, in certain circumstances your study doctor can find out which treatment you are receiving.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids the study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

If you decide to participate in this research project, the study doctor will also inform your local doctor.

4 What do I have to do?

You will need to start taking a medication given to you by the study researchers within 72 hours after your surgery. This medication (either a placebo or 500mg of vitamin C) is one tablet, taken

once per day, for fifty days. You cannot take any other supplements containing vitamin C during the treatment period.
You cannot take the following medication without alerting the researchers:

- Eostrogen (including the oral contraceptive pill)
- Anti-viral medication
- Warfarin

You can still take all your other regular medication.
You need to tell your researchers and cease taking the medication if you become pregnant.
You can still donate blood.
While you are participating in this trial, you will still need to attend to the routine care and appointment for your foot or ankle. Routine care commonly involves up to four post-operative visits. During these visits, your doctor will ask you some questions about how your foot or ankle is healing, the number of tablets you have taken, and if you have missed any.

These follow-up visits may be done via telehealth. Telehealth includes a videoconference or telephone consultation.

It is important that should you choose to participate in this study, you take the medication you have been provided once a day as per the instructions.

5 Other relevant information about the research project

This is a 'multi-centre' trial, and patients undergoing surgery at the following sites have been asked to participate:
Frankston public hospital
Frankston private hospital
Beleura Private Hospital
Holmesglen Private Hospital
Cabrini Brighton Private Hospital

This is a 'feasibility trial', with the possibility of the researchers conducting a much larger trial in the future. Your feedback and follow up is therefore very important. 100 people will be involved in the trial, 50 in each treatment group.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the study doctor or any of the study hospitals.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Your routine care will continue for your foot or ankle problem.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include decreased pain and swelling post-operatively. The results of this study may demonstrate benefit in vitamin C for people undergoing surgery in the future.

9 What are the possible risks and disadvantages of taking part?

Medical treatments can cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Side Effect	**How often is it likely to occur?**	**How severe might it be?**	**How long might it last?**
Stomach upset, eg vomiting, nausea, diarrhoea and bloating	Very rare (<0.01%)	Very mild	While medication is taken
Kidney stones	Very rare (<0.01%)	Very mild	While medication is taken

You cannot participate in this trial if you are pregnant, planning on becoming pregnant or breast-feeding. This is because we don't know how vitamin C effects on the unborn child or a newborn baby are not known.

You cannot participate in this trial if you are a vegan or do not eat animal products as the placebo medication contains a derivate of lactose, a milk product. Please ask your doctor if you have any questions about the medication provided.

You may not start another vitamin C or multivitamin medication during the trial, whether it is prescribed by your doctor or purchased 'over the counter' or online. Please alert the trial researchers immediately if you take another supplement, or have take a Vitamin C supplement three months prior to participating in the study.

In high doses (greater than 1000mg per day – double what this study is proposing) Vitamin C may affect the levels of medication such as warfarin, some antiviral medication, some chemotherapy agents and oestrogen. Please alert the study researcher if you are on any of these medications.

Both male and female participants are strongly advised to use effective contraception during the course of the research and for a period of 3 months after completion of the research project. You should discuss methods of effective contraception with your study doctor or general practitioner.

If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention if required. You must not continue in the research if you become pregnant.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support

will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

10 What will happen to my information?

No extra blood tests or x-rays are taken during the project, other than the x-rays that what would normally be required for routine care. This research does not involve the establishment of a tissue bank.

You will be informed of project results, and at the end of the study you will be informed if the tablet you took was vitamin C or placebo.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, there are some medicine vitamin C impacts on. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, or other alternative treatments that may include vitamin C. You should also tell your study doctor about any changes to these during your participation in the research project.

Some medication such as warfarin, anti-virals and chemotherapy agents may interact with high doses of vitamin C. Please alert your study researcher if you start these medications during the trial.

Your study doctor will also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify any member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you. The personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

• Unacceptable side effects
• Decisions made by local regulatory/health authorities.

15 What happens when the research project ends?

You will have your final visit with your treating doctor six months after your surgery. Once the medication has been given, no further medication is required or needed to be taken. If you wish to continue vitamin C, you can discuss this with your regular general practitioner but will be at your expense.

You will receive an email or a letter describing the outcome of the project approximately six months after all participants have had their final post-operative appointment.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Data about you will only be stored by using a special number, and only the researchers will have access to it. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities. the institution relevant to this Participant Information Sheet, Peninsula Health, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Information about your participation in this research project may be recorded in your health records at the hospital you have attended.

In accordance with relevant Australian and Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical

treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research project is being conducted by Dr Amy Touzell.

You will not benefit financially from your involvement in this research project.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Monash Health and governance approval given by Peninsula Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query is Dr Amy Touzell. She can be contacted via mobile 0484 739 500 or email amy.touzell@monash.edu

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 0484739550.

Clinical contact person

Name	*Dr Amy Touzell*
Position	*Investigator*
Telephone	*0484739550*
Email	*Amy.touzell@monash.edu*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	*Miss Lee-Anne Clavarino*
Position	Manager Office for Research
Telephone	03 9784 2679
Email	*researchethics@phcn.vic.gov.au*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	*Monash Health*
HREC Executive Officer	Deborah Dell
Telephone	03 9594 4605
Email	*deborah.dell@monashhealth.org*

Local HREC Office contact (Single Site -Research Governance Officer)

Reviewing HREC name	*Monash Health*
HREC Executive Officer	Mr Michael Kios Research Governance Manager, Research Support Services
Telephone	03 9594 4611
Email	*Michael.kios@monashhealth.org*

Appendix 2: Ethics Approval

Tel (03) 9594 4611
Fax (03) 9594 6306
Email: research@monashhealth.org

Research Support Services
Monash Health
Level 2, I Block
Monash Medical Centre
246 Clayton Road
Clayton Victoria 3168

24 June

2021 Dr

Amy Touzell
Peninsula Health

Department of Department of Surgery
Frankston Public Hospital
Hastings Road
Frankston VIC 3199

Dear Researcher,

Study Title: Can Vitamin C prevent Complex Regional Pain Syndrome in lower limb surgery? ERM Reference Number: 47498
Monash Health Reference: RES-21-0000-243A

The Monash Health HREC reviewed the above application at the meeting held on 06 May 2021. In addition, the HREC is satisfied that the responses to our correspondence of 11 May 2021 have been sufficiently addressed.

The HREC approved the above application on the basis of the information provided in the application form, protocol and supporting documentation.

This reviewing HREC is accredited by the Victorian Department of Health and Human Services under the National Mutual Acceptance, single ethical review system.

Approval

The HREC approval is from 23 June 2021.

Approval is given in accordance with the research conforming to the *National Health and Medical Research Council Act 1992* and the *National Statement on Ethical Conduct in Human Research (2018)*. The HREC has ethically approved this research according to the Memorandum of Understanding between the Victorian Department of Health and Human Services and the participating organisations conducting the research.

Approval is given for this research project to be conducted at the following sites and campuses:

- Peninsula Health, VIC
- Frankston Public Hospital, VIC
- Frankston Private Hospital, VIC
- Holmesglen Private Hospital, VIC
- Cabrini Brighton Private Hospital, VIC
- Beleura Private Hospital, VIC

Monash Medical Centre, Clayton
246 Clayton Road
Clayton
Tel: 9594 6666

Monash Medical Centre, Moorabbin
Centre Road
East Bentleigh
Tel: 9928 8111

Kingston Centre
Warrigal Road
Cheltenham
Tel: 9265 1000

Dandenong Hospital
David Street
Dandenong
Tel: 9554 1000

Casey Hospital
Kangan Drive
Berwick
Tel: 8768 1200

Community-based services across the South East

You must comply with the following conditions:

The Chief Principal Investigator is required to notify the Manager, Human Research Ethics Committee, Monash Health of:

1. Any change in protocol and the reason for that change together with an indication of ethical implications (if any)
2. Suspected Unexpected Serious Adverse Reactions (SUSARs), Serious Adverse Events (SAEs) or Significant Safety Issues (SSIs) in accordance with the NHMRC safety guidelines as adopted by Monash Health that occur with a Monash Health participant or with a participant from a site that Monash Health has provided HREC review.
3. Any unforeseen events that might affect continued ethical acceptability of the project.
4. Any expiry of the insurance coverage provided in respect of sponsored trials.
5. Discontinuation of the project before the expected date of completion, giving reasons.
6. Any change in personnel involved in the research project including any study member resigning from Monash Health &/or the study team.

At the conclusion of the project or every twelve months if the project continues, the Principal Investigator is required to complete and forward an annual progress report to the Committee.

Reminders to submit annual progress report forms will be forwarded to the researcher.

The Coordinating Principal Investigator is responsible for notifying Principal Investigators. The Coordinating Principal Investigator and Principal Investigators should forward a copy of this letter to their site's Research Governance Officer.

Approved documents

Documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Human Research Ethics Application	HREC/47498/ MonH-2021-266363(v2)	26 May 2021
Victorian Specific Module	-	11 August 2020
Participant Information and Consent Form	-	13 June 2021
Protocol	1	27 January 2021

Site-Specific Assessment (SSA)

SSA authorisation is required at all sites participating in the study. SSA must be authorised at a site before the research project can commence.

The completed Site-Specific Assessment Form and a copy of this ethics approval letter must be submitted to the Research Governance Officer for authorisation by the Chief Executive or delegate. This applies to each site participating in the research.

If you should have any queries about your project please contact the Research Support Services team via email research@monashhealth.org or via telephone: Sarah Niazmand on 9594 4747, Katharine Mahoney on 9594 4748 (NB Katharine is out of the office on Mondays), Julie Gephart on 9594 4090.

The HREC wishes you and your colleagues every success in your research.

Yours sincerely

Deborah Dell
Interim Director, Research Operations

All correspondence in regard to this study must be uploaded on ERM with both the Monash Health Reference Number and the Project ID.
Upon uploading, please also email the documents via email to research@monashhealth.org, along with the Monash Health Reference Number ERM Project ID and study title.

Checklist: Post-ethics approval requirements that must be met before a research project can commence at a study site.

Please ensure that as a PI (including the CPI) the following are completed at each study site.

Requirements	**Yes/No/NA**
Ethics approval notification The PI must send a copy to the RGO at that study site.	Yes
HREC Review Only Indemnity The PI must forward a copy of the signed HREC Review Only Indemnity to the RGO at that study site.	N/A
CTN Acknowledgement for Commercially Sponsored Studies The PI must forward a copy of the CTN Acknowledgement to Research Support Services.	N/A
CTN Lodgement for Collaborative Group/Investigator Driven Studies The PI or nominated delegate is requested to make an appointment with the Monash Health Research Support Services contact for the study deborah.dell@monashhealth.org or michael.kios@monashhealth.org so that the lodgment may be completed by both the investigator and Research Support Services. The banking details for payment to the TGA will need to be brought along to this appointment, in order to finalise notification to the TGA. The fee for lodging a CTN is $335.	N/A

SSA authorisation notification The PI must forward the SSA form and attached documents (e.g. CTRA) to the RGO so the authority approving the conduct of the trial, at that site, can complete and sign.	Yes
Radiation If applicable, the RGO must contact the Medical Physicist so that the study may be notified to the Radiation Risk Section of the Department of Health and Human Services.	No
Other Commonwealth statutory requirements Ensure compliance with the following e.g. Office of the Gene Technology Regulator, NHMRC Licensing Committee, NHMRC Cellular Therapies Advisory Committee.	N/A

Appendix 3:

Email sent to participants to thank them for participation in the trial and summarise results:

Dear [study participant],

Many thanks for your participation in the V-CRILL trial to help researchers determine whether Vitamin C helps prevent the development of Complex Regional Pain Syndrome following foot and ankle surgery.

This trial was a 'feasibility study' to help determine if patients would continue to take the medicines as requested, how easy it would be for patients to enter the trial as well are assess the impact of the use of Vitamin C over time in prevention of CRPS. The study has now been completed and data analysed. You have been contacted and advised of which group you were randomized to (Vitamin C or placebo).

Twenty-four patients were initially recruited. Three patients were lost to follow up and one patient withdrew their consent to participate. Twenty patients therefore completed the trial in its entirety. 9 patients were randomized to Vitamin C, 11 patients were randomized to placebo. Of the 20 patients, one patient developed Complex Regional Pain Syndrome. All patients followed up to completion took the the medication as requested and no patients reported any side effects from taking the medication. The data collected has been used to plan a larger, randomized controlled trial where an appropriate number of patients would be recruited to understand the effectiveness of Vitamin C to prevent CRPS.

Thank-you again for your participation in this important research. Dr Touzell has submitted her thesis for her Master of Surgery based on this paper and is currently awaiting assessment.

With kind regards,

Dr Amy Touzell on behalf of the Trial Team

Prof David Hunter-Smith

Prof Cylie Williams