PROMETHEUS

Promoting the use of SWATs; {*Host trial name,* recruitment/retention}

Statistical Analysis Plan

v1.0

York Trials Unit
Department of Health Sciences
University of York
York, YO10 5DD

Version date:

Author(s): -

Chief Investigator: -

Trial Coordinator: -

Contents

1. Guidance

This section provides guidance on how to create the Statistical Analysis Plan (SAP) using this template, for the Study Within A Trial (SWAT) that you are undertaking as part of the PROMETHEUS program; if you are undertaking a factorial design, please contact York Trials Unit as this template will need to be adapted.

This document should not be edited, or have text removed without prior discussion with the PROMETHEUS team, bar those parts which have been designed to be altered.

Throughout this document, wherever curly braces appear, there is a change required. If the text inside the curly braces is:

- In *italics*: replace the text with the relevant information requested to the specific SWAT that is being implemented; for instance {*Host trial name}* should be replaced with the name of the host trial in which the SWAT is embedded.
- In colour: delete as required. All statements relating to a recruitment SWAT are in a green font colour, similarly for retention they are in a blue font colour. You should delete all text in the colour not relating to your SWAT; for instance, if you are undertaking a recruitment SWAT, you would delete all the blue text.
- In **bold**: delete as required. In some instances, you will be required to choose one of the options, such as …{**will or will not**}; the correct phase corresponding to the SWAT in question should be selected. Otherwise, the text may be an additional comment, which can be included if applicable to your SWAT.
- Underlined: this text is notes for you as the author.

A combination of this formatting may be apparent in several sets of curly braces, in which case each of the above rules applies to each section.

Please ensure you have addressed all curly-braces within the document, including those on the title page. Please ensure all curly braces have been removed from the document, and anywhere that the format of the text has been altered to highlight it for the purpose of the template, ensure that the format is returned to normal, i.e. is in black non-italic font. Once the SAP is complete, please ensure the guidance section has been removed, and update the table of contents.

2. Definition of terms/acronyms

SAP	Statistical Analysis Plan
SWAT	Study Within A Trial
YTU	York Trials Unit

3. Introduction

This statistical analysis plan (SAP) provides details on the analysis that is to be undertaken by any person analysing the results from a Study within a Trial (SWAT) implemented through the PROMETHEUS program. This SAP has been designed to ensure that all analyses are undertaken in a consistent way, permitting the results to be combined in possible future meta-analysis.

Each host trial analysing their SWAT is expected to follow the analysis plan presented in this document. {However adjustments may be made to suit each individual trial if discussed and approved by the PROMETHEUS study team, and details of such changes should be noted here and in any subsequent reports.} The SAP has been developed and agreed prior to the end of data collection, and before any data is presented to the person responsible for the analysis.

4. Objectives

The PROMETHEUS program is looking at the effectiveness of a range of SWAT interventions. These can be categorised into two areas, recruitment and retention SWATs.

This SAP will give details on the **{**recruitment/retention**}** SWAT being undertaken in the **{***Host Trial Name***}** trial.

The SWAT will look at improving the **{**recruitment/retention**}** rate for the host trial, by **{***Details of the intervention being tested***}.**

4.1. Primary objective

The primary objective of this SWAT is to assess whether {*insert SWAT details*} changes the {recruitment/retention} rate in the host trial.

5. Outcomes

5.1. Primary Outcome

The primary outcome for this SWAT is {recruitment/retention} rate. This is defined as the proportion of {potentially eligible patients who agree to participate in the trial following an invitation/ consented participants who complete the primary outcome assessment for the host study}.

The numerator is the number of {patients recruited into the trial/number of complete primary outcome assessments, in this instance this is the number of {*insert details, {e.g. number of month 3 questionnaires returned}*}}, and the denominator is the number of {patients approached to enter the trial, in this instance this is the number {*insert how patients are approached, {e.g. number of packs sent out}*}/ participants who are expected to complete the outcome, i.e. {*insert details {e.g. the number who were still in the trial at this time point}*}}.

5.2. Secondary Outcomes

Secondary outcomes of interest in this SWAT include: {

- Proportion of patients randomised into the trial.
- Proportion of patients who decline to participate.
- Estimated cost of each additional participant recruited associated with the SWAT intervention, or cost of the intervention per person recruited.

- **{Time to consent {**only applicable in certain methods of consent**}.}**
- **{Time to randomisation.}**

In most cases the number recruited in the trial and the number randomised will be the same, in which case both outcomes will not need to be considered.

- Proximity of {**questionnaire completion/follow-up appointment attendance**} to due date.
- **{Number of follow-up** {**reminders/calls** {method of contacting participants}} **required**.}
- {**Completeness of follow-up questionnaire**}
- Proportion of consented participants who {**complete subsequent follow-up questionnaires/attend subsequent follow-ups**}
- Estimated cost-per retained participant.

}

6. Study Methods; design, sample size and randomisation

The study design, details of the recruitment strategies and population of interest can be found within the SWAT protocol for the host trial. Full details on the aspects such as treatment allocation, randomisation, blinding, selection of study population, and details on the specified follow-up time points are given in the protocol; a brief overview will be given here.

6.1. Design

{*Information on the design of the SWAT*}.

6.2. Sample Size

The sample size of this SWAT is driven by the size of the host trial, and as such no formal power calculation has been performed for this SWAT. The {*Host trial name*} trial {is expected to approach/recruited} {*Sample Size expected/obtained}* {patients/participants}. {*If any reason that the expected approach number/recruited number would not all be included in the SWAT, please give details here, such as if not all participants were expected to provide a phone number for a text messaging SWAT*}. Thus, the expected sample size of this SWAT is {*Sample Size for SWAT}* {patients/participants}.

6.3. Randomisation

{*Details on how participants are randomised into the SWAT, including information such as individual or cluster randomised, allocation ratio and method of randomisation*}

7. Data

Methods detailing data collection are detailed in corresponding protocol and reports.

7.1. Data Sharing

All host trial teams are required to sign the PROMETHEUS data sharing agreement, to permit any future meta-analysis of the SWATs, and as such {*Host Trial Name*} will share anonymised data with YTU. Data will be shared with YTU in {**dta, csv or sav**} file type within six months of the SWAT ending. To anonymise this dataset all identifiers such as date of

birth will be removed. The data will be randomly sorted to allow for a new participant ID to be allocated to each participant, with only the new ID provided to YTU, but both original and new kept by the trial team for data querying.

7.2. Transfer to York Trials Unit (YTU)

In line with the PROMETHEUS data sharing agreement, the dataset will be transferred in electronic format. Data will be shared in a secure manner, agreed with the PROMETHEUS team{**, and will be encrypted to ensure security**}.

7.3. Data Storage

Datasets transferred to the PROMETHEUS team at YTU will be transferred into a combined database on a secure server at the Department of Health Science, University of York. Professor David Torgerson will act as custodian for the combined dataset, and all data will be stored in line with the data protection procedures. Any data stored by the PROMETHEUS team will be saved as a dta file, using Stata version 15 or later, alongside the original datafile provided by the trial team.

7.4. Baseline Data

Demographic data including age at randomisation into the SWAT, gender and ethnicity (Caucasian/non-Caucasian) will be obtained where possible. This will allow subsequent future meta-analysis to be undertaken, and differences in effect between different populations to be assessed.

7.5. Outcomes

Follow-up data that will be reported, overall and by SWAT arm, will include: {

- The number accepting{**, not responding {only applicable to some consenting methods}**} and declining to participate in the trial
- The number of eligible patients
- **{The time taken to respond to an invitation}**

- Number {**returning/completing the questionnaire/assessment**} at the time point relating to the SWAT
- Number {**returning/completing the questionnaire/assessment**} at any subsequent time points
- Time taken to {**return the questionnaire/attend the assessment**}
- Number of drop-outs before time point
- Number of participants who were eligible for inclusion in SWAT
- Number of participants included in the SWAT, if different to that of those who were eligible.

}

8. Analysis

8.1. Software

The analysis will be undertaken using {*Software name and version*}. Any analysis undertaken by the PROMETHEUS team on behalf of the host trial team will be carried out using Stata version 15.0 (or later).

8.2. Blinding

The statistician analysing the SWAT {**will or will not**} be blinded to the SWAT allocation.

8.3. Participant Flow

A CONSORT flow diagram will be created to detail the flow of the {patients/participants} through the SWAT, including relevant details of the host trial wherever needed.

8.4. Baseline

All baseline demographics will be reported by SWAT trial arm, and overall. These will include, but are not limited to; age, gender, and ethnic group. In addition, details around the number of participants in each arm of the host trial, by SWAT arm, will also be given. No testing will be undertaken comparing baseline characteristics in the two arms.

8.5. Primary Analysis

1. The analysis will be two-sided, and conducted at a 5% significance level. {Unless otherwise has been agreed with the PROMETHEUS team}.
The primary outcome, {recruitment/retention} rate, will be compared using the absolute difference in {recruitment/retention} between the arms of the SWAT using logistic regression. {**The {stratification/minimisation} variable{s} that were used in the host trial will be included as {a covariate/covariates}, these are {insert variables used for stratification/minimisation; the host trial allocation will also be adjusted for.}** The results will be presented as the proportion in each arm (non-adjusted) and the difference in proportions (non-adjusted) as well as an odds ratio, with associated 95% confidence interval, and p-value. Model assumptions will be checked prior to use for all analysis. {Flexibility in choice of model is allowed where needed.}

8.6. Secondary Analysis

8.6.1. Withdrawals, loss to follow-up and missing data

Patients lost to follow up {i.e. those who responded positively to the invitation letter initially but drop out prior to randomisation/ did not {**attend the follow up appointment/complete the questionnaire**}} will be classed as 'lost to follow up' and will be included in the analysis. Missing data will be detailed per trial arm.

Similar to the primary analysis, any secondary outcomes that are proportions will be analysed using logistic regression. All proportions will be presented as un-adjusted proportion by arm, and difference in proportions; as well as an odds ratio, with associated 95% confidence interval, and p-value. All time-to-events will be analysed using a Cox-proportional hazard model, and results presented as hazard ratio, with associated 95% confidence interval, and p-value. {Flexibility in choice of model is allowed where needed, i.e. for overdispersion..}

{The proportion of patients who were randomised into the trial will be defined by the number of patients randomised over the number of patients approached; this proportion may be the same as the number who consented, and in which case will not be reported.

The proportion of patients who declined to participate will be the number of eligible patients who did not consent to participate in the trial, over the number of patients who were eligible to participate – where eligibility is defined by the inclusion and exclusion criteria of the host trial, which can be found in the {host trial name} protocol.

The estimated cost of each additional participant recruited associated with the SWAT intervention will be calculated by the total cost of the intervention, divided by the number of additional participants in the SWAT intervention arm{for equal allocation only - if unequal used, adjust this to reflect that}. Alternatively, the cost per person recruited is calculated by the total number of recruited in the intervention arm, over the total cost of the intervention.}

{**Time to consent will be calculated in days; it will be defined as the time between the estimated arrival time of the invitation pack, that is the date it was sent plus {*X*} days to allow for delivery, and the time that the patient consented to be in the trial. This will be compared using a Cox-proportional hazard model. {No information has been given here on the withdrawals or earlier completers, as these should not occur when looking at recruitment, someone cannot consent earlier than they were contacted.} All non-responders should be censored at 30 days after the expected arrival of their invitation pack.**}

{**Time to randomisation will be calculated in days; it will be defined as the time between the date of consent, and the date of randomisation. This will be compared using a Cox-proportional hazard model. Any participants who withdraw before randomisation should be censored at their withdrawal date. {No information has been given here on earlier completers, as these should not occur when looking at recruitment, someone cannot be randomised earlier than they were consented. Similarly, there should be no one who is not randomised who did not consent and thus no detail is given on their censoring.} }**

{The proximity of {**questionnaire completion/follow-up appointment attendance**} to due date will be compared using a Cox-proportional hazard model. The time between {**completion/attendance}** and the due date should be calculated in days. All participants who {**completed the questionnaire/attended the appointment}** early will have their time set to 0.1. Any participants who withdrew after the due date will be censored at the date of withdrawal, and all those who did not {**complete/attend}** will be censored at 30 days after the due date. }

{**The number of follow-up {reminders/calls} required will be compared using a Poisson regression model, or a zero inflated Poisson regression model if there is a large quantity of zeros. Similarly to the primary analysis, this will be adjusted for the {stratification/minimisation} variable{s} and the host trial allocation.**}

{**The completeness of the follow-up questionnaires will be compared using** logistic regression, adjusting for host trial allocation **{and the stratification/minimisation variables that were used for randomisation}.**

{The proportion of the participants who {**complete subsequent follow-up questionnaires/attend subsequent follow-ups**} will be compared defined by the number of participants who {**complete subsequent follow-up questionnaires/attend subsequent follow-ups**}, over the number of participants who are still in the trial at that time point. This will be compared using logistic regression, adjusting for host trial allocation **{and the stratification/minimisation variables that were used for randomisation}**. This analysis will be undertaken at every subsequent follow-up time point.

Estimated cost-per retained participant will be calculated as the total cost of the SWAT intervention divided by the number of additionally retained participants, where the

additionally retained participants is the difference in the number of retained participants in the two SWAT arms.

{Any outcomes that are continuous, rates, or counts, or are not already covered in the above text should be analysed appropriately, with the methods documented here. It is expected that the above text should cover most outcomes for standard SWATs}

9. SAP Revisions

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

2.

10. Roles and responsibilities

10.1. Signatures

Name	Trial Role	Signature	Date