

STATISTICAL ANALYSIS PLAN

Final

Aspirin4VLU

**A randomised, blinded, placebo controlled trial
of adjuvant low dose aspirin
for venous leg ulcers**

NIHI

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

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The undersigned have reviewed this document and find it to be consistent with the requirements of the protocol as it applies to their respective areas. The author/reviewer also finds this document to be in compliance with ICH-E9 as well as NIHI SOP BS-0004.



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10/2/2015
Date



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12.2.2015
Date

Preface

The purpose of this Statistical Analysis Plan (SAP) is to provide a detailed statement of the intended statistical analyses that will be performed in the analysis of data from the Aspirin4VLU. This document is intended to be stand-alone from the protocol and adhere to the main points in the analysis summary specified in the protocol. However it is envisaged that the SAP can undergo revision outside of the protocol.

It is not anticipated that revisions to the SAP that are in the spirit of the specified protocol analysis would require review by an ethics committee.

It is assumed that the study documentation provided by Data Management follows standard operating procedures. These procedures describe the process for setting up and maintaining study documentation, recording decisions affecting data handling, as well as methods of data capture and the algorithms to ensure accurate data are collected and maintained. It is assumed that the SAP will use data from a locked database that has been verified against the clinical record and is a true record of the data collected from the patient. Any data that are missing will be flagged and assumed to be undiscoverable.

The SAP will also outline the proposed layout of tables/figures that will be presented.

Scope

Please note that the scope of this SAP is intended to cover ONLY those main analyses described in the protocol. For additional research questions not detailed within this SAP and/or questions requiring further exploratory analyses please refer to other separate SAPs.

To keep within timeframe of issue of Biostatistics report, input into required analysis needs to be pre-specified in this analysis plan. Requests for additional analyses must be minimal after sign-off of this document. This enables all pre-programming programs to be performed ahead of database lock.

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1. INTRODUCTION

Leg ulcers are chronic, recurrent and have a major impact of the lives of elders. The vast majority of health care for leg ulcers is undertaken in the community, where district nurses alone have been estimated to spend up to a quarter of their time in leg ulcer care. Venous leg ulcers are the most common type of leg ulcer accounting for up to 8 out of every 10 people with leg ulcers.

There is limited but suggestive evidence for aspirin as an adjuvant for treating venous ulceration. Two small randomised controlled trials (n=71) evaluated 300 mg daily oral aspirin in addition to compression bandaging in patients with venous ulcers, with more people in the aspirin group healing in both trials (RR 1.91 and 1.41). However, this evidence is not sufficient to change practice.

The main barrier to further testing of aspirin is the belief that many older adults are already being treated with aspirin. However, two New Zealand venous ulcer trials showed aspirin use in such patients was low (similar to a trial in the UK). Only 30% of participants in the HALT trial (recruitment 2003-2005, n=368) and 17% in the PREPARE Pilot trial (recruitment 2007, n=41) were taking aspirin at baseline. Analysis of the HALT trial data found the 89 participants who were on low dose aspirin healed about 30% faster than those not on aspirin; the 150 mg dose was most effective (HR 1.77, 95%CI 1.13 to 2.75, n=33).

A definitive trial is required to provide more evidence of the effect aspirin when used with compression.

2. STUDY 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).

3. STUDY DESIGN

Please refer to the study protocol for a full description of the study design. This is 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. 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. Patients with venous leg ulcers who present for treatment to or already receiving treatment from the community-based district nursing services at the following trial centres will be recruited: Auckland, Counties Manukau, Waikato, and Southern District Health Boards, and Nurse Maude community nursing services in Christchurch. Baseline and 24 week assessments will be conducted by the research nurse. The patient will continue to receive district nursing care as per normal protocol.

3.1. Eligibility criteria

Participants will be eligible for inclusion if they:

- aged 18 years or older
- determined to have a venous leg ulcer (clinical indications of venous ulceration, ABI \geq 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

Participants will be excluded if they:

- 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

3.2. Randomisation

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 website. 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 participant will receive a randomly assigned unique double-blind trial treatment number.

3.3. Sample size

A sample size of 354 (177 in each group) would be sufficient to show a four week difference in time-to-healing at 90% power with an alpha of 0.05, and assuming 10% loss to follow up and 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). 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 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).

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.

4. STUDY OUTCOMES

4.1. Primary outcome

The primary outcome is time to healing over 24 weeks follow up period.

4.2. Secondary outcomes

The secondary outcomes are:

- Proportion of participants with a healed reference VLU at 24 weeks
- Change in estimated ulcer area between baseline and 24 weeks
- Change between baseline and 24 weeks in health related quality of life (HRQoL) using SF-36, CXVUQ and EQ5D
- Treatment adherence at 24 weeks
- Efficacy of blinding at 24 weeks
- Adverse events during 24 week trial period

5. DATA SOURCES

Data collected from the following Aspirin4VLU case report forms and questionnaires which will be extracted from the NIHI Oracle database into SAS for the analyses:

- Screening log
- Form A: Registration
- Form B: Baseline
- Form C: 24-week endpoint assessment
- Form Q: Participant questionnaire booklet
- Form M: Concomitant medications
- Form X: Adverse events

6. VARIABLE DEFINITIONS

The following definitions relate more specifically to the derived variables and non-standard definitions required for analysis of the data that are specific to the analyses referred to throughout this SAP. Please refer to the study protocol for a complete list of abbreviations set out for this study.

- **Ankle Brachial Index (ABI):** The ABI is an index of arterial insufficiency in the lower leg. An ABI < 0.8 indicates that there is a high probability that some arterial insufficiency is present. 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. ABI will be collected in form A question 5.01.

- **Healing:** Defined as intact skin without a scab and without the ulcer re-opening. Healing data will be obtained from clinical records. District nurses will visit patients on a weekly basis as part of normal care and record healing. 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 week within the 24 week visit that date of healing was first recorded. This data will be entered in form C questions 2.01 and 2.09.
- **Estimated ulcer area:** Obtained from measuring the maximum width(mm) and length(mm) of the reference ulcer (form B questions 2.02 and 2.03, and form C questions 2.02 and 2.03), and the ulcer area is calculated using the area of an ellipse formula:
$$\text{Ulcer area} = (\text{Length}/10) \times (\text{Width}/10) \times (\pi=3.1416 / 4)$$

E.g. if length=30mm and width=15mm
then estimated ulcer area=3 x 1.5 x 3.1416 / 4 = 3.53 cm²
- **Prognostic index:** calculated using following Margolis index formula from form B questions 2.01 to 2.03:
if (duration>6mths = N) and (ulcer area ≤ 5cm²) then prognostic index = 0,
if (duration>6mths = Y) or (ulcer area > 5cm²) then prognostic index = 1,
if (duration>6mths = Y) and (ulcer area > 5cm²) then prognostic index = 2
- **RAND-36 questionnaire:** The RAND-36 is a 36-item self-administered instrument to measure generic health-related quality of life. Participants' perceived health is measured across 8 domains (physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional functioning and mental health). Additionally, two summary component scores (physical and mental) will be obtained. RAND-36 domain and summary scores will be calculated at baseline and 24 weeks from form Q questions 1 to 11.04.
- **Charing Cross Venous Ulcer Questionnaire (CCVUQ):** The CCVUQ is a 21-item self-administered disease-specific instrument to measure health-related quality of life across four domains (social function, domestic activities, cosmesis and emotional status). CCVUQ domains will be calculated at baseline and 24 weeks from form Q question 12 to 19.
- **EuroQoI 5D (EQ5D):** The EQ5D is a 6-item self-administered generic instrument to measure health-related quality of life across 5 domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). A utility score associated with a health state is also generated. Measured at baseline and 24 weeks from form Q questions 20 to 25.
- **Treatment adherence:** Measured at 24 weeks using count of remaining capsules by the research nurse in form C question 5.04. Note participants are to take one capsule per day so a full course of study treatment is 168 capsules (if ulcer has not healed). A leeway of 10% either way has been allowed.

Treatment adherence will be coded as:

- If the ulcer is not healed at 24 weeks (form C question 2.01=No):
 - o And if question 5.04 is between 0 and 17 then treatment adherence = Yes

- And if question 5.04 is ≥ 18 then treatment adherence = No
- If the ulcer is healed at 24 weeks (form C question 2.01=Yes):
 - First work out number of days participant should have taken the capsules: date healed (form C question 2.09) minus randomisation date
 - Subtract this number from 168 to get number of capsules that should be remaining. Work out the 10% leeway range around this, and:
 - If question 5.04 is included in this range then treatment adherence = Yes
 - If question 5.04 is not included in this range then treatment adherence = No
 - E.g. If participant is randomised on 1 Feb and healed on 1 May then the difference is 89 days, and they should have $168-89=79$ capsules remaining (and with a 10% leeway either way this gives between 71 to 87 capsules remaining). So if question 5.01 is between 71 and 87 then participant is coded as treatment adherence = Yes. Otherwise they are coded as treatment adherence = No.
- **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. From form C questions 5.05 and 5.06.

7. BIostatISTICS QUALITY ASSURANCE

Well in advance of study data-lock, programming across all analyses will commence with dummy data. This will allow sufficient time to turn around the 'real' analyses as quickly as possible. Early programming will also allow for a preliminary run at merging of the various datasets into the correct data structure required for analysis. Specifically, the datasets in section 5 will be taken before data-lock and passed through the necessary biostatistical processes (which will include checking that all the datasets have been imported correctly into SAS and are all able to be correctly merged together).

8. ANALYSIS POPULATIONS

8.1. Intention to Treat

All treatment evaluations will be performed on the principle of 'Intention To Treat' (ITT) unless otherwise specified. The ITT population will consist of all randomised participants regardless of whether they actually satisfied the entry criteria, the treatment actually received and subsequent withdrawal or deviation from the protocol.

8.2. Per Protocol

A per protocol analysis will also be performed on the primary and main secondary outcomes in order to check the robustness of the results. A per protocol analysis involves looking at the major protocol violations such as treatment adherence, withdrawals and lost to follow-up. Criteria for defining the per protocol population will include consideration of the following: those who have complied with the treatment allocated, were exposed to the intervention as planned (i.e. used only assigned intervention), were not lost to follow-up, and who do not have major

protocol deviations pertaining to eligibility or the assessment of the treatment difference.

9. STATISTICAL ANALYSIS

All statistical analyses will be performed using SAS version 9.3 and R version 3.0.1. All statistical tests will be two-tailed and at 5% significance level throughout the analyses and all treatment evaluations will be performed on the principle of 'intention to treat' unless otherwise specified. No adjustments for multiplicity are planned for any of the outcomes.

Summaries of continuous variables which are normally distributed will be presented as means and standard deviations or medians and inter-quartiles for skewed data, while categorical variables will be presented as frequencies and percentages. Continuous variables will be compared with t-tests or Mann-Whitney tests and categorical data with chi-squared tests as appropriate.

The study statistician will conduct all the analyses. Blinded results will be presented to the PI and SC for interpretation. Unblinded results will be revealed to the SC only after interpretation of the blinded results has been determined.

A separate EXCEL file containing the SAP tables specific to this study will be provided based on all the analyses stated below (see Appendix I).

9.1. CONSORT statement

All participants who were invited to participate in this study should be accounted for and a CONSORT statement prepared. The reasons for non-participation will be discussed in relation to the external validity of the study and the pattern of protocol violations considered as potential sources of bias. Reasons for early withdrawal will be listed for all participants that prematurely discontinued intervention or the study. The number of participants that were screened but not randomised will also be presented from the Screening Log.

9.2. Participant accountability

Tables describing patient accountability will be produced. The number of participants who were screened, registered, fulfilled eligibility criterion, together with reasons for exclusion will be summarised in table 1a. The status of participants at each visit, and the number of major protocol violations will also be summarised in table 1a.

9.3. Baseline characteristics

Baseline demographic variables (age, sex, self-reported ethnicity, education), smoking status, history of ulceration, ulcer size, clinical history, current treatments (including compression system, use of pentoxifylline and use of statins) and health-related quality of life variables will be summarised for each intervention group in table 1b. Since any differences between the groups at baseline could only have occurred by chance, no formal significance testing will be conducted.

9.4. Concomitant medications

Concomitant medications (coded to the Anatomical Therapeutic Chemical, ATC, classification system) by number of events and people will be summarised for each intervention group in table 2a. Separate tables will be given for general ATC categories, and for the detailed ATC codes.

9.5. Primary outcomes analysis

The primary outcome is time to healing over 24 weeks follow up period. All analyses for the primary outcome will be ITT unless otherwise stated where participants that have not healed by 24 weeks or missing outcomes will be censored on the 24 week visit date. Analyses comparing the Aspirin and Placebo groups will be presented in table 3a.

Time to healing will be analysed using Cox regression modelling to take into account known covariates and the varying times since randomisation. The proportionality assumption will be checked using standard graphical techniques. The main analyses will be unadjusted. Kaplan Meier plots and log rank test will also be used.

9.5.1. Sensitivity analyses

The following sensitivity analyses will be conducted for the unadjusted primary outcome:

- Adjusted analyses including study centre, prognostic index and any important imbalances in baseline covariates
- Per Protocol analyses where participants that have any protocol violations (defined in section 8.2) will be excluded

9.5.2. Subgroup analyses

If the treatment effect for this outcome is significant (i.e. $p < 0.05$), then subgroup analyses will be reported. It is planned that subgroup analyses will be carried out on the following baseline variables: sex, age (dichotomised based on the median), ethnicity, ulcer size ($\leq 5\text{cm}^2$, $> 5\text{cm}^2$), ulcer duration ($\leq 6\text{mths}$, $> 6\text{mths}$), and compression system (2 layer, 3 layer, etc). The model will include the subgroup variable along with its interaction with treatment. A test of whether the treatment effect differs across the levels of the subgroup will be constructed by assessing the significance of the interaction term. The subgroups analyses will be presented as a forest plot.

9.6. Secondary outcomes analysis

Descriptive summary statistics for each group will be presented for all secondary outcomes collected in form C in table 2b. Participants with missing outcome data will be excluded from this table.

The distribution of all continuous endpoints will be assessed for normality and skewed data will be subjected to an appropriate transformation before analysis. Non-parametric analysis (Mann-Whitney tests) will be used if data is skewed and cannot be transformed to be normally distributed.

9.6.1. Proportion healed

The proportion of participants with healed ulcers at 24 weeks between the groups will be analysed using chi-squared tests. Crude incidence rates, relative risks (RR), absolute risk differences, number needed to treat (NNT), and corresponding 95% confidence intervals will also be calculated. For the ITT analyses participants with missing outcomes will be assumed to be not healed. Per protocol analyses will also be conducted where participants that have any protocol violations (defined in section 8.2) will be excluded. Results will be presented in table 3b.

9.6.2. Change in ulcer area

Change in ulcer area between baseline and 24 weeks will be analysed using linear regression (ANCOVA). The model will include the treatment group and the baseline ulcer area measure. For the ITT analyses missing 24 week outcomes will be replaced with the baseline ulcer area (so assuming no change). Results will be presented in table 3c.

9.6.3. Change in quality of life

Change between baseline and 24 weeks in each of the HRQoL scores (SF-36 domains and summary scores, CCVUQ domains and the EQ5D domains) will be analysed using linear regression (ANCOVA). Each model will include the treatment group and the baseline ulcer area measure. For the ITT analyses missing 24 week outcomes will be replaced with the baseline value (so assuming no change). Results will be presented in table 3c.

9.6.4. Treatment adherence

Treatment adherence at 24 weeks will be presented as counts and percentages, and the difference between the treatment groups will be analysed using chi-squared test. Missing data will be excluded. Results will be presented in table 3b.

9.6.5. Efficacy of blinding

The level of agreement between the efficacy of blinding reported at 24 weeks by the participant and the research nurses will be calculated using a weighted Kappa statistic. Missing data will be excluded. Results will be presented in table 3b.

9.6.6. Adverse events

All adverse event data collected on the form X will be reported and coded to ICD10-AM criteria. All safety data will be summarized in the form of frequency distributions, descriptive statistics, and tabulations. This includes adverse events (serious and non-serious), for the duration of the study.

Adverse event counts by number of events and people will be summarised in table 4a. Separate tables will be given for general categories, and for the detailed codes. Table 4b will summarise the adverse event counts by categories collected in form X (type and relationship to study treatment), and separate tables will also be given for the incidence rate ratios and incidence density comparing the two treatment groups. Line listings will also be produced in order to examine adverse events that are serious and related to treatment, multiple adverse events for a participant on the same date and bleeding adverse events, see tables 4c to 4e.

10. DATA SAFETY AND MONITORING BOARD

The Data Safety and Monitoring Board (DSMB) will be responsible for safeguarding the interests of trial participants, assessing the safety of the intervention during the trial, and monitoring the overall conduct of the clinical trial. The DSMB will meet every 6 months with the scope for additional meetings should the DSMB deem it necessary. The first meeting will take place before the trial to consider the DSMB charter and this SAP. The second meeting will take place 6 months after the first person has been randomised into the study.

The purposes of each meeting are: (1) to monitor the safety of the intervention during the trial for all adverse events and serious adverse events defined by study protocol; (2) to review withdrawals. The DSMB will be advisory to the study SC. The SC will be responsible for promptly reviewing the DSMB recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes to the study conduct are required.

Only closed sessions will be held which will involve the DSMB members and the study statistician. For each DSMB meeting the study statistician will put together blinded closed reports that contain the treatment group ID and send to the DSMB members. The key to treatment group ID is kept in an Oracle treatment table and is only accessible to the Lead Data Manager or delegate. The Lead Data Manager or delegate will access the Oracle treatment table and provide to the DSMB members separately the key to the treatment group ID. In this way the study statistician will remain blinded to the reports provided to the DSMB and the Lead Data Manager will not have access to the DSMB report. The report will contain the following results: participant accountability, baseline characteristics, concomitant medications, analysis of proportion ulcers healed and ulcer area at 24 weeks (to be included from the third DSMB meeting to allow for sufficient data), and all adverse event tables.

Note analysis of proportion ulcers healed and ulcer area at 24 weeks have been included in the DSMB report, even though they are secondary outcomes. It is conceivable that aspirin would worsen wound healing enough to be a safety concern, or that tolerance of treatment would be poor enough to make the trial results uninformative.

The report should provide information that is as accurate as possible, however as the data will not have been locked there may be outstanding queries. The reports should be sent to DSMB members at least one week prior to the date of the meeting.

For full details of DSMB and content of study reports see following documents:

- Aspirin4VLU DSMB charter.doc
- Aspirin4VLU DSMB table templates.xls

11. PEER REVIEW

The statistical analysis and report for the primary outcome will be peer reviewed by an independent member of the NIHI Biostatistics team (not involved in the study).

12. BUDGET

Level of involvement and engagement of statistical analyses as well as details prepared in the statistical report will depend on the study budget for Biostatistics team. Please note that for any additional analysis that is not specified in this statistical analysis plan or beyond the given budget, additional allowance will be required for further analyses in consultation with the principal investigator and/or operations manager.

13. DISSEMINATION

At the end of study (after data lock), all planned statistical analysis will be carried out. A statistical analysis report will be produced to summarise the main findings. ANNEX tables will be attached to present all detailed results.

The study statistician will therefore take full responsibility on this report (provided in PDF format) and attached tables (read-only). The study statistician does not take any responsibility for any modifications made in the interpretation, conclusions, or tables/figures beyond those presented in statistical analysis report.

Note that the purpose of the statistical report (produced from the analyses specified in this plan) is to present the results and assist the client (internal or external) to interpret the findings. It is not meant to be used for further dissemination.

APPENDIX I: LIST OF TABLE TEMPLATES

Section 1. Randomisation and baseline information

Table 1a. Participant accountability

Table 1b. Baseline variables

Section 2. Descriptive summary of follow-up data

Table 2a. Concomitant medication counts

Table 2b. 24 week endpoint assessment

Section 3. Analysis

Table 3a. Primary outcome analysis

Table 3b. Secondary outcome analysis (binary)

Table 3c. Secondary outcome analysis (continuous)

Section 4. Adverse events

Table 4a. Adverse event counts

Table 4b. Adverse events by categories and analysis

Table 4c. Line listing of adverse events that were related to treatment and serious

Table 4d. Line listing of multiple adverse events for a participant on the same date

Table 4e. Line listing of bleeding adverse events

