# Low Dose Corticosteroids and Theophylline in the Treatment of Chronic Obstructive Pulmonary Disease – the TASCS Study (Theophylline and Steroids in COPD Study)

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Statistical Analysis Plan

**Version 4.0**

Prepared by:

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Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

Approved by: Date: 14th Sept 2018

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## Synopsis

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| Study Title | Low dose corticosteroids and theophylline in the treatment of COPD – the TASCS Study (Theophylline and Steroids in COPD Study) |
| Clinical Phase | IV |
| Study Rationale | This trial aims to assess the effect of low dose theophylline, singly or in combination with low dose oral prednisone, on COPD exacerbations, quality of life, and secondary clinical outcomes compared with placebo over 48 weeks. The study has been designed with clinically important outcomes, in order to be feasible in multiple centres in China. The inclusion criteria ensure that the results are generalisable to the majority of symptomatic patients with COPD. |
| Trial Design | This is a multi-centre, double blind, randomised, controlled trial comparing low dose theophylline alone or in combination with low dose prednisone, versus placebo over 48 weeks in patients with COPD. |
| Study Intervention | This is a trial with a 3-arm blinded, double dummy comparison:<br>1. placebo and placebo<br>2. low-dose theophylline and placebo<br>3. low-dose theophylline and low dose oral prednisone. |
| Study Medications & Dose | Prednisone 5 mg daily, slow release theophylline 100mg bd and matched placebos |
| Intervention Duration | 48 weeks |
| Rationale for Number of Participants | 1650 patients are required to detect 20% relative risk reduction (80%power, 2-tailed alpha) for comparison of low dose theophylline and low dose prednisone versus placebo (arm 3 vs arm1) for the primary outcome, number of COPD exacerbations per patient over 48 weeks, annualised to 12 months in a 3-arm trial. A 20% risk reduction, with baseline of 1 exacerbation per year, 15% drop out, 12 months follow up and 80% power would require 550 patients per arm. In addition, low dose theophylline administered alone will be compared with placebo (arm 2 vs arm 1). |
| Study Endpoints | <u>Primary Outcome</u><br>The primary outcome for this study is the difference between the three treatment groups in<br>• COPD exacerbation rate<br><br><u>Secondary Outcomes</u><br>• Time to first severe exacerbation requiring hospitalisation or death<br>• Quality of Life using the St George's Respiratory Questionnaire<br>• COPD Assessment Test (CAT), score out of total 40<br>• Pre-bronchodilator spirometry<br>• Post-bronchodilator spirometry<br><br>Analyses will include difference in exacerbation rates between the two groups at 12-, 24 and 48 weeks. Quality of life will be assessed by the change in quality of life between randomisation and 48-weeks visit measured by the SGRQ. |

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| | Study specific Adverse Events and Serious Adverse Events assessments will be recorded including those recorded in the participant diary, phone visits and at 12 weekly study visits, serum theophylline levels collected at baseline, 12- and 48-weeks in a subgroup of 100 participants will be stored and analysed at the end of the participant follow up. In addition, the ACTH stimulation test will be performed at and 50-weeks in another subgroup of 100 participants. Symptoms attributable to corticosteroid and theophylline toxicity will be recorded at each patient visit. |
| Medication Adherence | Medication compliance will be assessed by residual tablet count at each study visit. Good compliance is defined as taking > 80% of study medication. |
| Inclusion Criteria | Patients will be eligible for inclusion if they<br>• Are current or former smokers (> 10 pack years)<br>• 40-80 years of age<br>• Have a clinical diagnosis of COPD<br>• Have a post-bronchodilator FEV1 < 70% predicted<br>• Have FEV1/FVC ratio < 0.7 after bronchodilator |
| Exclusion criteria | Patients will be excluded if, in the opinion or knowledge of the responsible clinician:<br>• Life expectancy of less than 12 months<br>• Exacerbation or respiratory infection within 4 weeks prior to randomisation<br>• Patient is taking and requires maintenance oral corticosteroids<br>• Patient is on domiciliary oxygen<br>• There has been previous pulmonary resection<br>• Previous sensitivity to, or intolerance of theophylline<br>• Coexistent illness precluding participation in the study (epilepsy, chronic liver disease, unstable cardiovascular disease, diabetes, active malignancy)<br>• Inability to complete quality of life questionnaire<br>• Concomitant major illness that would interfere with visits, assessments and follow-up<br>• Have evidence of chronic liver disease, or transaminase or GGT elevation > 1.5 x ULN<br>• Random blood glucose level > 8 mmol/L<br>• High chance in the view of the treating physician that the patient will not adhere to study treatment and follow up<br>• Current asthma<br>• Pregnancy or breast feeding |
| Number of Participants | 1650 participants |
| Centres | Centres will be recruited in China |
| Treatment Administration | Patients will be randomized to receive either theophylline and placebo 2 tabs twice a day or prednisone and theophylline 2 tabs twice a day or placebo and placebo 2 tabs twice a day for 48 weeks.<br>Randomisation will be stratified by smoking status and centre.<br>Returned by participant tablets will be counted at study visit. |

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| Safety Evaluation | Safety for individual participants will be assessed on an ongoing basis by physical examination including vital signs, laboratory assessments, and monitoring of adverse events. Symptoms attributable to corticosteroid and theophylline toxicity will be sought and specifically recorded at each patient visit. A subgroup of 100 participants, will have serum theophylline measured at baseline, 12- and 48- weeks. Another subgroup of 100 participants, , will have the ACTH stimulation test performed at 48 weeks. |
| Efficacy Evaluation | Data will be collected from participant visits at baseline, 12, 24, 36, and 48 weeks. |
| DSMC Analysis | Safety data will be reviewed at 6-12 month intervals and/ or when 25%, 50 %, 75% and 100 % participants have been randomised. Thereafter safety data review will be at the discretion of the DSMC and/or the Steering Committee. |
| Ethical Approval | Application for ethical approval for the conduct of the study will be submitted to the Human Research Ethics Committee (HREC) of the University of Sydney, followed by submission to either HREC at each participating hospital or to a central ethics committee (or equivalent) as appropriate in accordance with the national and local regulatory and research ethics guidelines applicable in China. |

# 1 Administrative Structure

This statistical analysis plan has been prepared using the Protocol Version 2.0, dated 27 May, 2015.

All analyses will be conducted using SAS Enterprise Version 7.1 or higher.

# 2 Introduction

This trial aims to assess the effect of low dose Theophylline, singly or in combination with low dose oral Prednisone, on COPD exacerbations, quality of life, and secondary clinical outcomes compared with placebo over 48 weeks. The study has been designed with clinically important outcomes, in order to be feasible in multiple centres in China.

The purpose of this statistical analysis plan is to define the statistical methods and data presentations that will be used for the reporting of data from this study.

# 3 Statistical analysis

## 3.1 General statistical considerations

All statistical tests will be two-tailed and a P value of <0.05 will determine statistical significance. Treatment evaluations will be performed on the principle of 'intention to treat' (ITT) unless otherwise specified. Methods of handling missing data for the primary and secondary endpoints are described below.

Summaries of continuous variables which are normally distributed will be presented as means and standard deviations, or as medians and inter-quartile ranges for skewed data. Categorical variables will be presented as frequencies and percentages. Mock tabular and graphical presentations for the final analysis report are shown in the Appendix.

Pre-specified subgroup analyses will be conducted regardless of whether statistically significant treatment effect on the primary outcome is observed in the overall sample.

No formal adjustments for multiplicity of testing will be applied, but outcomes will be ordered by degree of importance (ie, primary versus secondary) and significant test results will be interpreted in light of the multiple comparisons made.

## 3.2 Blinding

The persons responsible for developing this SAP will be kept blind until after the SAP has been signed off, trial close-out is complete, and data lock is done. The unblinded statistician(s) responsible for interim monitoring and liaising with the DSMB will therefore not provide input to the SAP. The results will not be unblinded to the rest of the study team until the final statistical report has been completed.

## 3.3 Analysis populations

All analyses except safety will be conducted on the ITT population; that is, by analysing all patients according to the group they were randomised to and regardless of protocol compliance.

The per-protocol (PP) analysis set will consist of all ITT subjects who completed study, and have no major protocol violations (no protocol non-compliance) and have not withdrew from study due to investigator decision, ineligible and other reason. The primary efficacy analysis will be based on the ITT set. Analysis based on the PP set will also be conducted as a sensitivity analysis.

## 3.4 Subject Disposition

The total number of subjects, who are randomly assigned will be summarised. Reasons for early withdrawal will be listed for all participants that prematurely withdrew from the study. The number of participants that were screened but not randomised will be presented and the reasons for their non-participation will be listed (where available). Numbers of participants who were randomised, fulfilled eligibility criteria, and number randomised by study centre, will be summarised as shown in the Appendix. The summaries will be presented by treatment and overall groups.

Consort diagram will be produced accordingly (see Appendix figure 1).

## 3.5 Missing data handling

### 3.5.1 Missing outcome data

As the amount of missing data for the primary outcome is anticipated to be minimal, all participants will be included up until the date of death or date of final visit, or date of withdrawal or lost to follow-up. However, in case of subjects who withdrew earlier in the study without any follow-up data, if more than 5% of the data for primary outcome are missing, a sensitivity analysis will be conducted using multiple imputation using chained equations (MICE). Same for continuous secondary outcomes, such as SGRQ total score or CAT score, if more than 5% of the data are missing, a sensitivity analysis will be conducted.

### 3.5.2 Missing covariate data

Missing covariate data will not be replaced unless covariates which are included in primary analysis (see 3.10.1).

## 3.6 Demographic and baseline characteristics

A description of the baseline characteristics will be presented by treatment and overall groups as outlined in the mock tables. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarised by using mean ±standard deviation (SD) or median ± quartiles (Q1-Q3).

Baseline measures for all patients will be tabulated for the following variables:

1. Socio-demographic and admission characteristics

- Age
- Sex
- Height
- Weight
- BMI
- Smoking History
- Smoker Pack Years
- Biomass Exposure History
- Fumes or Smoke (Years)
- Dust Exposure History
- Dust Exposure(Years)
- COPD SYMPTOMS
    - Cough
    - Mucus or sputum
    - Shortness of breath
    - COPD exacerbations/worsening symptoms
    - Number of episodes requiring antibiotics, corticosteroids or both in previous year.
    - Number of hospital admissions in the previous year

2. Medical history
    - Ever been given a diagnosis of Asthma by a doctor
    - Ever been given a diagnosis of Tuberculosis by a doctor
    - Ever had surgery on Lungs
    - Any other serious lung disease
    - Ever Had Sleep Apnoea
    - Any allergies to any medications
    - Diabetes Mellitus
    - Epilepsy
    - Liver disease
    - Chronic Kidney Disease
    - Coronary Heart Disease
    - Heart Failure
    - Any other heart condition
    - Stroke
    - Osteoporosis
    - Other significant medical condition
3. Baseline chemistry data
    - Haemoglobin (g/L)
    - Platelet count ( $10^9$/L)
    - Total white blood cell count ( $10^9$/L)
    - Neutrophils ( $10^9$/L)
    - Lymphocytes ( $10^9$/L)
    - Monocytes ( $10^9$/L)
    - Eosinophils ( $10^9$/L)

- Basophils ( $10^9$/L)
- Sodium (mmol/L)
- Potassium (mmol/L)
- Chloride (mmol/L)
- Bicarbonate (mmol/L)
- Glucose (mmol/L)
- Blood Urea Nitrogen (mmol/L)
- Creatinine (μmol/L)
- SGPT Alanine Aminotransferase (U/L)
- SGOT Aspartate Aminotransferase (U/L)
- Gamma Glutamic Transpeptidase (U/L)
- Lactate dehydrogenase (U/L)

### 3.7 Analysis of compliance and concomitant therapies

Compliance with study drug will be summarised using the following variables:

- Medication Compliance
- Study drug discontinued for 5 days or more
- Number of days discontinued
- Reason for discontinuation

### 3.8 Bronchodilator spirometry and signs

Data for spirometry from both pre-bronchodilator and post-bronchodilator will be collected using FEV1 and FVC related parameters over follow-up visits, and will be summarized by treatments and time points.

Vital signs including Systolic and Diastolic blood pressure, Heart rate, respiratory rate and weight will be collected according to the scheduled visits.

### 3.9 Subset clinical measures

Theophylline (mg/L) will be summarized among subset of participants at baseline, 12 weeks and 48 weeks, by treatment and overall.

Cortisol test results will be also summarized among subset of participants at baseline and final visit accordingly.

### 3.10 Primary outcome analysis

The primary analysis will be conducted without imputation of missing data; however, imputations will be performed in the event the primary outcome is missing for more than 5% of subjects.

All COPD exacerbations will be obtained from phone call visits, patient diary card collected at clinical visits and adverse event form. Possible duplicate information from above three sources will be checked and removed.

### 3.10.1 Main analysis

Frequency of COPD exacerbations (annualised rate) per subject and total mean rate will be summarised overall and by treatment arms. For each subject, the study duration will be calculated from randomisation to the end of study, either final visit, date of death, date of withdrawal or date of lost-to-follow-up, whichever comes first. Then individual follow-up person years will be used to calculate the overall annual event rate per 100 person years. Multiple events of exacerbations per subject will be counted in the analysis. The annual events rate of exacerbations of COPD will be analysed using Negative Binomial regression using treatment as independent variable. The primary analysis will be adjusted by stratification factors including hospitals and smoking status, and baseline key risk factors including sex, exacerbations in previous year and post-bronchodilator percent predicted FEV1 at screening. Rate ratio will be estimated comparing treatment arms to placebo arm.

To overcome the potential issue of multiple testing among three treatment groups, the primary comparison is pre-specified as the treatment group of low-dose theophylline and low dose oral prednisone versus combination of other two groups (low-dose theophylline along and placebo group). If the primary comparison is significant, the comparison between two treatment groups versus placebo group separately will be conducted.

### 3.10.2 Sensitivity analysis

Incidence of COPD exacerbation will be also analysed using log-binomial model. Subjects with at least one exacerbation during follow-up will be counted as incidence of event and incidence rate will be calculated among all randomised patients and relative risk (rate ratio) is estimated comparing treatment arms to placebo arm.

Analysis based on the PP set will also be conducted as a sensitivity analysis

### 3.10.3 Adjusted analysis

To take into account the possible clustering effect of hospitals, generalised linear mixed model will be conducted as a sensitivity analysis using hospital sites as random effect. Additional baseline covariates will be also adjusted as fixed effects in the model, including hospitals, smoking status, sex, exacerbations in previous year, post-bronchodilator percent predicted FEV1 at screening, plus age, baseline LABA/ICS and exacerbations treated with antibiotics or coticosteriods in the preceding year.

### 3.10.4 Subgroup analysis

Pre-specified subgroup analysis will be conducted using subgroups at baseline below.

Age (<65 and >=65 years)
Sex (Female and Male)
Smoking status (Current smoker, past smoker and never smoker)
On steroid at baseline (Yes and No)
COPD exacerbation in last 12 months (Yes and No)
SGRQ score (<85 vs >=85)
CAT score (<20 vs >=20)
FEV1 thresholds (<50% and >=50%)

Eosinophils ($10^9$/L) (<0.30 vs >=0.30)
Eosinophils ($10^9$/L) (<0.20 vs >=0.20)
Eosinophils ($10^9$/L) (<0.15 vs >=0.15)

## 3.11 Secondary outcome analysis

All COPD exacerbations will be classified as severe, moderate and mild types. Each type of COPD exacerbations will be analysed using same approach as main analysis.

Definition of a severe COPD exacerbation – recorded COPD exacerbation (worsening COPD symptoms : dyspnea, cough, sputum, or wheeze) requiring hospitalisation.
Definition of a moderate COPD exacerbation – COPD exacerbations (worsening COPD symptoms : dyspnea, cough, sputum, or wheeze) requiring treatment with antibiotics, or oral corticosteroids or combination of both.
Definition of mild COPD exacerbation – COPD exacerbations (worsening COPD symptoms : dyspnea, cough, sputum, or wheeze) with cough, sputum production or dyspnea or other, or not treated.

Time to first severe COPD exacerbation will be also analysed.

The following continuous endpoints will be also collected during follow-up visits.

- SGRQ total score and sub-domain scores.
- COPD Assessment Test (CAT) score.
- Spirometry test results.

### 3.11.1 Main analysis

- Time to first severe exacerbation will be analysed using a Cox regression model and Kaplan-Meier estimates. K-M plot will also be presented (figure 2).

The following continuous endpoints will be analysed as change from baseline using analysis of covariance (ANCOVA). Each model will include the effect of treatment as well as the baseline value of the outcome

- SGRQ total score and sub-domain scores will be summarized be summarised by visits and analysed using ANCOVA for treatment effect at week 48 adjusted by baseline measurements.

- For COPD Assessment Test (CAT), score out of total 40 will be summarised by visits and analysed using ANCOVA for treatment effect to CAT at week 48 adjusted by baseline measurements.

- Pre-bronchodilator spirometry will be summarised by visits and analysed using ANCOVA to evaluate the continuous spirometry measures at week 48 adjusted by baseline measurements.

- Post-bronchodilator spirometry will be summarised by visits and analysed using ANCOVA to evaluate the continuous spirometry measures at week 48 adjusted by baseline measurements.

### 3.11.2 Sensitivity analysis

Continuous endpoints were measured repeatedly during follow-up. Means and 95% confidence intervals over time will be presented by treatment. The overall mean difference (and 95% CI) between treatment arms will be calculated using a repeated-measure linear mixed model. Fixed effects will include the baseline value of the parameter, the allocated treatment, study visits (as a categorical variable) and the interaction between treatment and study visits. Within-subject correlations will be modelled via a repeated effect with an unstructured covariance matrix or, in case of convergence issues, a compound-symmetry covariance matrix.

### 3.12 Safety outcome analysis

Adverse drug reactions deemed possibly, probably or definitely related to study treatment as determined by the treating physician at site will be summarised as the number and proportion of patients experiencing at least one event. These will be summarised by category of event and overall numbers of events. Adverse events will be coded using MedDRA and summarised by System Organ Class (SOC). Additional categories of interest will be defined and summarised. All description of adverse events will be provided to investigators to define the categories of interest during blinded review.

In addition to the number of patients with at least one event, we will report the total number of events. Proportions of patients with adverse drug reactions will be compared between treatment arms using Fisher's exact test, both overall and by category. This will be repeated for serious adverse drug reactions. A listing of all adverse drug reactions will be reported (in an appendix).

A list of proposed figures and tables is included.

## APPENDIX 1 - Tables and figures for final analysis report

*Note: screening tables are reproduce from DSMB report which is useful for cross-checking with CONSORT diagram.*

- Table 1: Screening numbers by sites
- Table 2: Reasons of screening failure
- Table 3: Subject disposition
- Table 4: Inclusion and exclusion criteria

*Note: Baseline information will be combined into one table for main paper.*

- Table 5: Baseline characteristics
- Table 6: Medical history
- Table 7: Baseline clinical chemistry

*Note: descriptive results for both baseline and follow-up measurements.*

- Table 8: Anthropometric and vital signs by visits
- Table 9: SGRQ by visits
- Table 10: Bronchodilator spirometry by visits
- Table 11: Theophylline by visits (subset only)
- Table 12: Medication compliance by visits
- Table 13: COPD treatment by visits
- Table 14: CAT Score

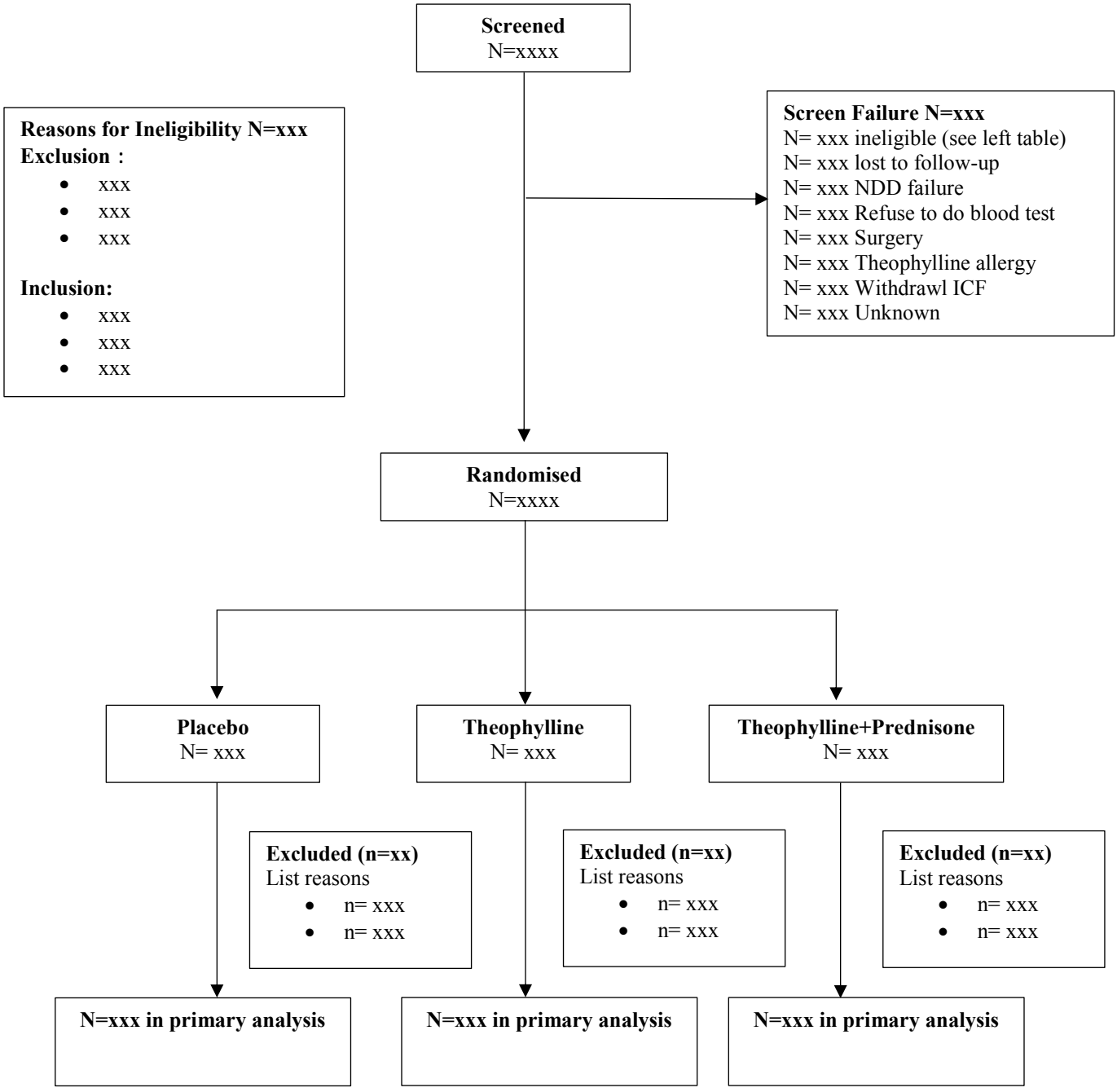
*Note: primary and secondary outcomes with modelling results.*

- Table 15: COPD exacerbation rate
- Table 16: COPD exacerbation (extended)
- Table 17: Secondary outcomes

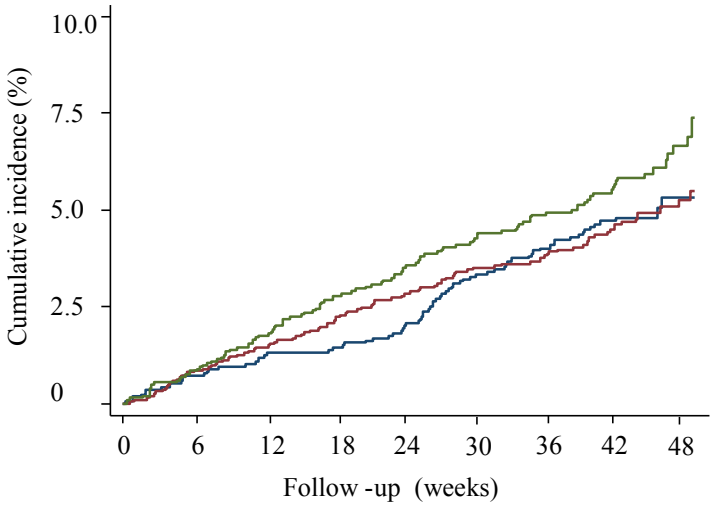
- Table 18: ACTH simulation (subset only)
- Table 19: Adverse events

*See separate file for templates of above tables, TASCS Final analysis mock tables v1.xlsx*

- Figure 1: CONSORT Diagram for TASCS (illustration only, subject to change)



- Figure 2: Survival plot showing time to first COPD severe exacerbation (illustration only)




- List 1: Severe adverse events

| Subject ID | Treatment | AETERM | Severity | Relationship to Study Drug | Action Taken | Outcome | AE Start Date | Date Resolved |
|---|---|---|---|---|---|---|---|---|
| xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |