NCT #: NCT02499380

Statistical Analysis Plan (SAP)

Title:	Changes in lung physiology and cardiac performance in patients with emphysema post bilateral RePneu Coil Treatment
Investigational Device:	PneumRx® RePneu® Coil System
Study Type:	Post-market, multicenter, single-arm, study of the CE Marked PneumRx, Inc. RePneu Coil System whithin intended use
Study No.:	CLN0017
Sponsor:	PneumRx Inc. 530 Logue Avenue, Mountain View, CA 94043, USA
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Draft V0.2	[redacted]	April 10, 2018	Comments from sponsor incorporated
Final V1.0	[redacted]	April 20, 2018	Comments from sponsor incorporated and finalization

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LIST OF ABBREVIATIONS

6MWD	6 Minute Walk Test
AATD	Alpha-1 Antitrypsin Deficiency
AE	Adverse Event
BLVR	Bronchoscopic Lung Volume Reduction
BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed tomography
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
eCRF	Electronic Case Report Form
FEV_1	Forced Expiratory Volume
FVC	Forced Vital Capacity
HRCT	High Resolution Computed Tomography
ITT	Intent-to-Treat population
LPS	Lung Perfusion Scintigraphy
LVR	Lung Volume Reduction
mMRC	Modified Medical Research Council
PT	Preferred Term
RV	Residual Volume
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
TLC	Total Lung Capacity
Tx1	RePneu procedure 1
Tx2	RePneu procedure 2
Tx3	RePneu procedure 3

1 INTRODUCTION

1.1 Scope of this Document

This Statistical Analysis Plan (SAP) describes the planned statistical analysis of the RePneu study CLN0017. The SAP is based on the relevant sections of the protocol revision A (dated 19 August 2014) and the annotated eCRF (electronic Case Report Form) (dated 15 January 2018). This SAP was prepared based on the AMS Standard Operating Procedure ST-02.01.

The SAP contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol. It includes detailed descriptions for executing the statistical analyses of all variables and describes how analyses are to be presented.

This SAP addresses both the safety listings during the ongoing study and the final analyses (see section 2 for the types of analyses planned). All versions of the SAP will be filed in the trial master file. Summary of changes and justification for each revision will be recorded in the version history. The SAP version used for the final analysis will be finalized prior to data base lock.

1.2 Study Design

This CLN0017 Study is a prospective, multicenter, open label, single-arm study. The objective of this post-marketing study is to advance the understanding of mechanism of action of the CE marked RePneu Coil by observing changes in lung physiology and cardiac performance in patients with emphysema treated with the RePneu Coils, when used as intended.
Investigators will have been trained and/or re-trained in the proper use and operation of the RePneu System, and will have performed several commercial procedures prior to initiation of any treatment.

Subjects must meet all of the following inclusion criteria to be entered into the study:

1. Adult subjects diagnosed with emphysematous type of COPD.
2. CT scan indicates bilateral emphysema, with sufficient lung parenchyma for coil deployment (based on PneumRx CT scoring) criteria.
3. Subject has post-bronchodilator FEV1 ≤45% predicted.
4. Subject has Total Lung Capacity >100% predicted.
5. Subject has residual volume (RV) ≥175% predicted.
6. Subject has marked dyspnea scoring ≥2 on mMRC scale of 0-4.
7. Subject read, understood and signed the Informed Consent form.
8. Subject has received Pneumococcal and Influenza vaccinations consistent with local recommendations and/or policy

Subjects will be excluded from the study if any of the following conditions apply:

1. Subject has co-morbidities that may significantly reduce subject's ability to improve exercise capacity (e.g. severe arthritis, planned knee surgery) or baseline limitation not due to dyspnea.
2. Subject has a change in FEV1 >20% (or, for subjects with pre-bronchodilator FEV1 below 1 L, a change of > 200 mL) post-bronchodilator unless investigator can confirm by other means that subject does not have asthma.
3. Subject has severe gas exchange abnormalities as defined by:
   a) a. PaCO2 >55 mm Hg
   b) b. PaO2 <45 mm Hg on room air (High altitude criterion: PaO2 <30 mm Hg)
4. Subject has severe pulmonary hypertension defined by right ventricular systolic pressure >50 mm Hg via right heart catheterization and/or echocardiogram.
5. Subject has evidence of other severe disease (such as, but not limited to, lung cancer or renal failure), which in the judgment of the investigator may compromise survival of the subject for the duration of the study.
6. Subject is pregnant or lactating, or plans to become pregnant within the study timeframe.
7. Subject has an inability to tolerate bronchoscopy under moderate sedation or general anesthesia.
8. Subject has clinically significant bronchiectasis.
9. Subject has had previous LVR surgery, lung transplantation, lobectomy or other BLVR treatment in either lung.
10. Subject has participated in studies to treat COPD using high dose radiation.
11. Subject has been involved in pulmonary drug or device studies within 30 days prior to this study.
12. Subject is chronically taking >20 mg prednisone (or equivalent dose of a similar steroid) daily.
13. Subject requires high level chronic immunomodulatory therapy to treat a moderate to severe chronic inflammatory autoimmune disorder.
14. Subject is on any type of antiplatelet or anticoagulant therapy which cannot be stopped for seven (7) days prior to procedure.
15. Subject has a sensitivity or allergy to Nickel.
16. Subject has a known sensitivity to drugs required to perform bronchoscopy.
17. Subject has been diagnosed with alpha-1 antitrypsin deficiency (AATD).
18. Subject has any other disease, condition(s) or habit(s) that would interfere with completion of study and follow-up assessments, would increase risks of bronchoscopy or assessments, or in the judgment of the investigator would potentially interfere with compliance to this study or would adversely affect study outcomes.

It was planned to enroll 60 patients into two sites which should be bilaterally treated. Due to an early termination of the study the total number of enrolled patients will not be as high as planned.

The follow up visits shall be performed 1 month post each procedure and then 3 months post final treatment. The final study follow up visit shall be performed 1 year post first treatment.

1.3 Objectives of the Study

The objective of this post-marketing study is to advance the understanding of the mechanism of action of the CE marked RePneu Coil by observing changes in lung physiology and cardiac

performance in patients with emphysema treated with the RePneu Coils, when used as intended.

Primary Endpoint:
Changes at 3 months post final treatment and 12 months post first treatment in:

- 6 Minute Walk Distance (6MWD)

Secondary Endpoints:
Changes prior and post procedure at Tx1, Tx2 and optional Tx3 in:

- Geometry (roundness) of major lung airways as defined by the ratio of major versus minor diameter measured from 3 bronchoscopic still images prior and post procedure taken in the lobar airway of the carina leading to segmental airways or while in any segmental airways of the same lobe of the carina leading to sub-segmental airways)
- Static and dynamic pulmonary compliance measurement prior to and post treatment including closing volumes, closing capacity and small airways function

Changes at 3 months post final bilateral treatment and 12 months post first treatment in:

1. Physical activity and energy expenditure measured over a period of a week using multi-axial accelerometer.
2. Forced expiratory volume in one second (FEV_1)
3. St. George's respiratory questionnaire (SGRQ)
4. Residual volume (RV)
5. Residual volume/total lung capacity (RV/TLC)
6. Diffusion capacity (DLCO)
7. mMRC dyspnea scale
8. Cardiovascular parameters such as heart rate, heart ejection fraction, systemic blood pressure
9. Body composition including BMI, fat per mass
10. Static and dynamic pulmonary compliance measurement using esophageal balloon

Changes at 12 months post first treatment in:

11. Ventilation and perfusion single photon emission tomography (V/P SPECT) or Quantitative lung perfusion scintigraphy (LPS)
12. Diaphragm position during exhalation (Comparison of diaphragm apex to rib landmarks using frontal HRCT)
13. Lung density distribution (post CT image data processing and reconstruction)

The study was prematurely terminated due to recruitment. Given the limited number of patients included in the database, the following data was not entered into the database and subsequently not analysed for the following endpoints:

1. Geometry (roundness) of major lung airways as defined by the ratio of major versus minor diameter measured from 3 bronchoscopic still images prior and post procedure taken in the lobar airway of the carina leading to segmental airways or while in any segmental airways of the same lobe of the carina leading to sub-segmental airways)
2. Static and dynamic pulmonary compliance measurement prior to and post treatment including closing volumes, closing capacity and small airways function
3. Physical activity and energy expenditure measured over a period of a week using multi-axial accelerometer.
4. heart ejection fraction, systemic blood pressure
5. fat per mass
6. Ventilation and perfusion single photon emission tomography (V/P SPECT) or Quantitative lung perfusion scintigraphy (LPS)
7. Diaphragm position during exhalation (Comparison of diaphragm apex to rib landmarks using frontal HRCT)
8. Lung density distribution (post CT image data processing and reconstruction)
9. St. George's respiratory questionnaire (SGRQ)

1.4 Overview of Assessments

The CLN0017 Study visits are planned as follows:

Baseline Visit: Participant agrees to be a part of the study and signs the informed consent. Baseline tests for primary and secondary endpoints will be performed. **Participant is evaluated and selected for RePneu procedure and has met inclusion/exclusion criteria.**

First and Second Procedure visit: Participant undergoes the RePneu Procedure in accordance with manufacturer Instructions for Use. Procedure data will be collected.

Third Optional Procedure: Patient will receive an additional 1-3 coils in each treated lobe, at the discretion of the treating investigator if the initial coil dose did not bring the expected benefit.

The procedures shall be performed no closer together than 4 weeks and if possible no longer than 8 weeks apart.

Follow up Visit (s): The follow up visits shall be performed 1 month post each procedure and then 3 months post final treatment. The final study follow up visit shall be performed 1 year post first treatment.

Follow-up visits will occur at the hospital in which the coil implantation procedure was performed.

An overview of the assessments can be found in Table 1.

Table 1: Visit Schedule

Procedure/Assessment	**Visit 1 Baseline Screening (at least 7 days prior to Tx1)**	**Tx1 RePneu Placement**	**Visit 2 1 month post Tx1**	**Tx2 RePneu Placement (4-8 weeks post Tx1)**	**Visit 3 1 month post Tx2**	**Optional Tx3 RePneu Placement (4-8 weeks post Tx2)**	**Visit 3 3 months post final Tx**	**Visit 4 12 months post Tx1**
Informed Consent	X							
Inclusion/ Exclusion	X							
Focused physical exam including vital Signs and SpO_2	X	X	X	X	X	X	X	X
Spirometry	X						X	X
Lung volumes	X						X	X
6MWT	X						X	X
mMRC	X						X	X
Concomitant medication / O_2 Use	X	X	X	X	X	X	X	X
Pregnancy testing	X	X		X		X	X	X
Bronchoscopic still images		X		X		X		
Static and dynamic pulmonary compliance	X						X	X
Body composition	X							
V/P SPECT or Lung perfusion scintigraphy	X							
Chest X-Ray	X							
Bronchoscopy / Coil Placement		X		X		X		
Adverse Events	X	X	X	X	X	X	X	X

2 TYPES OF PLANNED ANALYSES

2.1 Final analysis

The final analysis shall consist of all analyses described in this document. The details of the analyses are described in section 4. Additionally, Appendix I: Overview of tables, figures and listings to be produced provides an overview of all tables, plots and listings to be produced as well as the appropriate analysis set.

2.2 Interim analyses

Interim analyses will not be performed for this study.

For data cleaning and quality purposes an overview of safety variables will be created in the form of an Excel listing monthly.

3 GENERAL ANALYTICAL CONSIDERATIONS

3.1 Analysis Set

The ITT population will include all subjects who have met the inclusion/exclusion study criteria defined in the protocol.

3.2 Subgroup Analyses

No Subgroup Analyses will be done for this study.

3.3 Analytical Methods

The analysis will be performed in SAS® (version 9.4. or higher).

3.3.1 Descriptive statistics

Continuous variables will be displayed including arithmetic mean, standard deviation (SD), minimum (min), median and maximum (max). Additionally, the number of patients in the analysis set (ITT), those contributing to the analysis (N) and the number of patients not included in the analysis due to missing data (missing) will be displayed.

The Change from Baseline will be calculated for each patient individually and averaged for values at baseline (mean, SD, min, median, max at baseline), values at each visit (mean, SD, min, median, max at visit) and the change from baseline to each visit.

Categorical variables will be displayed as frequencies and percentages (i.e. absolute and relative frequencies). If not specified otherwise, the percentages will be based on all patients respectively procedures available for analysis (non-missing and missing). The number of patients with missing data will also be summarized.

3.3.2 Effectiveness and Safety Analyses

The endpoints will be analyzed with a paired t-test, which will compare baseline to 3-month post final treatment and 12-months post first treatment follow-up values. A p-value of <0.05 will be considered statistically significant. Adverse events will be categorized into medically relevant categories and presented as frequency counts and percentages. All results tables and plots shall clearly display the total number of patients in the analysis set (N) and the number of patients with evaluable data (n).

Output designs or minor changes in the tables may be adapted to programming and/or sponsor demands.

3.3.3 Listings

Listings will be sorted by patient and visit, if applicable. All listings will include unique subject identifier (subject ID). Individual listings may be subdivided into several smaller listings, if deemed sensible for manageability during programming.

3.4 Missing/Inconsistent Data

3.4.1 Imputation

Analyses will be based upon observed data without imputation.

3.4.2 Inconsistent data

In general, discrepant data shall be queried and resolved. Handling of inconsistent data and rules for self-evident corrections are specified in the Data Handling Manual.

3.4.3 Dates

Dates will be collected in a day/month/year format. It is possible that the full date is not always available. If the day is missing, the missing day shall be imputed as the 1st of the month. If the month is missing, the missing month shall be imputed as January. If the imputed date lies before the date of the first procedure, than the new date will be calculated as *hospital discharge date after the first procedure +1.*

3.5 Derived Datasets, Variables and Terms

Derivations will be specified in a footnote where feasible.

The Body Mass Index (BMI) will be calculated as
BMI = weight in kg/ height in m^2.

Change from Baseline will be calculated as
mean(parameter)[time slot]- mean(parameter)[baseline].

Percentage change from Baseline will be calculated as
*mean{(parameter[time slot]- parameter[baseline])/parameter[baseline]*100}*

4 CHANGES COMPARED TO THE PROTOCOL

This SAP contains the following changes compared to the protocol:

1. The follow up visits shall be performed 3 months post final treatment and not 4 months post final treatment as stated in the protocol
2. No Subgroup Analyses will be done.
3. The ITT Analysis will consider subjects with unilateral treatment. There will not be a per-Protocol analysis.
4. Due to very slow recruitment the study was prematurely terminated. Given the limited number of patients included in the database, compared to the plan the following data was not entered into the database and subsequently not analysed for the following endpoints:
    1. Geometry (roundness) of major lung airways as defined by the ratio of major versus minor diameter measured from 3 bronchoscopic still images prior and post procedure taken in the lobar airway of the carina leading to segmental airways or while in any segmental airways of the same lobe of the carina leading to sub-segmental airways)
    2. Static and dynamic pulmonary compliance measurement prior to and post treatment including closing volumes, closing capacity and small airways function
    3. Physical activity and energy expenditure measured over a period of a week using multi-axial accelerometer.
    4. heart ejection fraction, systemic blood pressure
    5. fat per mass
    6. Ventilation and perfusion single photon emission tomography (V/P SPECT) or Quantitative lung perfusion scintigraphy (LPS)
    7. Diaphragm position during exhalation (Comparison of diaphragm apex to rib landmarks using frontal HRCT)
    8. Lung density distribution (post CT image data processing and reconstruction)
    9. St. George's respiratory questionnaire (SGRQ)
    10. Chest X-Ray
5. Variables that were not planned to be documented according to protocol but have been documented:
    1. Pregnancy testing at visit 3 (3months post final Tx) and visit 4 (12 months post Tx1)

2. Static and dynamic pulmonary compliance at Baseline, visit 3 (3months post final Tx) and visit 4 (12 months post Tx1)

6. Due to the small number of patients there will not be any tables presented for secondary endpoints

5 PLANNED ANALYSES

5.1 Overview of safety variables

For data cleaning and data quality purposes an overview of safety variables will be created in the form of an Excel listing monthly.

5.2 Study Patients

A listing with general information on the study patients will be provided, including:

- Study site
- Informed consent date
- Termination date and reason for discontinuation (if applicable)
- Death (yes/no) and, if yes, death date and whether death is emphysema related or unrelated to emphysema

5.2.1 Patient Disposition

The patient accountability will be assessed for the final analysis by showing the number of patients at the following times:

- Patients enrolled
- Patients included in analysis sets
- Patients received the first procedure
- Patients received the second procedure
- Patients at 3-Months Follow-Up
- Patients at 12-Months Follow-Up
- Patients completing the study

The Patients who permanently discontinued the study before the end of the study will be presented in a listing, including the reason for discontinuation. A flow chart will be created on request.

5.2.2 Protocol Deviation

A listing with information on protocol deviations will be provided, including:

- Inclusion/Exclusion Criteria not met
- Lost-to-follow-up
- Unilateral treatment
- 1 month post treatment 1 Visit not done
- 1 month post treatment 2 Visit not done
- 3 months post final treatment Visit not done
- 12 months post treatment 1 Visit not done

5.3 Baseline Data

Continuous data will be summarized using descriptive statistics (mean, SD, min, median, max). Additionally, the number of patients included in the patient set (N), number of patients contributing to the analysis (n) and the number of patients not included in the analysis due to missing data (missing) will be displayed.

Categorical variables will be displayed as frequencies (p/n) and percentages (i.e. absolute and relative frequencies). Unless otherwise noted, percentages will be based on the patients available for analysis (non-missing). The number of patients with missing data will be also be summarized.

All baseline analyses will be based on the Intention-to-treat Set (ITT).

Furthermore, all of the baseline data mentioned in the following subsections 5.3.1-5.3.6 including text specifications will be listed.

5.3.1 Enrollment by site

A table showing the number and percentage of enrolled patients by site will be provided for the final analyses.

5.3.2 Demographics and vital signs

A table summarizing the following demographics parameters and vital signs will be presented for the final analyses:

- age at Baseline Visit (continuous)
- gender (male, female) (categorical)
- ethnicity (Hispanic or Latino, not Hispanic or Latino) (categorical)
- race (American Indian or Alaska Native, Black of African American, Asian, White, Native Hawaiian or Other Pacific Islander, other) (categorical)
- Body Mass Index (continuous)
- height (continuous)

- weight (continuous)
- Systolic blood pressure (continuous)
- Diastolic blood pressure (continuous)
- Heart Rate (continuous)
- Temparature (continuous)
- SpO_2 (continuous)

5.3.3 Baseline Characteristics

A table showing the following baseline characteristics will be presented for the final analyses:

- FVC in L (continuous)
- FVC % predicted (continuous)
- FEV1 in L (continuous)
- FEV1 % predicted (continuous)
- (FEV1 in L/FVC in L) in % (continuous)
- RV in L (continuous)
- RV % predicted (continuous)
- 6MWT in m (continuous)
- mMRC (0, 1, 2, 3, 4) (categorical)
- mMRC (continuous)

5.3.4 Medical History

A table summarising the medical history (comorbidities) will be created by assessing the parameters from the eCRF (in dataset *mh*) for final analyses

5.3.5 History and Characterization of Emphysema

A table will be created to show the history and characterization of the emphysema for final analyses by the following:

- How many YEARS has the subject been diagnosed with emphysema
- Number of unscheduled PHYSICIAN visits
- Number of EMERGENCY ROOM visits
- Number of HOSPITALIZATIONS

5.3.6 Treatment of Emphysema

A table summarising the treatment of emphysema will be created by assessing the parameters from the eCRF (in dataset *emphtreat*) for final analyses.

5.4 Procedural analyses

For the following sections tables will be created to describe the RePneu® procedures.

Additionally a listing will be prepared to show

- the coils per procedure,
- the total coils implanted,
- the total bronchoscopy time and the total fluoroscopy time,
- the post-procedural hospital stays and
- the type of medication prescribed in preparation for the procedure as well as the corresponding name of the medication, the medication start and stop date and the total daily dosage (will only be done for final analyses)

5.4.1 Number of Devices implanted

A table summarizing treatment lobes and coils implanted will be presented for all procedures and separately for each procedure:

- Coils Per Procedure (continuous)
- Total Coils Implanted (upper right lobe, upper left lobe, lower right lobe, lower left lobe, middle right lobe) (categorical)

5.4.2 Procedure Time

A table showing the total bronchoscopy time and the total fluoroscopy time in minutes (continuous) will be created for all procedures and separately for each procedure.

5.4.3 Post-Procedure Hospital Stay

A table summarizing the post-procedure hospital stay in days (continuous) will be prepared for all procedures and separately for each procedure.

The post-procedural hospitals stay in is calculated as

post-procedural hospitals stay = discharge date (exdisdtu) – admission date (exprdt) in the dataset *bcproc*.

5.5 Safety analyses

A listing for adverse events will be provided for the final analyses, consisting of the following information of each AE:

- Site
- Subject ID
- AE Term
- SOC
- PT
- AE start date
- AE stop date
- Duration of AE
- Procedure dates
- Days post procedures
- Seriousness, including the primary reason for classification as serious
- Relation to device
- Relation to procedure
- Event outcome

5.5.1 Adverse events

A table showing the number and percentage of events as well as the number and percentage of patients with at least one event will be provided for any AE and for AE according to SOC and PT.

5.5.2 Serious adverse events

A table showing the number and percentage of events as well as the number and percentage of patients with at least one event will be provided for any serious AE and for serious AE according to SOC and PT.

5.5.3 Device and Procedure Related Adverse Events

A table showing the number and percentage of events as well as the number and percentage of patients with at least one event will be provided for any device and procedure related AE and for device and procedure related AE according to SOC and PT.

5.5.4 Deaths

A listing for deaths will be provided for the final analysis, consisting of the following information:

- Subject ID
- Date of death
- SOC

- PT
- Time slot
- Related to emphysema
- Related to device
- Related to procedure
- Timing of death

If no deaths occur, the output will be produced either way. In this case a programmers note will be shown, stating that no deaths occurred throughout the study.

5.5.5 Device Removal

A listing for all removed devices will be created if any devices have been removed at the time of the analysis.

5.6 Effectiveness analyses

The following summary listing of effectiveness parameters will be produced for the final analyses showing the following parameters at baseline, at assessed visits, change from baseline to assessed visits and, for some variables, if the MID was reached for (Responder):

- 6MWT in m over time (Responder: >=25m)
- Forced expiratory volume in one second (FEV1) (Responder: >=10%)
- Residual volume (RV)
- Residual volume/total lung capacity (RV/TLC)
- Diffusion capacity (DLCO)
- mMRC dyspnea scale
- Heart rate
- Body composition including BMI

5.6.1 Primary effectiveness endpoint

Changes at 3 months post final treatment and 12 months post first treatment in:

- Minute Walk Distance (6MWD)

The change from baseline as continuous variable and the responder analysis as categorical variable will be presented.

5.6.2 Secondary effectiveness endpoints

Due to the small sample size, the secondary effectiveness endpoints will only be listed. The assessments and change from baseline will be presented per patient in the efficacy listing.

APPENDIX I: OVERVIEW OF TABLES, FIGURES AND LISTINGS TO BE PRODUCED

Overview of planned tables

Programmer Note: Please adapt the numbering of subgroup tables as may be necessary.

Table Number	Title	Analysis Set for Final Analyses	Subgroup Analyses[1]
14.1.1	Patient accountability	ITT	No
14.1.2	Study terminations	ITT	No
14.2.1	Enrollment by site	ITT	No
14.2.2	Demographics	ITT	No
14.2.3	Baseline characteristics	ITT	No
14.2.4	Medical history	ITT	No
14.2.5	History and characterization of emphysema	ITT	No
14.2.6	Treatment of emphysema	ITT	No
14.3.1	Number of devices implanted	ITT	No
14.3.2	Procedure time	ITT	No
14.3.3	Post-procedure hospital stay	ITT	No
14.6.1	Adverse events	ITT	No
14.6.2	Serious adverse events	ITT	No
14.6.3	Device and procedure related adverse events	ITT	No
14.7.1	Change from baseline in 6MWT in m	ITT	No
14.7.2	Number and percentage of patients achieving change in 6MWT in m ≥25	ITT	No

Overview of planned figures (on request)

Figure Number	Title	Analysis Set For Final Analyses
1	Patient accountability	ITT

Overview of planned listings

Listing Number	Title	Analysis Set For Final Analyses
16.1	Study Patients	ITT
16.2	Protocol Deviation	ITT
16.3	Baseline Data	ITT
16.4	Procedural Data	ITT
16.4	Overview of safety variables	ITT
16.5	Overview of deaths	ITT
16.6	Overview of effectiveness variables	ITT