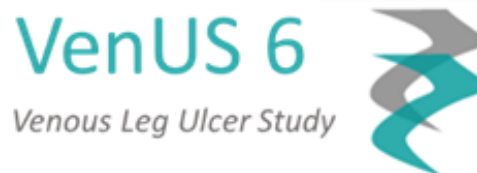| VenUS 6 |
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| **A randomised controlled trial of compression therapies for the treatment of venous leg ulcers (ISRCTN67321719)** |
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| Studies Within A Trial - Statistical Analysis Plan |

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Contents

1. Background and rationale

We will undertake three studies within a trial (SWATs) to assess the effectiveness for methods to improve recruitment and retention. Strategies have been registered with the Medical Research Council SWAT repository prior to activity commencing.

1.1.1. Recruitment SWAT

A recent review showed that tailoring or shortening the patient information sheet given to participants makes little or no difference to recruitment. [1] None of the studies included in the review, however, tested the use of information graphics ("infographics") to enhance recruitment. The evidence around the effectiveness of infographics in a health context is limited but persuasive. Infographics have been shown to improve patient knowledge; both in relation to personally relevant information such as discharge instructions, and statistical information such as the association of age with cancer risk. [2, 3] While a further study with patients, students and doctors found that infographics did not increase knowledge when compared to plain language summaries, the infographics did improve reader experience and user-friendliness. [4]

These findings suggest that there may be the potential for infographics to increase potential participant experience and understanding of health research leading to increased recruitment.

We will therefore use the registered SWAT protocol 116 (https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/) to evaluate the effects of presentation of the study design to participants on recruitment rate. Participants will be randomised (at the site level) to receive an infographic (visual document explaining the study) plus the standard patient information sheet (PIS) or just the PIS.

1.1.2. Retention SWATS

Retention SWAT 1

Many recruitment and retention strategies routinely include some element of thanks within them. Although we often do this, there is little to no evidence to suggest this might work. Recent evidence suggests that those saying thank you often underestimate its effect. [5] Therefore, there is a need to test the impact of thanks in the context of trial recruitment and retention.

We will use a 2 by 2 factorial design to simultaneously evaluate the effect of two retention strategies: a participant newsletter and a thank you card sent in advance of follow up questionnaires. These two strategies have been registered as separate SWATs on the SWAT repository (https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/): SWAT protocols 28 and 119. Participants will be randomised to receive 1) newsletter and thank you card; 2) newsletter only; 3) thank you card only; 4) neither the newsletter nor the thank you card. These will be sent at Month 4 and Month 9 following randomisation to the VenUS 6 trial.

Retention SWAT 2

Effective low-cost strategies to improve retention in trials are needed. Growing evidence supports providing pens along with postal questionnaires to encourage continued trial

participation. Previous studies found that including a pen could increase response rates [8] and may elicit responses from participants who had previously failed to return questionnaires [9]. Similarly, more recent evidence indicates a favourable effect on completion rates, along with a reduction in the time taken to return questionnaires [7]. Further, the inclusion of a pen might reduce the number of reminders needed to prompt questioner completion [6]. These findings suggest that pens could act as a sufficient non-monetary incentive to increase retention in trials.

We will therefore undertake SWAT protocol 138 (https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/) to evaluate the effect of including a pen on retention rates. Participants will be randomised to receive 1) a pen; 2) no pen. These will be sent at Month 3 following randomisation to the VenUS 6 trial.

2. SWAT objectives

Recruitment SWAT

- To investigate whether providing an infographic (visual document explaining the study) plus the standard patient information sheet (PIS) improves recruitment to VenUS 6.

Retention SWAT 1

- To investigate whether providing a newsletter and/or thank you card improves retention to VenUS 6 at 6 months post-randomisation.

Retention SWAT 2

- To investigate whether providing a pen with a study questionnaire improves response rates to the VenUS 6 3 month questionnaire.

3. Randomisation
Generation of the allocation sequence for each of the three SWATs will be undertaken independently by a researcher not involved with the follow up of participants.

Recruitment SWAT

For the recruitment SWAT, cluster randomisation at the site level will be used to reduce cross contamination. The allocation ratio will be 1 to 1.

Retention SWAT 1

For retention SWAT 1, the allocation ratio will be 1:1:1:1.The randomisation sequence will be stratified by main trial allocation and will use randomly varying block sizes.

All participants recruited into the VenUS 6 trial will be eligible and randomised for the SWAT.

Retention SWAT 2

For retention SWAT 2, randomisation will be stratified by main trial allocation and will use randomly varying block sizes. The allocation ratio will be 1 to 1.

All participants recruited into the VenUS 6 trial will be eligible and randomised for the SWAT.

4. Sample size

As is usual with embedded trials, the sample size is constrained by the number of patients approached about the study (recruitment SWATs) or actively participating within the host trial (retention SWATs), hence a formal power calculation to determine sample size has not been conducted.

5. Outcomes

5.1. Primary outcome

Recruitment SWAT

The primary outcome of this embedded trial will be the proportion of SWAT participants in each group who are randomised into the host trial of those approached for consent in each group.

Retention SWAT 1

The primary outcome of these embedded SWATs will be the proportion of SWAT participants that return their 6 month questionnaire in each group of those sent the 6 month questionnaire in each group.

Retention SWAT 2

The primary outcome of this embedded SWAT will be the proportion of SWAT participants who return their 3 month post-randomisation questionnaire in each group of those that are sent the 3 month questionnaire.

Table 1: SWAT Primary Outcomes and Analysis Sets

SWAT	Analysis Set	Event of interest	Details
Recruitment SWAT 1	Eligible patients that are approached for consent to the host trial	Randomisation into the host trial	Y = 0 if not randomised Y = 1 if randomised
Retention SWAT 1	All participants that are sent the M6 CRF	Return of the M6 CRF to YTU	Y = 0 if not returned Y = 1 if returned
Retention SWAT 2	All participants that are sent the M3 CRF	Return of the M3 CRF to YTU	Y = 0 if not returned Y = 1 if returned

5.2. Secondary outcomes

Recruitment SWAT

Secondary outcomes will include the proportion of patients in each group who are screened but are deemed to be ineligible do not go on to be randomised versus those screened as eligible and proceed to be approached for consent and/or recruited, and the cost-effectiveness of the intervention.

Table 2: Recruitment SWAT Secondary Outcomes and Analysis Sets

Outcome	Analysis Set	Event of interest	Details
Approach for consent	All patients screened for participation in the host trial	Approach for consent to participation in the host trial	Y = 0 if not approached Y = 1 if approached
Cost Effectiveness	Cost of infographic printing (direct and indirect costs)	Difference in cost per recruited participant	

Retention SWAT 1

Time to response will serve as a secondary outcome. Withdrawal after the questionnaire is sent but before a response is provided or where no response is provided and the next follow up time point has become due, will be handled as competing events.

Whether a reminder notice is required, completeness of response, and cost of the intervention per participant retained will serve also as secondary outcomes.

Table 3: Retention SWAT 1 Secondary Outcomes and Analysis Sets

Outcome	Analysis Set	Event of interest	Details
Time to response	All participants that are sent the M6 CRF	Return of the M6 CRF to YTU	(T_i, ϵ_i) for participant i T_i denotes the event time (any type of event) $\epsilon_i = 1$ if M6 CRF returned, $\epsilon_i = 0$ if a competing event occurs
Reminder notice required	All participants that are sent the M6 CRF	M6 Reminder notice sent	Y = 0 if no reminder notice sent Y = 1 if reminder notice sent
Completeness of response	All participants that are sent the M6 CRF	-	Y = 0 if M6 CRF not returned Y = 1 if M6 CRF returned, but scores cannot be generated for either the EQ-5D-5L or VEINES-QoL Y = 2 if M6 CRF returned, and a score can be generated for exactly one of the EQ-5D-5L or VEINES-QoL Y = 3 if M6 CRF returned, and scores can be generated for both of the EQ-5D-5L and VEINES-QoL

	Cost of newsletter and thank you card printing (direct and indirect costs)	Difference in cost per retained participant	
Cost Effectiveness			

Retention SWAT 2

Time to response will serve as a secondary outcome. Withdrawal after the questionnaire is sent but before a response is provided or where no response is provided and the next follow up time point has been come due, will be handled as competing events.

Whether a reminder notice is required, completeness of response, and cost of the intervention per participant retained will serve also as secondary outcomes.

Table 4: Retention SWAT 2 Secondary Outcomes and Analysis Sets

Outcome	Analysis Set	Event of interest	Details
Time to response	All participants that are sent the M3 CRF	Return of the M3 CRF to YTU	(T_i, ϵ_i) for participant i T_i denotes the event time (any type of event) $\epsilon_i = 1$ if M3 CRF returned, $\epsilon_i = 0$ if a competing event occurs
Reminder notice required	All participants that are sent the M3 CRF	M3 Reminder notice sent	Y = 0 if no reminder notice sent Y = 1 if reminder notice sent
Completeness of response	All participants that are sent the M3 CRF	-	Y = 0 if M3 CRF not returned Y = 1 if M3 CRF returned, but scores cannot be generated for either the EQ-5D-5L or VEINES-QoL Y = 2 if M3 CRF returned, and a score can be generated for exactly one of the EQ-5D-5L or VEINES-QoL Y = 3 if M3 CRF returned, and scores can be generated for both of the EQ-5D-5L and VEINES-QoL
Cost Effectiveness	Cost of newsletter and thank you card printing (direct and indirect costs)	Difference in cost per retained participant	

6. Analysis

Analyses will be conducted using the latest available version of Stata, and will follow intention to treat principles with participants analysed as part of the groups to which they were allocated.

For the retention SWAT any participants who were deceased or withdrawn from postal follow up prior to the time point being reached will be excluded.

For binary outcomes (recruitment, response to questionnaire and reminder required), relative differences between groups will be presented in terms of the odds ratio (together with appropriate two-tailed 95% confidence intervals). These data will also be reported descriptively in terms of frequencies and proportions.

For completeness of response an ordinal outcome will be used: Not returned, returned but scores cannot be generated for either quality of life outcome (EQ5D5L, VEINES QOL), returned but a score cannot be generated for one of the quality of life outcomes, returned and scores can be generated.

For time to event outcomes (time to response), relative differences between groups will be presented in terms of hazard ratios (and appropriate two-tailed 95% confidence intervals).

6.1.   Primary Outcome Analyses
<u>Recruitment SWAT</u>

The primary analysis will compare the difference in recruitment rates between those receiving the infographic in addition to the PIL and those not receiving the infographic. This outcome will be analysed using mixed effect logistic regression with a fixed effect for SWAT allocation and a random intercept for site.

<u>Retention SWAT 1</u>

The difference in questionnaire returns at 6 months will be analysed using a mixed effect logistic regression model including each intervention (thank you card and newsletter) and VenUS 6 treatment allocation as a fixed effects and site as a random intercept.

Adjusted odds ratios and corresponding 95% CIs will be obtained from this model. A further mixed effect logistic regression model will be fitted including the same terms as specified above, in addition to an interaction term for the combined effect of the two SWAT interventions. This model will be used to derive estimates of the interaction between the interventions (on the multiplicative scale).

<u>Retention SWAT 2</u>

The difference in retention rates at 3 months will be analysed using a mixed effect logistic regression model including each intervention (pen), VenUS 6 treatment allocation as a fixed effect and site as a random effect. Adjusted odds ratios and corresponding 95% CIs will be obtained from this model.

6.2.   Analysis of Secondary Outcomes

<u>Recruitment SWAT</u>

The difference in the proportion of those responding to a recruitment invitation who received the infographic in addition to the PIL but who do not go on to be randomised, and those not receiving the infographic but who do not go on to be randomised will also be analysed using a similar model to the primary outcome.

The difference in cost per recruited participant between those offered the infographic and those not offered the infographic will be calculated. In addition to the direct costs of the

infographic, it may also be necessary to include the cost of staff time spent administering the recruitment packs.

Retention SWAT 1

The difference in the proportion of participants requiring a reminder letter mailing will be analysed using a similar model to the primary outcome. The difference in completeness of responses at 6 months will be analysed using a proportional odds model using a similar adjustments to the primary outcome.

The difference in cost per retained participant between those sent a thank you card and those not sent the thank you card will be calculated. In addition to the direct costs of the thank you card and postage, it may also be necessary to include the cost of staff time spent administering the mail out (for example filling and labelling envelopes).

The secondary outcomes at 12 months will be analysed as described above for the 6 month outcomes.

Retention SWAT 2

The difference in the proportion of participants requiring a reminder letter mailing will be analysed using a similar model to the primary outcome. The difference in completeness of responses at 3 months will be analysed using a proportional odds ordinal logistic regression model using a similar adjustments to the primary outcome.

The difference in cost per retained participant between those sent a pen and those not sent the pen will be calculated. In addition to the direct costs of the pen and postage, it may also be necessary to include the cost of staff time spent administering the mail out (for example filling and labelling envelopes).

The secondary outcomes at 12 months will be analysed as described above for the 6 month outcomes.

7. SAP Revisions

Amendment/addition to SAP and reason for change	New version number, name and date

8. Roles and responsibilities

Sign-off of the Statistical Analysis Plan by, as a minimum, the person writing the SAP, a relevant senior statistician, and the Chief Investigator.

Name	Trial Role	Signature	Date
Prof. Jo Dumville	Chief Investigator		
Prof. Catherine Hewitt	Senior Statistician		
Charlie Welch	Trial Statistician		
Catherine Arundel	Trial Manager		

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