# Aspirin4VLU

# A randomized, blinded, placebo controlled trial of adjuvant low dose aspirin for venous leg ulcers (*ClinicalTrials.gov* NCT02158806)

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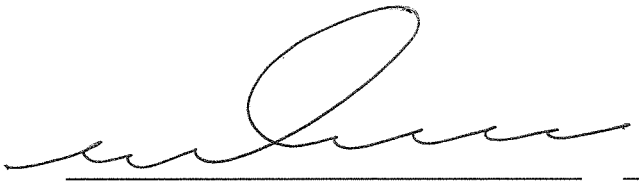
| Assoc Prof Andrew Jull<br>**Principal Investigator** |  | 19 May 2015 |
| **NIHI Signatory:** | **Signature:** | **Date:** |
| Prof Chris Bullen<br>**Director** |  | 19/5/2015 |

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| Aspirin4VLU Protocol Version 1.0 | 20 August 2014 | Original |
| Aspirin4VLU Protocol Version 1.1 | 6 May 2015 | Amendment 1 |

# Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ABI | Ankle Brachial Index (also known as Ankle Brachial Pressure Index) |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CVI | Chronic Venous Insufficiency |
| CXVUQ | Charing Cross Venous Ulcer Questionnaire |
| DHB | District Health Board |
| DSMB | Data Safety Monitoring Board |
| HRQoL | Health-Related Quality of Life |
| ICD-10 AM | International Classification of Disease version 10 Australian Modification |
| ITT | Intention to Treat analysis |
| mg | Milligram |
| NIHI | National Institute of Health Innovation |
| PI | Principal Investigator |
| RR | Relative Risk (also known as Risk Ratio) |
| SAE | Serious Adverse Event |
| SCOTT | Standing Committee on Therapeutic Trials |
| RAND-36 | RAND 36-Item Health Survey |
| VLU | Venous Leg Ulcer |

# 1. Overview of trial

**Title of Trial**: Low dose adjuvant aspirin for venous leg ulcers: a randomised trial.

**Investigators and Trial Centres:** The overall design and conduct of this investigator-initiated study will be the responsibility of the Steering Committee. This a collaborative trial designed and coordinated jointly by independent investigators at the National Institute of Health Innovation (University of Auckland), the Dept. of General Practice and Primary Care (University of Auckland), and Auckland District Health Board, with input from clinicians at Auckland DHB, Counties Manukau DHB, Waikato DHB, the Nurse Maude Association Christchurch, and the Southern DHB. Publication of data from this trial will be the responsibility of the Steering Committee. The trial will be co-ordinated from the NIHI, with participants recruited from patients attending the district nursing services at Auckland DHB, Counties Manukau DHB, Waikato DHB, the Nurse Maude Association Christchurch, and the Southern DHB.

**Trial Period:** Oct 2014 – Oct 2017

**Clinical Phase**: Phase III

**Objectives:** The objective of this trial is to determine the effectiveness of low dose aspirin compared to placebo when used in addition to compression therapy for venous leg ulcer healing.

**Duration of Treatment**: The maximum duration of treatment is 24 weeks (or less if the ulcer heals within 24 weeks).

**Trial Design and Methodology**
A prospective community-based, double-blind, placebo-controlled, randomised trial with participants receiving either 150 mg aspirin daily for up to 24 weeks or matching placebo. Block randomisation will be used, stratified by trial centre and prognostic index (ulcer size and duration) to ensure a balance of participants within trial centres and for participants likely to be slow healers. Participants in both arms will also receive compression therapy (with system of choice guided by patient and/or clinical preference) as delivered through district nursing services at the trial centres. Assessment of health-related quality of life will be carried out at baseline and at the end of the trial treatment period. The patient will continue to receive district nursing care as per normal protocol.

**Inclusion/exclusion criteria:** Patients with leg ulcers will be eligible for *inclusion* if they meet the following criteria:

- Aged 18 years or older
- Determined to have a venous leg ulcer (clinical indications of venous ulceration, ABI ≥ 0.8, and other causative aetiologies ruled out)
- Able to tolerate compression therapy
- Able to provide written informed consent
- Confirmation with participant's general practitioner that the participant can take low dose aspirin or placebo.

Potentially eligible participants will be *excluded* if they meet any of the criteria below:

- Pregnant or breast-feeding women
- History of myocardial infarction, stroke, transient ischaemic attack, angina or significant peripheral arterial disease
- History of adverse effects related to aspirin use

- Currently using aspirin, or other anti-platelet or anticoagulant therapy
- Participant has any other existing condition or treatment that is a contraindication to use of aspirin or to participation in the trial
- Participant has any other existing condition where treatment with aspirin is indicated.

**Test Product:**
- Aspirin 150 mg daily + compression bandaging

**Reference Therapy:**
- Placebo daily + compression bandaging

**Primary Outcome:**
Time to complete healing over 24 weeks. Complete healing is defined as full epithelialisation of the ulcer with no scab.

**Secondary outcomes:**
- Proportion with healed reference VLU at 24 weeks
- Change in estimated reference ulcer area from baseline to 24 weeks
- Adherence with aspirin
- Change in health-related quality of life from baseline to 24 weeks
- Adverse events
- Efficacy of blinding.

***Sample size:*** A sample size of 354 (177 in each group) will be sufficient to show a **four week** difference in time-to-healing at 90% power with an alpha of 0.05, assuming the median time-to-healing in the control group over a six month follow up is 92 days and allowing for 10% loss to follow up.

***Statistical analysis:*** All analyses will use intention-to-treat in accord with a Statistical Analysis Plan developed *a priori*. Time-to-event data will be analysed using Kaplan Meier plots, log rank test and Cox regression. Simple incidence rates, relative risks and 95% CIs will be obtained for all binary variables in the first instance, with multiple logistic regression analysis if necessary to adjust for imbalance. Continuous outcomes will be analysed using multiple linear regression and adjusted for baseline value and other covariates if needed. A *kappa* will be calculated for the evaluation of the efficacy of blinding.

# 2. Background

## 2.1 Prevalence of leg ulceration

Leg ulceration is a chronic, relapsing and remitting condition. Recurrence within five years is 30-70%.[1,2] Period prevalence for leg ulceration is 1.13/1000 New Zealand adults per year and increases with age (80+ years 13/1000).[3] New Zealand has a rapidly ageing population with the proportion of older people expected to increase from 12% to 25% of the population by 2020-2030.[4] Thus the number of people with leg ulcers can be expected to double from a current estimate of 5506 per year in 2011 to 9781 per year in 2031 (*Statistics New Zealand* population projections series 5). Venous leg ulcers comprise the majority (up to 84%) of all leg ulcers.[5,6]

## 2.2 Economic Implications of Leg Ulceration

Leg ulcers represent a significant cost to community services as they are slow to heal and the majority of patients require nursing care at least once per week plus general practitioner consultations. It has been estimated that district nurses in Auckland spend approximately 25% of their time on venous ulcer management.[7] An audit of a New Zealand district nursing service in 1999 found the average cost of treatment with compression was $906 for a first time ulcer and $1205 for a recurrent ulcer (pers. comm. Richard Milne). The actual cost ranged from $156 to $5626 depending on time to healing. The average cost of an unhealed ulcer at 12 weeks was found to be $1405 compared to $535 for those that healed by 12 weeks in a New Zealand clinical trial.[8]

## 2.3 Effects of Leg Ulceration on Health

Leg ulceration is reported as having an impact on virtually every aspect of daily life and is associated with feelings of powerlessness, loss of control, and states of hopelessness.[9-13] Pain, sleep impairment, and reduced mobility are commonly reported,[10,12,14-17] work capacity can be restricted and personal finances adversely affected.[9,18] Social activities may be avoided in order to reduce the risk of injury to legs,[19] or minimized due to negative body image, with loneliness a frequent consequence.[11,14,20] In New Zealand, leg ulceration has been shown to have a significant adverse impact on health-related quality of life as measured by the SF 36-Item Health survey; RAND-36 is a version of SF-36.[21]. Ulcer healing improves quality of life as measured by a disease-specific tool in a New Zealand trial,[22] and earlier healing will increase patients' quality of life, especially in the older people who more commonly have leg ulcers.

## 2.4 Treatments for Venous Ulceration

The therapeutic mainstay in management of venous ulceration is graduated compression bandaging (changed once weekly) or stockings (removed daily). No single system of compression is more effective than other systems, although multi-component systems are superior to single component systems and systems that contain an elastic layer are better than those with inelastic components.[23] However, 30-60% of patients still remain unhealed after 12 weeks of treatment with compression therapy.[24-27] In a New Zealand trial (n=368), the proportion of participants with unhealed venous leg ulcers after 12 weeks treatment with compression bandaging was 50%.[8]

Compression bandaging should only be applied in the absence of significant arterial disease. The threshold normally employed for the use of compression is an ankle brachial pressure (ABI) index of 0.8.[28] An ABI is the ratio of the systolic blood pressure at the arm over the systolic blood pressure at the ankle. A normal adult value for the ABI is between 0.9 and 1.2. Levels lower than 0.8 are thought

to indicate the presence of moderate arterial disease, although selected patients with an ABI of between 0.6-0.8 can safely receive reduced levels of compression bandaging.[18]

The only available adjuvant to compression in New Zealand is oxpentifylline (also known as pentoxifylline or Trental), which increases healing rates by 60% (Relative Risk 1.56, 95%CI 1.14 – 2.13),[29] but there are real barriers to its routine use: [1] pentoxifylline is not registered in New Zealand for routine management of venous leg ulcers; [2] while prescribing no longer requires special authorisation, having previously done so means general practitioners are perhaps not familiar with the drug; [3] the drug is only partially subsidized (co-payment of ~$20.00 per month); and [4] the drug must be taken three times per day increasing polypharmacy in the elderly. Effective affordable additional treatments for venous leg ulceration are needed, ideally incurring little extra cost to health services or patients. One promising adjuvant treatment for venous leg ulceration is oral aspirin.

## 2.5 Aspirin as a potential treatment

Two randomised trials of oral aspirin in addition to compression have been reported.[30,31] Combined into a meta-analysis (figure 1), the pooled healing rate favoured 300 mg aspirin at 16 weeks (RR 1.62, 95%CI 0.99 – 2.65). However, there are methodological issues with these trials. Both trials excluded patients commonly seen in clinical care who would be treated with compression – those with small ulcers or those with slightly reduced blood flow to the lower leg (ankle brachial index 0.8 to 0.9). Further, the trial regimens likely excluded many of the very old (who have increased incidence of VLU) as the average ages in the trials were 64.1 years and 59.5 years. Most importantly, the trials were too small to provide the substantive evidence needed to change current practice.

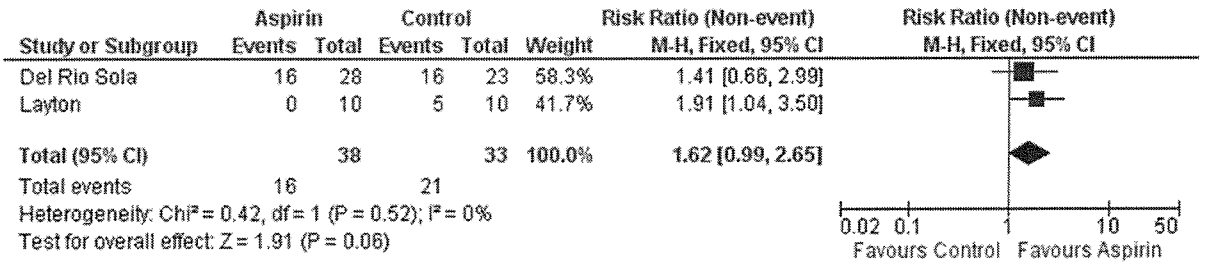



Figure 1. Meta-analysis of two trials of comparing aspirin plus compression to placebo plus compression

Platelet inhibition by aspirin is achieved by doses lower than 300 mg. However, variability in response to low-dose aspirin, independent of compliance, has been described. Aspirin formulation, obesity, and rate of platelet turnover are all associated with low response.[32] While a 150 mg dose is at the higher end of the low-dose range,[33] it offers a responsible compromise dose that allows for variability in response to low-dose aspirin as well as increased risk with the very old. A secondary analysis of data from the HALT trial (led by the applicant, n=368)[8] found 150mg aspirin was associated with the strongest effect on VLU healing rates, (adjusted for baseline ulcer size and duration, Hazard Ratio 1.77, 95%CI 1.13–2.75).

Anecdotally, the main barrier to further testing of aspirin for VLU healing has been the view that it would be difficult to recruit VLU patients, as many would be older adults thought to already be taking aspirin for other indications. However, two New Zealand VLU trials showed aspirin use was only 30% of participants in one (recruitment 2003-2005) and 17% in the second (recruitment 2007).[8] [34] The low use of aspirin was not explained by contraindications. These findings are similar to the 34% of VLU patients taking aspirin in a 2010 audit of 50 VLU patients in Christchurch (pers.comm., Cathy Hammond).

## 2.6 Biological plausibility of aspirin as treatment for venous ulcers

Venous ulceration is the most severe presentation of chronic venous insufficiency (CVI). It results from a chronic inflammatory process that starts with the haemodynamic forces (turbulent blood flow and altered shear stress) produced by venous hypertension, activating leukocytes and causing platelet aggregation (Figure 2). The activated leukocytes initiate an acute inflammatory response in CVI that becomes a chronic inflammatory state as inflammatory mediators remain upregulated.[35,36] Patients with CVI have significantly higher platelet counts compared to normal controls or people with other endogenous inflammatory disease or non-venous leg ulcers.[37,38]Accompanying leukocyte activation, the aggregated platelets also become activated. Platelets in patients with CVI have also

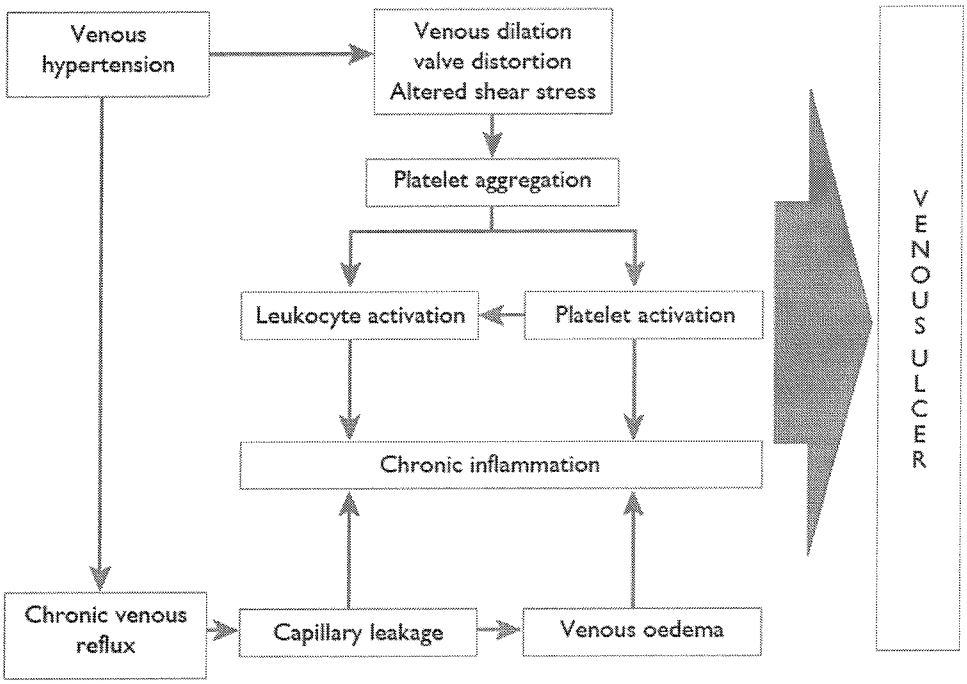



Figure 2: Simplified outline of pathophysiology of venous ulceration.

been found to have increased reactivity compared to normal controls,[39] and the number of platelet microparticles (shed by activated platelets) are significantly increased in people with CVI compared to normal controls.[38] Activated platelets appear also to be involved in the chronic inflammatory processes through production of CD40 ligands that prompt endothelial cells to produce inflammatory process components including reactive oxygen species, chemokines, and adhesion molecules.[40,41] Activated platelets also influence cellular adhesion directly (P-selectin expression) and indirectly (through synthesis of interleukin-1β), release extracellular matrix-degrading matrix metalloproteases (MMP-2 and MMP-9) and chemokines that trigger recruitment of monocytes or promote differentiation of monocytes into macrophages to maintain inflammation.

Aspirin could plausibly affect venous ulcer healing through two actions. First, aspirin inhibits platelet aggregation (and hence activation) through the irreversible inhibition of platelet cyclooxygenase. Aspirin also inhibits vessel-wall cyclooxygenase though the blocking prostacyclin synthesis, although it requires higher doses of aspirin to achieve vessel-wall inhibition of cyclooxygenase than platelet cyclooxygenase;[42] synthesis in venous-wall tissue is inhibited by doses of aspirin greater than 81mg.[43] Second, aspirin, through inhibiting the cyclooxygenase pathway, may also have an effect on inflammation.[44] Prostaglandins are released during the inflammatory response and may amplify blood vessel permeability through the mediators such as histamine and bradykinin.[45] The need for cheap, easily accessible adjuvant treatments, the emerging role of platelets in the pathophysiology

of venous ulceration and the positive randomised pilot evidence all suggest the need for a definitive randomised controlled trial of aspirin as an adjuvant treatment for venous ulceration.

### 2.7 Clinical Safety Summary

Low dose enteric coated aspirin is licensed for general sale in New Zealand and can be purchased over the counter without a prescription. It is considered a relatively safe medication. The main side effects of aspirin are gastrointestinal upset and bleeding, but the absolute risk of major gastrointestinal bleeding in primary prevention is small. The Antithrombotic Triallists Collaboration found the rate of extra-cranial bleeds (which were mainly composed of gastrointestinal bleeds) in five primary prevention trials of daily aspirin (n=96,456, mean follow up 7 years) was only slightly increased compared to controls treated with placebo (0.10% in aspirin-treated patients compared to 0.07% in patients who did not receive aspirin, an annual absolute increase of three events per 10,000 patients receiving aspirin).[46] There was also a small increase in the rate of haemorrhagic strokes (0.04% in aspirin-treated patients compared to 0.03% in controls, an annual absolute increase of one event per 10, 000 patients receiving aspirin). This increase in haemorrhagic stroke was offset by a small decrease in the rate of ischaemic stroke (0.16% in aspirin-treated patients compared with 0.18% in controls, an annual absolute decrease of two events per 10,000 patients receiving aspirin). The doses used in the studies ranged from 75 mg daily to 500 mg daily but the effect of dose on bleeds was not examined. However, a large population-based study of 2,105 cases with upper gastrointestinal bleeding or perforation obtained from the UK-based General Practice Register and 11,500 randomly sampled controls found 150 mg daily doses were associated with an equal risk of bleeding (RR 2.0, 95%CI 1.5 to 2.6) to that of 300 mg doses (RR 2.0, 95%CI 1.4 to 2.8), and only slightly more than that seen with 75 mg daily doses (RR 1.9, 95%CI 1.6 to 2.4).[47]

The risk of bleeding is increased with age, diabetes and smoking. The US Preventive Services Task Force states the evidence is insufficient to determine a risk/benefit for cardiovascular disease prevention in people aged over 80 years.[48] Approximately one third of participants in our large New Zealand VLU (HALT) trial were aged 80 or older.[8] However, equipoise does exist and a large Australian primary prevention trial is now underway with 100mg aspirin in participants aged 70 years or older.[49] Excluding patients older than 79 years would reduce the generalisability of any VLU trial when more evidence is needed in order to determine risk/benefit for the older age group.

### 2.8 Rationale for a clinical trial

The ageing population and substantial anticipated increase in people with VLU (especially in the very old), the need for cheap, accessible adjuvant treatments, the role of platelets in the pathophysiology of VLU and the encouraging evidence for aspirin all point to the need for a definitive randomised controlled trial of low dose aspirin as an adjuvant treatment for VLU using a trial population that is as open as clinically possible and thus similar to that encountered every day in clinical practice.

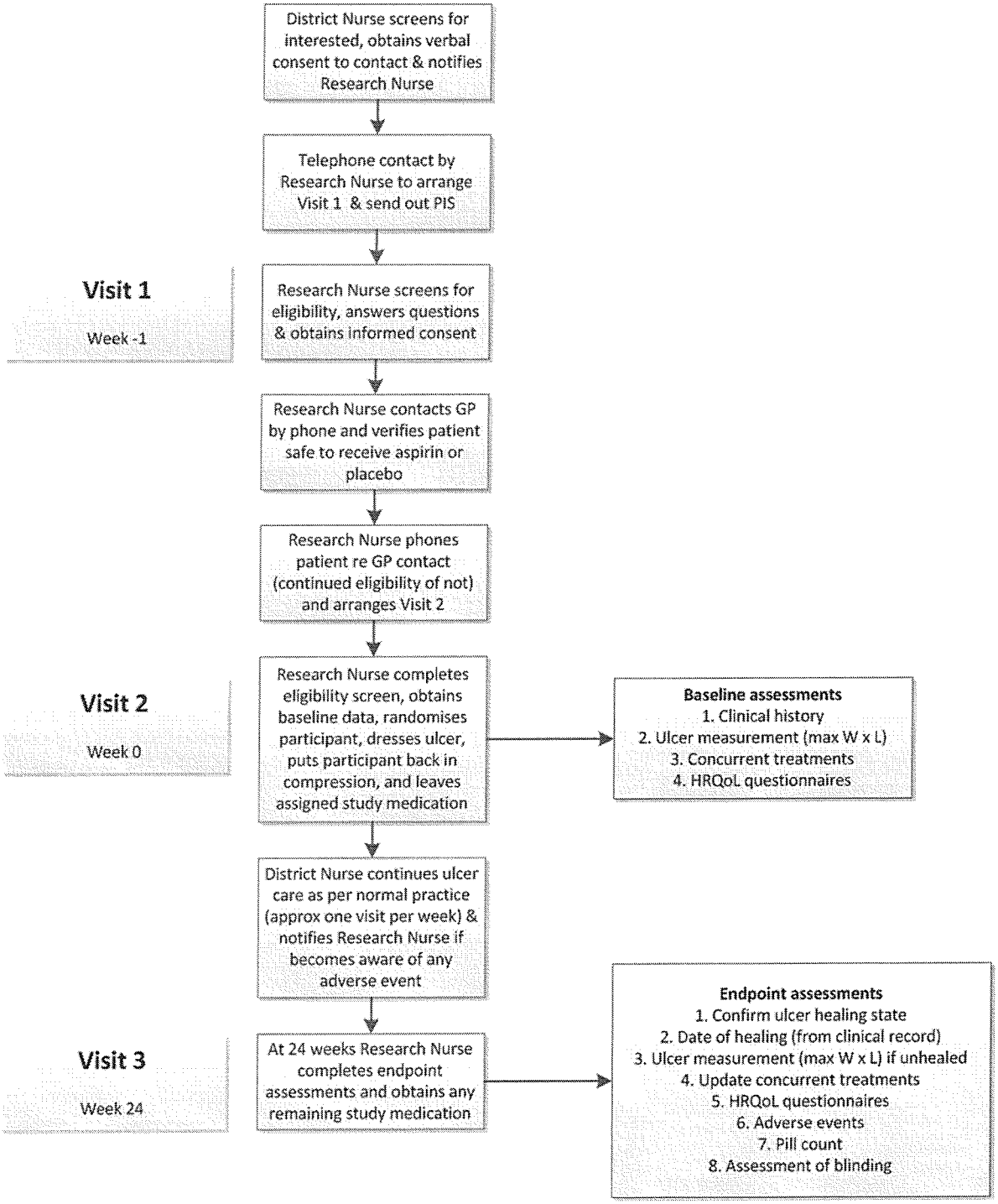
## 3. Objectives

The main aim of this trial is to evaluate the effectiveness of low dose aspirin compared to placebo when used in addition to compression therapy for VLU time-to-healing over 24 weeks follow up. Other aims include estimating the effect of aspirin on proportion of patients healed, adverse events, adherence and health-related quality of life (HRQoL).

# 4. Trial Design

A prospective community-based, double-blind, placebo-controlled, randomised trial with participants receiving either 150 mg aspirin daily for up to 24 weeks or matching placebo. Block randomisation will be used, stratified by trial centre and prognostic index (ulcer size and duration) to ensure a balance of participants within trial centres and for participants likely to be slow healers. Participants in both arms will also receive compression therapy (with system of choice guided by patient and/or clinical preference) as delivered through district nursing services at the trial centres. The district nurse will identify potential participants, obtain verbal consent from them to be contacted by the research nurse if the patient is interested in the trial and notify the research nurse at each trial centre.

## 5. Trial Plan Schematic



# 6. Recruitment

## 6.1 Recruitment source & process

Patients with venous leg ulcers who present for treatment to or already receiving treatment from the community–based district nursing services at trial centres previously involved in the National Institute of Health Innovation's (NIHI) leg ulcer trials will be recruited. These centres are based within Auckland, Counties Manukau, Waikato, and Southern District Health Boards, and Nurse Maude community nursing services in Christchurch. The same model of recruitment is used as was successfully employed in previous venous leg ulcer trials in New Zealand (figure 4). A 0.5 FTE Research Nurse will be seconded to the trial from each trial centre (employing authority will be reimbursed).

The District Nurse will identify potential participants, obtain verbal consent from them to be contacted by the Research Nurse if the patient is interested in the trial and notify the research nurse at each trial centre. The Research Nurse will screen the patients for eligibility. Eligible patients will be consented, assessed, and randomised by the Research Nurse at a location convenient to the patient. The location may be a clinic, the patient's home or workplace. Once randomised, the participant will receive the allocated treatment from the Research Nurse, who will also conduct the endpoint visits at 24 weeks after randomisation, again at a location convenient to the participant. In between Research Nurse visits the participants will continue to receive normal care by the District Nurses.

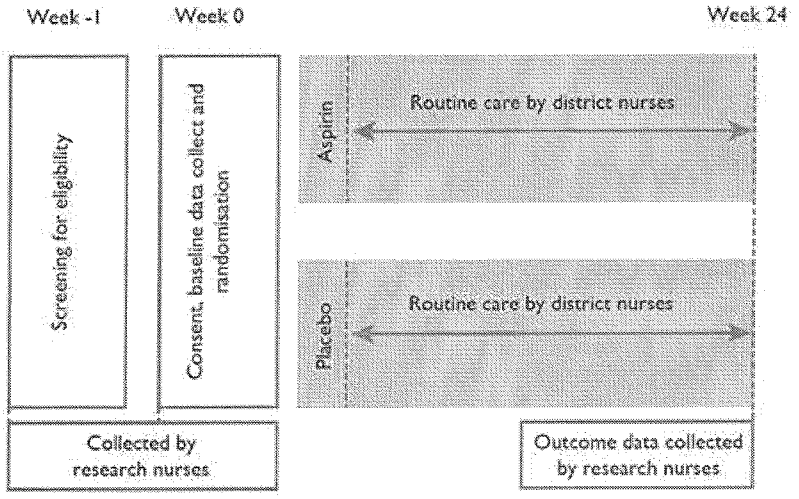



Figure 3: Flow chart of proposed study.

## 6.2 Case definition

Only patients with venous leg ulcers being treated through the trial centres will be recruited. A patient will be considered to have a purely venous leg ulcer where other causative aetiologies (diabetes, rheumatoid arthritis, malignancy) have been ruled out, the ulcer appears clinically venous (presentation may include any or all of the following: moist, shallow, irregular shape; haemosiderian pigmentation; venous eczema; ankle oedema; ankle flare; lipodermatosclerosis), and the trial participant has an Ankle Brachial Index (ABI) ≥ 0.8 to rule out arterial insufficiency. For the purposes of this trial, an incident leg ulcer will be considered to be any break in the skin on the leg (below the knee) that has been present for four or more weeks. If a patient known to a service presents with a new episode of ulceration, has a prior history of venous leg ulceration, is considered to have a

current venous leg ulcer, they will be candidates for participation. Patients with prevalent ulcers meeting the case definition already in treatment will also be eligible for inclusion.

### 6.3 Eligibility criteria

Patients with leg ulcers will be eligible for *inclusion* if they meet the following criteria:

- Aged 18 years or older
- Determined to have a venous leg ulcer (clinical indications of venous ulceration, ABI ≥ 0.8, and other causative aetiologies ruled out)
- Able to tolerate compression therapy
- Able to provide written informed consent
- Confirmation with participant's general practitioner that the participant can take low dose aspirin or placebo.

Potentially eligible participants will be *excluded* if they meet any of the criteria below:

- Pregnant or breast-feeding women
- History of myocardial infarction, stroke, transient ischaemic attack, angina or significant peripheral arterial disease
- History of adverse effects related to aspirin use
- Currently using aspirin, or other anti-platelet or anticoagulant therapy
- Participant has any other existing condition or treatment that is a contraindication to use of aspirin or to participation in the trial
- Participant has any other existing condition where treatment with aspirin is indicated.

## 7. Randomisation and allocation concealment

On registration (week -1) participants will be assigned a unique sequential registration number using numbers generated by the NIHI data management. When a registration number has been allocated, the participant's initials and date of birth and the date of registration must be recorded. This registration number will be used to identify the participant throughout all periods of the trial. Once a registration number has been assigned, it may not be used again.

Immediately after baseline data have been recorded, consented patients who fulfil entry criteria will be randomised by computer to one of the two trial groups using stratified blocked randomisation with varying block sizes of 2 and 4. The randomisation sequence will be prepared by the trial statistician and loaded into a secure database. Randomisation will be stratified by trial centre and prognostic index (based on ulcer and duration) which will isolate any centre effect in clinical management and ensure a balance on key prognostic variables known to influence healing at 24 weeks. Each treatment pack is uniquely numbered and is allocated using the randomisation sequence. The Research Nurse accesses the randomisation web-page, completes data entry, and generates the allocation using a computerised tablet. The allocated treatment is then given to the participant by the Research Nurse.

# 8. Concomitant Therapy

If a concurrent medication or therapy is administered, the generic name of the medication or supplement and the date(s) and frequency of administration will be recorded on "Concomitant Medication" Case Report Form (CRF) M. Throughout the trial, the participant's general practitioner, nurse practitioner or consultant specialists are free to provide whatever ancillary treatments are required for the appropriate medical management of trial subjects. Where treatment is necessary by procedure or medication for which aspirin is contraindicated, participants should stop taking the trial treatment.

# 9. Withdrawal criteria

If, at any time after randomisation, significant intolerance to the trial treatment is suspected, the trial treatment can be discontinued. Should participants require discontinuation of trial treatment for any reason (see below), or if they elect to cease taking treatment, follow-up visits and data collection will continue as scheduled as if they were continuing with the randomised treatment. Participants may have the trial treatment discontinued if one or more of the following occurs:

- The participant makes a voluntary decision to withdraw from follow-up, or from the treatment.
- The participant has a serious clinical adverse event, intercurrent illness, or other medical condition that indicates to the clinical team that continued treatment with the trial medication is not in the best interest of the participant. The trial treatment will be discontinued if the participant develops any life threatening or seriously disabling illness or is admitted to hospital.
- The trial is terminated.

If the participant discontinues treatment due to a serious adverse event, the participant will be followed until the event resolves or there is a return to a clinically acceptable medical status. Trial outcomes

## 9.1 Primary outcome measure

Time to complete healing (defined as intact skin without a scab) is recommended as an outcome to be included in research by the Cochrane Collaboration Wound Review Group and a 24 week follow up period is considered a minimum. Time to event data will be obtained from clinical records. District nurses visit patients on a weekly basis as part of normal care and record healing (average number of district nurse visits was 1.1 per week in the HALT trial). At 24 weeks, the Research Nurse will determine if the reference ulcer is healed. If the reference ulcer is healed, the research nurses will access clinical records to determine the date of healing was first reported during the 24-week period. If the reference ulcer is unhealed, the Research Nurse will determine from the clinical record whether the reference ulcer had healed at any time prior to 24 weeks. If there is no mention of healing then the ulcer will be assumed to have been unhealed during the 24 weeks. If the reference ulcer is recorded as healed during that time, the unhealed ulcer will be assumed to be a recurrent ulcer and the date healing is first recorded will be assumed to be the healing date.

## 9.2 Secondary outcome measures

The following secondary outcome measures will be assessed in all participants at 24 weeks after randomisation:

- Proportion of participants with a healed reference VLU at 24 weeks.

- Estimated change in ulcer area – obtained from measuring maximum width and length of reference ulcer at baseline and endpoint and the ulcer area at each time point estimated using the calculation for area of an ellipse.[50] See rationale above for not using more complex methods of ulcer measurement.

- Change in HRQoL: Measured at baseline and at 24 weeks. Each person's perception of his or her general health will be assessed using the RAND 36-item Health Survey (a version of SF-36), EQ5D and ulcer-related health using the CXVUQ.[51,52] The EQ5D and SF-36 are well-validated questionnaires for assessing quality of life in New Zealand and generating utility values for economic analyses.[53,54] [55,56]. However, they may not be as responsive as a disease-specific instrument to changes in ulcer state (healed *versus* unhealed) over the short-term.[22,57] Consequently, the CXVUQ will also be used, as it has been found to be very responsive to changes in VLU healing state.[22]

- Adverse events: Measured throughout the 24-week follow up. Standard definitions of adverse events will be used and adverse events reports will be reviewed by one of the medically-qualified co-investigators and coded using the ICD-10 AM. All participants will be issued with a Clinical Trial Card, stating their participation in the trial and the possibility they are receiving low dose aspirin. If the participant presents with signs and symptoms of a serious adverse event, such as myocardial infarction, stroke, or extra-cranial bleed, the Clinical Trial Card will recommend they discontinue trial treatment and appropriate treatment initiated. These participants will still be included in follow up at 24 weeks.

- Treatment adherence: Measured at 24 weeks by count of remaining capsules by the Research Nurse.

- Efficacy of blinding: Measured at 24 weeks, the efficacy of blinding will be tested by asking patients which treatment they believed they received, and asking the same question of the research nurses.

# 10. Data collection and follow-up

## 10.1 Baseline assessments

Screening information will be obtained from a telephone contact with the patient at week -1. Eligible patients will be visited at Week -1 and, once consented, the following baseline data will be collected immediately prior to randomisation:

- Demography: age, sex, self-reported ethnicity.

- Ulcer area and duration: Reference VLU area (area > 5 $cm^2$) and duration (duration for > six months) provide data for a prognostic index for VLU healing with 24 weeks of compression.[58] The index assigns scores of 0, 1 or 2 based on absence of both factors, presence of one factor, or presence of both factors. Sophisticated tools for measuring ulcer area are either too expensive (e.g. Silhouette™) or no longer supported by the manufacturer in New Zealand (e.g. Visitrak™). A simpler method of estimation using the formula for area of an ellipse has been shown to be highly correlated with ulcer area, both in the literature (r = 0.951)[50] and internal data from one of our previous trials (r = 0.92).[8] Ulcer duration will be obtained from patient recall. Where more than one VLU is present, the largest ulcer will be the reference ulcer.

- ABI: An ABI < 0.8 indicates that there is a high probability that some arterial insufficiency is present (positive predictive value = 95% in a general practice population).[59] Use of compression therapy where significant arterial disease is present can result in severe ischaemia in the leg,

with risk of necrosis. Consequently ABIs are routinely obtained for all patients with incident ulcers under the care of each of the trial centres taking part in the proposed trial, to confirm suitability for compression therapy. An ABI will be obtained from the clinical records for each participant. Where a potential participant already in treatment has an ABI obtained more than three months prior to the eligibility screen, a new ABI will be obtained prior to inclusion to ensure no development or progression of arterial disease.

- Clinical history and concomitant medications.
- Compression system: Details of the patient's current treatment regime will be recorded.
- Health-related quality of life (HRQoL) instruments: The RAND 36-item Health Survey [51], EQ5D,[54] and the Charing Cross Venous Ulcer Questionnaire (CXVUQ)[52] will be administered.

## 10.2 Schedule of trial visits and procedures

| | Visit 1 | Phone/email contact | Visit 2 | District Nurse | Visit 3 Research Nurse |
|---|---|---|---|---|---|
| **Timing**<br>**Case Record Form** | **Week -1**<br>**A** | **Week-1 to 0** | **Week 0**<br>**B** | **Weeks 1-24**<br>**X** | **Week 24**<br>**E** |
| **General data** | | | | | |
| Eligibility criteria | X | | X | | |
| Age & sex | X | | | | |
| Ethnicity | X | | | | |
| Informed consent | X | | | | |
| Clinical history | X | | | | |
| Record or obtain ABI | X | | | | |
| Confirm safety with GP | | X | | | |
| Confirm with participant visit 2 | | X | | | |
| **Clinical information** | | | | | |
| Concomitant medications | | | X | | X |
| Compression system | | | X | | X |
| Ulcer measurement (max W x L) | | | X | | X |
| **Other data collection** | | | | | |
| Quality of life measures | | | X | | X |
| Adverse events | | | | X | X |
| Pill count | | | | | X |
| Testing blinding | | | | | X |
| End of trial participant survey | | | | | X |
| **Treatment allocation** | | | | | |
| Trial medication | | | X | | |

Form X will be completed by Research Nurse, but Research Nurse may be notified by District Nurse of possible adverse event.

## 10.3 Visit 1: Registration

- Answer any questions about trial.
- Obtain informed consent.
- Obtain patient's name, date of birth, sex and self-reported ethnicity.

- Obtain relevant history for inclusion/exclusion
- Record or obtain ABI.
- Assess eligibility criteria.

### 10.4 Between Visit 1 and Visit 2

- Email/fax contact with participant's GP to confirm safe to receive aspirin
- Arrange visit 2 if patient eligible to receive aspirin.

### 10.5 Visit 2: Baseline assessment and randomisation

- Complete eligibility assessment.
- Answer any questions about trial.
- Review concomitant medication and record compression system in use.
- Carry out assessments of health-related quality of life (RAND 36, EQ5D, and CXVUQ).
- Measure ulcer size and obtain history of duration from participant
- Randomise participant.
- Give participant allocated trial treatment.

### 10.6 Visit 3: 24 weeks after randomisation

- Determine if reference ulcer healed
- Obtain date healed from clinical record if healed
- Review concomitant medication and record compression system in use.
- Obtain remaining trial medication and count capsules.
- Carry out assessments of health-related quality of life (RAND 36, EQ5D, and CXVUQ).
- Assess blinding.
- Complete an "End of Trial Participant" survey to give feed-back on their trial experience.

## 11. Statistical Considerations

### 11.1 Sample Size

We estimate that 354 participants will be required. A sample size of 318 would be sufficient to show a **four week** difference in time-to-healing at 90% power with an alpha of 0.05, assuming the median time-to-healing in the control group over a six month follow up is 92 days (the median time to healing suggested by a previous bandaging trial for VLU patients over 24 weeks).[60] These data equate to a hazard ratio for VLU healing of 1.45, which is smaller than that suggested by our re-analysis of data from a cohort in a previous VLU trial (hazard ratio for VLU healing 1.77 for 150 mg dose). A four week difference was the minimal important difference that would most frequently

persuade people to use aspirin in a small commissioned survey of older people in Auckland, was the time interval used in a Canadian venous ulcer trial (http://clinicaltrials.gov/ct2/show/study/NCT00202267) and is lower than clinically significant differences used to calculate the sample sizes in two large venous ulcer trials conducted in the United Kingdom (the VenUS II and III trials [61,62]). Although both the HALT trial and the PREPARE Pilot achieved very high follow up rates (99% and 100%),[8,34] we have allowed for 10% loss to follow up, and thus a sample of 354 (177 in each group) will be required. Even if recruitment were lower than anticipated, using the same assumptions as above, a sample of 238 inflated to 264 (132 in each group) to allow for 10% loss to follow up would be sufficient to show a four week difference in time to healing with 80% power with an alpha of 0.05.

We assume that 70% of patients presenting with leg ulcers to the trial centres will have VLU. This assumption is supported in the literature [5,6] and in an audit of patients presenting to the Nurse Maude Association in Christchurch in 2010 (pers. comm., Catherine Hammond, see below).

- In Auckland DHB, the most recent data (2011) shows the service received 309 referrals from multiple sources (mainly general practitioner and internal sources). Extrapolating this data to the 18 month recruitment period, Auckland DHB would receive 463 new assessment requests of which 324 new patients would have VLU, assuming 70% of these referrals had venous ulceration.

- In Christchurch, reorganisation of services since the Earthquake has increased the number of people with wounds now seen at Nurse Maude. Between November 2012 and October 2013, 999 new patients were seen and analysis suggested 499 had VLU (pers. comm, Chris Hendry, November 2013). This is a substantial increase over 2010 when Nurse Maude undertook 426 new assessments on patients with leg ulcers and 297 patients (69.7%) were assessed as having VLU (pers. comm., Catherine Hammond, Nurse Practitioner). Rather than use the more recent data, we have used the 2010 data to ensure recruitment is justified even with conservative estimates. Extrapolating the 2010 data to the 18 month recruitment period, Nurse Maude would receive 639 new assessment requests of which 447 new patients would have VLU, assuming 70% of new assessments had venous ulceration. If the 2012-13 data is correct, ~750 patients would have VLU.

- In Counties Manukau DHB, the district nursing service undertook 212 new Doppler ultrasound assessments on patients with leg ulcers in 2010 (pers. comm., Trish Johns, Nurse Specialist). No data is available on how many patients were assessed as having VLU, or how many patients received compression therapy. Extrapolating the data on assessments to the 18 month recruitment period, Counties Manukau DHB would receive 318 new assessment requests, of which 222 new patients would have VLU assuming 70% of new assessments had venous ulceration.

- In Southern DHB (Dunedin), the leg ulcer clinic treats about 120 patients per year with compression (pers. comm., Emil Schmidt, Nurse Specialist, Oct 2013). Extrapolating the data on compression to the 18 month recruitment period, Southern DHB would have 180 patients with VLU.

- In Waikato DHB, the district nursing services put an average of 14 new patients per month into compression for VLU (pers. comm., Julie Betts, Nurse Practitioner, Oct 2013). Extrapolating the data on compression to the 18 month recruitment period, Waikato DHB would have 252 new patients with VLU.

Based on these data around **1425** new patients with VLU are likely to present to the above services during the 18 month recruitment period. Data from the HALT trial and the recent audit at Christchurch support the assumption that 30% will be using aspirin and an additional 10% will be using other anticoagulant medications, making these patients ineligible. Assuming therefore that around 40% of patients will be ineligible on these bases, a pool of **855** new patients with VLU would be eligible to take part in the proposed trial. The recruitment pool will be greater when prevalent cases at the start of the trial are considered for inclusion. We are confident that high participation rates are readily achievable, based on our past experience showing VLU patients are highly motivated to participate in research in New Zealand. The recruitment rate in the HALT trial was 93%, in the Auckland Leg Ulcer Study 68%, and in the PREPARE pilot 100% of those registered.

## 11.2 Statistical Analysis

All statistical analyses will be performed using SAS version 9.3 (SAS Institute Inc. Cary NC) Data analyses will be specified *a priori* in a statistical analysis plan (SAP) prepared by the trial statistician (and agreed upon by all members of the Steering Committee). The SAP will be available as a public domain document. Data from the Case Record Forms (CRFs) will be entered into password secured Oracle databases hosted by NIHI via the web by the Research Nurse. The data will be extracted into SAS for analysis on the trial's completion. No interim analyses are planned.

### *11.2.1 Baseline Characteristics*

Data on demographic characteristics (sex, age, self-reported ethnicity), history of ulceration, ulcer size, clinical history, current treatments (including compression system) and health-related quality of life will be collected. Since any differences between randomised groups at baseline could only have occurred by chance, no formal significance testing will be conducted.

### *11.2.2 Treatment effect*

All data analyses will be carried out on an intention-to-treat basis [63]. Time-to-event data will be analysed using Kaplan Meier plots and log rank test, and Cox regression will be used to take into account known covariates and the varying times since randomisation. The assumption of proportionality will be checked using standard graphical techniques. Simple incidence rates, relative risks, absolute risks and numbers needed to treat, and 95% CIs will be obtained for all binary outcomes in the first instance, with subsequent multiple logistic regression analysis conducted if necessary to adjust for imbalance in covariates. Continuous outcomes will be analysed using multiple linear regression and adjusted for baseline value and other covariates if needed. Adverse events will be analysed using incidence rate ratios. A *kappa* will be calculated for the evaluation of the efficacy of blinding. Should aspirin prove effective in the primary analysis, heterogeneity of effects on time to healing will analysed using subgroups specified *a priori* in the Statistical Analysis Plan.

### *11.2.3 Tolerability of treatment*

All randomised participants will be included in this analysis. Comparison of the frequency of treatment withdrawal because of suspected intolerance between the aspirin group and the placebo group will be tested using Chi-square statistics. The number of participants discontinuing treatment prematurely for any reason will be summarized by treatment group and by reasons for discontinuation. The incidence of all suspected adverse treatment reactions will be summarized by treatment group.

### *11.2.4 Procedures to account for missing data*

For the main analyses, all participants lost to follow-up will be presumed to have an ulcer that remained unhealed.

# 12. Ethical Approval and Informed Consent

## 12.1 Ethics Committee

Ethical approval of the trial protocol and protocol-related documents will be sought from a Health & Disability Ethics Committee.

## 12.2 SCOTT Committee

No New Zealand manufacturer currently produces a 150 mg dose of aspirin. Therefore Medsafe have advised approval for an exemption for clinical trial of a new medicine under s30 of the Medicines Act is required. Section 30 clinical trial exemption was obtained in October 2014 (TT50-5199 (1700). Optimus Healthcare Ltd will be the compounding pharmacy for the trial. The company meets the GMP requirements for Medsafe in New Zealand and has been involved in preparation of medicines for other trials.

## 12.3 Informed Consent

District nurses will screen patients for potential participants. If a patient expresses interest in participating in the trial, the district nurse will obtain verbal consent to forward the patient's name and telephone number to the Research Nurse. After contact by the Research Nurse, if the patient wishes to participate in the trial, Visit 1 will be arranged and informed consent will be obtained during that visit if the patient wishes to participate in the trial.

# 13. Adverse Event reporting

## 13.1 Definition of an adverse event

An adverse event (AE) is any untoward clinical occurrence in a participant and does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of trial treatment, whether or not it is considered related to the product. In this trial an AE will include any illness, sign, symptom, or clinically significant abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the treatment(s) under trial.

## 13.2 Notification of adverse events

During the trial information about AEs will be sought at the 6 month trial follow-up visit by the research nurse. AEs reported from the district nursing service or other health practitioners should be reported on a CRF X as soon as possible after notification.

AE data will be aggregated and reported by the trial statistician at intervals specified by the Data Safety Monitoring Board (DSMB).

Serious adverse events

### *13.2.1 Definition of a serious adverse event*

An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening

  NOTE: The term "life-threatening" in the definition of "serious" 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 which hypothetically might have caused death if it were more severe.

- Requires in participant hospitalisation or prolongation of existing hospitalisation

  NOTE: In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) to the hospital or assessment ward for observation and/or treatment that would not have been appropriate outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.

- Other important medical events, that may not be immediately life threatening or result in death or hospitalisation but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

*13.2.2 Notification of serious adverse events*

Timely and complete reporting of all SAEs is necessary to identify events that are treatment related or potentially treatment related, thereby allowing: (1) a greater understanding of the overall safety profile of the treatment; (2) appropriate modification of trial protocols; and (3) adherence to regulatory requirements.

SAEs are to be documented on a CRF X and reported to the project manager within one day (24 hours) of detection. Participant deaths or SAEs that occur within 30 days after stopping the trial treatment should also be reported.

All CRF Xs require sign off by the authorised medical practitioner at NIHI who will assess the AE (blinded to treatment allocation) to determine whether the AE is a possible SAE.

If the AE is a possible SAE, the participant will be withdrawn from treatment, the trial treatment collected by the research nurse and the possible SAE will be notified to the participant's GP.

The Principal Investigator will have the overall responsibility of ensuring that all events are reported to the regulatory authorities in the appropriate timeframes. The project manager will have the responsibility to ensure that SAEs are appropriately monitored and reported. As participants with AEs will not be unblinded during the trial, there will be no expedited reporting on serious suspected adverse drug reactions.

Participants experiencing AEs that cause interruption or discontinuation of trial treatment, or those experiencing SAEs that are present at the end of their participation in the trial will receive follow-up as appropriate, which may involve referral to the participant's general practitioner.

All AEs will be classified by a medical coder at the NIHI who will be blind to treatment allocation. Standard definitions of adverse events will be used and graded using the Common Terminology Criteria for Adverse Events v3.0.

## 13.3 Unblinding

The NIHI **will not** provide an emergency unblinding service. If the participant develops a condition during the course of the trial such that treatment with aspirin is necessary, or that treatment with aspirin is contraindicated, treatment providers should assume that the trial medication is aspirin. The participant will discontinue trial treatment at that stage.

## 13.4 Data Safety and Monitoring

The HRC DMCC declined to constitute a DSMB under their auspices as the trial was considered low risk. We have therefore constituted an DSMB using the approach recommended by Ellenberg et al[64] and consisting of a leading statistician (Chair), and two other members of the University of Auckland who are not involved with the trial. The DSMB will draw up their own terms of reference and will be free to review any information or study process in addition to the reviews of safety data. This framework proposes that if two or more of the following criteria are met then an independent DSMB is required:

- The trial is intended to provide definitive information about the effectiveness and/or safety of a medical intervention.
- There are prior data to suggest that the intervention being studied has the potential to induce potentially unacceptable toxicity.
- The trial is evaluating mortality or another major endpoint such that inferiority of one treatment arm has safety as well as effectiveness implications.
- It would be ethically important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not fully addressed.

The trial statistician will provide the DSMB with reports on safety data. Such an approach has been used with other trials of low risk interventions at NIHI.

The project manager will monitor trial conduct at each centre to ensure that the trial protocol is being adhered to. All participant records will be reviewed to ensure that compliance with inclusion/exclusion criteria and consent procedures. Participant identity will also be verified through comparison with admission records and the endpoint date healed will be verified against the source clinical record.

# 14. Clinical Supplies

## 14.1 Trial Treatment Identification

The following trial treatments will be used in this trial:

| SUPPLIER | TREATMENT | INGREDIENTS | DESCRIPTION |
|---|---|---|---|
| **Treatment group** Optimus | Aspirin | Aspirin (150 mg) | Capsules |
| **Control group** Optimus | Placebo | | Capsules |

## 14.2 Handling and Dispensing of Trial Treatment

Optimus Healthcare Ltd will be responsible for assuring that the quality of the trial treatments during manufacture. All capsules used in the trial will be maintained under the direct responsibility of the manufacturer and the project manager. The trial treatments will be dispatched by the manufacturer to the NIHI, where they will be stored at room temperature until forwarded to the trial centres at the initiation of the trial. It will be the project manager's responsibility to ensure that an accurate record of trial treatments issued to the trial centres is maintained.

Following randomisation each participant will receive one of the following trial treatments:

**Group 1: Treatment group**

| *Time point* | *Treatment group* |
|---|---|
| Randomisation | 168-day supply of aspirin |

**Group 2: Control group**

| *Time point* | *Treatment group* |
|---|---|
| Randomisation | 168-day supply of placebo |

## 14.3 Packaging and Labelling

The packaging of trial treatments will meet the requirements of the Medicines Regulations 1984 and Medsafe, and will include lot number, number of capsules, name of manufacturer, and directions for use. In addition, each shipment will be labelled "For Clinical Trial Use Only".

The trial treatments will be available in a bottle containing the full course of trial medication. Each bottle will have a treatment number that will be unique to the course of treatment. The unique treatment number will be recorded on the CRF when it is given to the participant to ensure the allocated treatment has been received and to provide a record should parts of the batch need to be tracked.

### 14.4 Treatment supply records

It will be the responsibility of the project manager to ensure that an inventory of the trial treatments is maintained at the NIHI. Records will include:

- Amount received from the manufacturer and placed in inventory at NIHI.
- Label ID numbers or lot number.
- Dates of treatment inventory movement.
- Amount dispatched to each trial centre.

### 14.5 Treatment on completion of trial

Participants will be asked to return all unused aspirin capsules to the research nurse. Returned capsules will be disposed of at the end of the trial follow-up period by the Research Nurse in accord with local DHB protocol.

## 15. Relevance to Health

The trial contributes to the goal of improving outcomes for individuals and populations with disease as follows:

- *More people could be healed* - Even with good compression 30-60% of patients remain unhealed after 12 weeks of compression therapy in clinical trials.[24-27] New Zealand trials suggest a baseline healing rate of 50% at 12 weeks and aspirin could increase this proportion to 65% at 12 weeks and 75% at 24 weeks.
- *Improved quality of life* - Ulcer healing improves quality of life,[22] and earlier healing will increase patients' quality of life, especially in the older people who more commonly have leg ulcers.

The trial also contributes to the goal of cost-effective sustainable solutions as follows:

- *Reduced costs* - The average cost of 12 weeks venous ulcer treatment is NZ$972, a figure inflated by patients that remain unhealed. The average cost of healed patients for a 12-week period is NZ$535 compared to NZ$1405 for those that remain unhealed.[8] Increasing the number of patients healed early will decrease the overall spend on this patient group.
- *Reduced burden on district nursing services* - As people's ulcers heal they no longer need district nursing and other related services for leg ulcer management, freeing up these resources.
- *Easier access to a low cost, effective adjuvant* - Aspirin is a safe, inexpensive, over-the-counter medication, with very few barriers to patient use or practitioner recommendation.

## 16. Dissemination of Results

### 16.1 Trial registration

The trial is registered on *ClinicalTrials.gov*, which is a World Health Organization compliant public domain trials register. The trial registration number is NCT0215886. We will seek to publish the trial protocol in an appropriate peer-reviewed journal.

### 16.2 Academic/professional colleagues

Academic and practitioner colleagues will be informed via articles submitted to high impact peer-reviewed journals as well as local practice magazines (e.g. NZ Doctor, Kai Tiaki and New Zealand Nursing Review).

The results will be widely disseminated both nationally and internationally through publications and meetings; coverage would be sought in vehicles such as New Scientist and ABC Science Online. Summary reports will be sent to the New Zealand Wound Care Society, the Australian Wound Management Federation, the Royal New Zealand College of General Practitioners and the College of Nurses to assist in promoting evidence-based practice. In addition, many District Health Boards have specialist leg ulcer services and the results will be sent to these services.

### 16.3 Participants & the public

At the end of the trial, all participants will receive a letter of thanks for participating in the trial, a brief summary of the trial results and their significance, and any future research plans. The public will be informed of results via local media coverage (newspapers, web news, and magazines such as *Mana*).

### 16.4 Iwi/ Māori

The Māori Research Advisory Committee of the National Institute of Health Innovation will advise on the other methods of dissemination of information to the Māori community and providers. The Māori Research Advisory Committee of the NIHI will advise the research group on other appropriate methods of dissemination of information to Māori.

## 17. Administrative Section

### 17.1 Adherence to the Protocol

Except for changes to eliminate an immediate hazard to participants, the approved protocol will be followed as specified. Any significant protocol deviation will be documented in the Trial Log.

### 17.2 Protocol Revisions

All revisions will be discussed with, and approved by, the Trial Steering Committee. Revisions will be deemed to either be substantial or non-substantial in alignment with the Standard Operating Procedures for Health & Disability Committee version 1.0 (May 2012). The following will be considered substantial amendments:

- Significant changes to the design/methodology of the trial
- Significant changes to the type or number of procedures participants will undertake in the trial
- Changes relating to the safety of the physical or mental integrity of participants, or to the risk/benefit assessment for the trial
- Significant changes to the trial's documentation (such as participant information sheets)
- The appointment of a new investigator for the trial
- Any other significant change to the trial protocol or the information provided in the application for approval.

If the revision is a substantial amendment, the principal investigator will submit it to the appropriate Ethics Committee for their consideration.

The following will be considered minor amendments for which Health & Disability Ethics Committee review will not be sought:

- Minor or administrative changes to trial documentation
- Changes to the research team other than the appointment of a new investigator
- Changes in funding arrangements, except where these may alter the ability of participants to access publicly funded compensation in the event of injury
- Changes in arrangements for recording or analysing trial data.
- Extension of the trial beyond the expected end date given in the application form, except where this is related to other changes that are substantial.

### 17.3 Data confidentiality and security

Electronic data will be stored and backed-up on the NIHI servers.

### 17.4 Reporting schedule

The principal investigator will provide annual reports of the progress, or completion, termination or discontinuation of the trial to the Health & Disability Ethics Committee and to the funder of this trial. Except where specified in Section 10, safety reports will be provided to the Health & Disability Ethics Committee with the annual report.

### 17.5 Record retention policy

The project manager will copies of paper CRFs (or electronic files), and source documents for the period required by the Privacy Legislation and the Health (Retention of Health Information) Regulations 1996 (10 years from date of termination of trial). Research staff involved in the trial at the trial centres will not destroy any records associated with the trial.

If the principal investigator or any co-investigators withdraw from the trial (e.g. relocation, retirement), any records they hold will be transferred to a mutually agreed upon designee (e.g. another co-investigator). Notice of such transfer will be given in writing to the NIHI.

### 17.6 Insurance

This research is not conducted principally for the benefit of the manufacturer of the aspirin capsules. Therefore participants may be entitled to compensation from the Accident Compensation Corporation (ACC) for personal injury suffered as a result of treatment given as part of the trial (section 32 (4) of the Injury, Prevention, Rehabilitation and Compensation Act 2001 and section 13 of the Injury, Prevention, Rehabilitation and Compensation Amendment Act (No 2) 2005).

### 17.7 Ownership of data and publication policy

Individual trial data will remain the property of individual trial participants. The NIHI will have the responsibility for storage, protection and retrieval of trial data. The Principal Investigator will have the responsibility for the safe guardianship and storage of the data. All access, analyses and dissemination of data will be the responsibility of the Steering Committee, with advice sought from NIHI Māori Advisory Committee where necessary.

Processes regarding publication of the trial and the final trial results will be documented in the Aspirin4VLU publication guidelines. In short, all publications will be approved by the Steering Committee, who will be named on all papers and presentations. Trial participants, the research nurses at trial centres, members of the Management Committee who are not part of the Steering Committee, and trial sponsors will be acknowledged in all papers and in all presentations resulting from this trial. The Aspirin4VLU media plan will detail the process to follow for publicising the trial and the trial findings via the media.

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# Appendix 1: Trial personnel

## Project Sponsor

Funding has been obtained from the Health Research Council of New Zealand, PO Box 5541, Wellesley St, Auckland 1141, New Zealand, telephone: +64 9 379 8227 [Project grant number: HRC 14/269]. The design, conduct, analyses and interpretation of trial results will be made independent of the trial sponsor.

## Coordinating Centre (NIHI) Management Committee

| Name | Position | Telephone | Email |
|---|---|---|---|
| Andrew Jull | Senior Research Fellow | 923-4259 | a.jull@auckland.ac.nz |
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| Sheila Fisher | Business Manager | 923-4717 | s.fisher@ auckland.ac.nz |
| Varsha Parag | Senior Biostatistician | 923-4710 | v.parag@ auckland.ac.nz |
| John Faatui | Data Manager | 923-4552 | j.faatui@auckland.ac.nz |

## Trial Treatment provided by:

Participants in the treatment group will receive aspirin 150 mg in a capsule. Participants in the control group will receive a matching placebo. The aspirin and placebo capsules will be obtained from Optimus Healthcare Ltd, 4 Walls Street, Penrose. The contact details for Optimus Healthcare Ltd are listed below:

| | | | |
|---|---|---|---|
| Nish Vythilingam | Pharmacist | 021 859-566 | pharmacist@optimus health.co.nz |

## Appendix 2: Steering Committee

The Aspirin4VLU steering committee will consist of the investigators who are responsible for developing and maintaining the trial design, statistical analysis, presentation and publication of results. The committee will meet at least once every six months to review problems and issues raised by the Trial Management Committee. Members who live outside of Auckland may attend the meetings, or participate via conference call.

### Membership

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# Appendix 3 – Informed Consent Procedures

### Informed Consent

Written consent MUST be obtained from all participants. The signed consent will be filed in the participant's trial file. For written consent to be valid the participant must be suitably informed of the trial so that they can make an independent choice about whether to participate. The participant should receive a copy of the consent form. Issues to be covered in the information sheet should be reviewed carefully with each participant. Do not assume that every person has read the information sheet or that they can read. The consent form should be signed and dated by the participant. The potential participant should have details (refer information sheet) regarding:

- The purpose of the trial.
- An explanation of who the researchers are.
- An explanation of why the participant qualifies for the trial.
- The type of participants studied and the number likely to be involved.
- The length of the trial.
- The length of time and the procedure of the assessment, interventions, including any special tests.

  The potential risks/benefits to the person.

The potential participant should be informed (See information sheet) that:

- The supply of information by the participant is entirely voluntary.
- The participant may refuse to answer any of the questions or refuse any of the clinical examination. They do not have to give a reason for doing so.
- All participants have the right to access their data and/or to remove it from the trial.
- All participants have the right to have questions answered.
- A person outside of the trial is available to be contacted should they have any concerns i.e. a health advocate

The participant should be aware (See information sheet) that:

- Personal information will be collected about them but that this information will be kept strictly confidential.
- That the information will be kept in a locked cabinet at the trial site and/or in a locked room at the National Institute of Health Innovation, School of Medicine, University of Auckland.
- All computerised information will be password protected on a computer.
- No one, other than the trial investigators, will have access to this data.
- All information will be published or presented in a way that no individual can be identified.

## Appendix 4 – Summary of Protocol Amendments

| Page | Section heading | Amendment / (Reason) |
|---|---|---|
| Whole document | Header | Protocol – Version 1, date 20 August 2014<br>To: Protocol – Version 1.1, date 6 May 2015 |
| Whole document | | From: National Institute of Health Innovation<br>To: National Institute for Health Innovation<br>(Wording error) |
| 1 | | From: Principal investigator<br>To: Principal Investigator<br>(Grammar error) |
| 5 | | From: Assoc Prof Chris Bullen<br>To: Prof Chris Bullen<br>(Change of title) |
| 6 | Abbreviations | From SF-36 Short Form 36 questionnaire<br>To: Rand 36-item Health Survey<br>(Change of questionnaire name for trial)<br>Add: ICD-10 AM - International Classification of Disease version 10 Australian Modification |
| 9 | 2.3: Effects of Leg Ulceration on Health | From: SF-36 Short Form 36 questionnaire<br>To: Rand 36-item Health Survey<br>(Change of questionnaire name for trial) |
| 16 | 7: Randomisation and allocation concealment. Para 1 | From: When a registration number has been allocated, the participant's initials and date of birth and the date of registration must be recorded alongside the registration number in the database.<br>To: When a registration number has been allocated, the participant's initials and date of birth and the date of registration must be recorded.<br>(Clarification of procedure) |
| 16 | 7: Randomisation and allocation concealment. Para 2 | From: The randomisation sequence will be prepared by the trial statistician and loaded into a secure website.<br>To: The randomisation sequence will be prepared by the trial statistician and loaded into a secure database.<br>(Clarification change)<br><br>From: Each participant will receive a randomly assigned unique double-blind treatment pack/randomisation number. The allocated treatment will be given to the participant by the Research Nurse.<br>To: Each treatment pack is uniquely numbered and is allocated using the randomisation sequence. The Research Nurse accesses the randomisation web-page, completes data entry, and generates the allocation using a computerised tablet. The allocated treatment is then given to the participant by the Research Nurse. |

| | | |
|---|---|---|
| | | (Clarification of procedure) |
| 17 | 9.1 Primary outcome measure | From: At 24 weeks, the research nurse will visit the participant and determine if the reference ulcer is healed. If the ulcer is healed, the research nurses will access the participant's clinical records to determine the most recent week proximate to the 24 week visit date of healing was recorded.<br>To: At 24 weeks, the Research Nurse will determine if the reference ulcer is healed. If the reference ulcer is healed, the research nurses will access clinical records to determine the date of healing was first reported during the 24-week period. If the reference ulcer is unhealed, the Research Nurse will determine from the clinical record whether the reference ulcer had healed at any time prior to 24 weeks. If there is no mention of healing then the ulcer will be assumed to have been unhealed during the 24 weeks. If the reference ulcer is recorded as healed during that time, the unhealed ulcer will be assumed to be a recurrent ulcer and the date healing is first recorded will be assumed to be the healing date.<br>(Clarification of procedure) |
| 18 | 10.1 Baseline assessments Para 1 | From: Eligible patients will be visited at Week 0 and,<br>To: Eligible patients will be visited at Week -1 and,<br>(Correction to visit week) |
| 18 | Bullet one: Change in HRQoL | From: ... general health will be assessed using the SF-36, EQ5D and ulcer-related health using the CXVUQ.[51,52] The EQ5D and SF-36 are well-validated questionnaires<br>To: ... general health will be assessed using the Rand 36-item Health Survey, EQ5D and ulcer-related health using the CXVUQ.[51,52] The EQ5D and Rand 36-item Health Survey are well-validated questionnaires.<br>(Change of questionnaire name for trial) |
| 18 | Bullet two: Adverse Events | From: and graded using the Common Terminology Criteria for Adverse Events v3.0 or other grading criteria as required by the Data Safety Monitoring Board.<br>To: and coded using the ICD-10 AM.<br>(Clarification of actual coding) |
| 19 | Bullet 3: HRQoL Instruments | From: The Short Form Health Survey (SF-36).<br>To: The Rand 36-item Health Survey<br>(Change of questionnaire name for trial) |
| 20 | 10.5: Visit 2: Baseline assessment and randomisation | From: Carry out assessments of health-related quality of life (SF 36, EQ5D, and CXVUQ).<br>To: Carry out assessments of health-related quality of life (RAND 36, EQ5D, and CXVUQ).<br>(Change of questionnaire name for trial) |
| 20 | 10.6: Visit 3: 24 weeks after randomisation | From: Carry out assessments of health-related quality of life (SF36, EQ5D, and CXVUQ).<br>To: Carry out assessments of health-related quality of life (RAND 36, EQ5D, and CXVUQ).<br>(Change of questionnaire name for trial) |
| 22 | 11.2 Statistical Analysis. | From: Data from the Case Record Forms (CRFs) will be entered |

| | | |
|---|---|---|
| | Para 1 | into a trial centre specific Excel spreadsheet in webfolder hosted by NIHI by the Research Nurse.<br>To: Data from the Case Record Forms (CRFs) will be entered into password secured Oracle databases hosted by NIHI via the web by the Research Nurse.<br>(Change of procedure) |
| 23 | 12.2 SCOTT Committee | From: No New Zealand manufacturer currently produces a 150 mg dose of aspirin and therefore Medsafe have advised approval for an exemption for clinical trial of a new medicine under s30 of the Medicines Act is required. Optimus Healthcare Ltd will be the compounding pharmacy for the trial.<br>To: No New Zealand manufacturer currently produces a 150 mg dose of aspirin. Therefore Medsafe have advised approval for an exemption for clinical trial of a new medicine under s30 of the Medicines Act is required. Section 30 clinical trial exemption was obtained in October 2014 (TT50-5199 (1700). Optimus Healthcare Ltd will be the compounding pharmacy for the trial.<br>(Information updated) |
| 23 | 12.3 Informed Consent | From: If a patient meets the inclusion criteria, and expresses interest in participating in the trial,<br>To: If a patient expresses interest in participating in the trial,<br>(Clarification change) |
| 25 | 13.4 Data Safety and Monitoring | From: The Health Research Council's Data Monitoring Core Committee (HRC DMCC) has been approached to constitute a Data Safety Monitoring Board (DSMB). However, the HRC DMCC declined to constitute a DSMB under their auspices as the trial was considered low risk.<br>To: The HRC DMCC declined to constitute a DSMB under their auspices as the trial was considered low risk.<br>(Clarification change) |
| 35 | Steering Committee | From: Associate Professor Chris Bullen<br>To: Professor Chris Bullen<br>(Change of title) |
| 35 | Steering Committee | From: Ngaire Kerse Tel: 64 9 923<br>To: Ngaire Kerse Tel: 64 9 923 4467<br>Add Tel: for Jill Walters: Tel: 307 4949 ext 28371<br>(Incomplete information) |