CLEAR

A 2x2 factorial randomised open label trial to determine the clinical and cost- effectiveness of hypertonic saline (HTS 6%) and carbocisteine for airway clearance versus usual care over 52 weeks in bronchiectasis

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STATISTICAL ANALYSIS PLAN
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This document and all preceding versions will be stored in the Trial Master File for this trial

Contents

ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
ANCOVA	Analysis of covariance
BE	Bronchiectasis
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography scan
DMP	Data Management Plan
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQol five dimension five level questionnaire
EudraCT	European Clinical Trials Database
FEF	Forced Expiratory Flow
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
HRQoL	Health-Related Quality of Life
HRCT	High Resolution Computed Tomography scan
HTS	Hypertonic Saline
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number Register
ITT	Intent-To-Treat
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health Research
MACRO	Clinical Trials Database
mITT	Modified Intention to Treat
PICO	Population, Intervention, Comparison and Outcome(s)
PP	Per-Protocol
PQE	Partially Qualifying Exacerbation
QALY	Quality adjusted life year
RSSQ	Respiratory and Systemic Symptoms Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SGRQ	Saint George's Respiratory Questionnaire
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study within a Trial
TSC	Trial Steering Committee
TSQM	Treatment Satisfaction Questionnaire for Medication
UK	United Kingdom
QoL-B	Quality of Life – Bronchiectasis

1. BACKGROUND AND DESIGN

1.1 Research Hypothesis

Hypertonic Saline (HTS) (6%) and/or the oral mucolytic carbocisteine will result in better outcomes than usual care over 52 weeks in patients with Bronchiectasis (BE).

1.2 Study Aim

To deliver a United kingdom (UK) multicentre study that will determine the clinical and cost -effectiveness of hypertonic saline HTS (6%) and carbocisteine for airway clearance versus usual care over 52 weeks in BE using a 2x2 factorial randomised open label trial.

1.3 Study Objectives

1.3.1 Primary objective

The primary objective is to determine whether HTS (6%) and/or carbocisteine reduces the mean number of exacerbations over 52 weeks post randomisation.

1.3.2 Secondary objectives

To determine whether HTS and/or carbocisteine:

i. Improves disease specific health related quality of life (HRQoL) at 52 weeks
ii. Reduce time to next exacerbation
iii. Reduce number of days of antibiotics for exacerbations over 52 weeks
iv. Improve generic HRQoL
v. Are acceptable from a patient satisfaction perspective at 52 weeks
vi. Are associated with Adverse Events (AEs)
vii. Improve lung function

The study will also assess:

viii. The cost-effectiveness of the four treatment options
ix. Patient adherence to HTS and carbocisteine over 52 weeks and how this impacts on the overall results.

1.4 Sub-Study Aim

The data obtained in the CLEAR trial will also be used to answer or validate further questions:

i. A sub-study will be included which aims to validate and measure the sensitivity of the EMBARC definition for exacerbations in bronchiectasis. The study will compare the criteria in the EMBARC definition to the criteria of a modified Fuch's definition for diagnosing pulmonary exacerbations in bronchiectasis patients. The sub study is described in detail in the protocol Appendix 2.
ii. A sub-study will be included which aims to explore the use of mySpiroSense for remote spirometry during periods of stability (weekly measurements and measurements on the morning of study visits) and at the start and end of exacerbations in an adult bronchiectasis population. The sub study is described in detail in the protocol Appendix
iii. An EME Sub study will be included which aims to measure sputum viscosity (G') and elasticity (G'') (which combined give a single summary measure of sputum viscoelasticity called the yield stress, T_c) at the initial visit and 2 weeks following commencement of treatment with HS and/or CS. The overall aim of this study is to provide mechanistic insight into the action of HS and/or CS in bronchiectasis. The sub study details is described in the protocol appendix 5.

i and ii not being carried out within NICTU and are therefore not detailed in this SAP. iii is being carried out within NICTU. See separate EME SAP for further detail.

1.5 SWATs Aim

There will also be Study within a Trial (SWATs) completed which aim to explore the effect of methods used to optimise recruitment and retention.

The SWATs are described in detail in the protocol Appendix IV.

1.6 EME Sub Study Aim

Primary Objective:

The primary objective is to measure sputum viscosity (G') and elasticity (G'') (which combined give a single summary measure of sputum viscoelasticity called the yield stress, T_c) at the initial visit and 2 weeks following commencement of treatment with HTS and/or Carbocisteine.

Secondary Objectives:

1). Measure sputum viscoelasticity (yield stress, $T_{c)}$, at 8 weeks following commencement of treatment with HTS and/or Carbocisteine.
2). Evaluate sputum inflammation as measured by IL-6, IL-8 and 8-isoprostane levels at the initial visit, 2 and 8 weeks following commencement of treatment with HTS and/or Carbocisteine.
3). Evaluate sputum bacterial load/composition at the initial visit, 2 and 8 weeks following commencement of treatment with HTS and/or Carbocisteine.

The overall aim of this study is to provide mechanistic insight into the action of HTS and/or Carbocisteine in BE

The EME sub study is described in detail in the protocol Appendix V.

1.7 Study Design

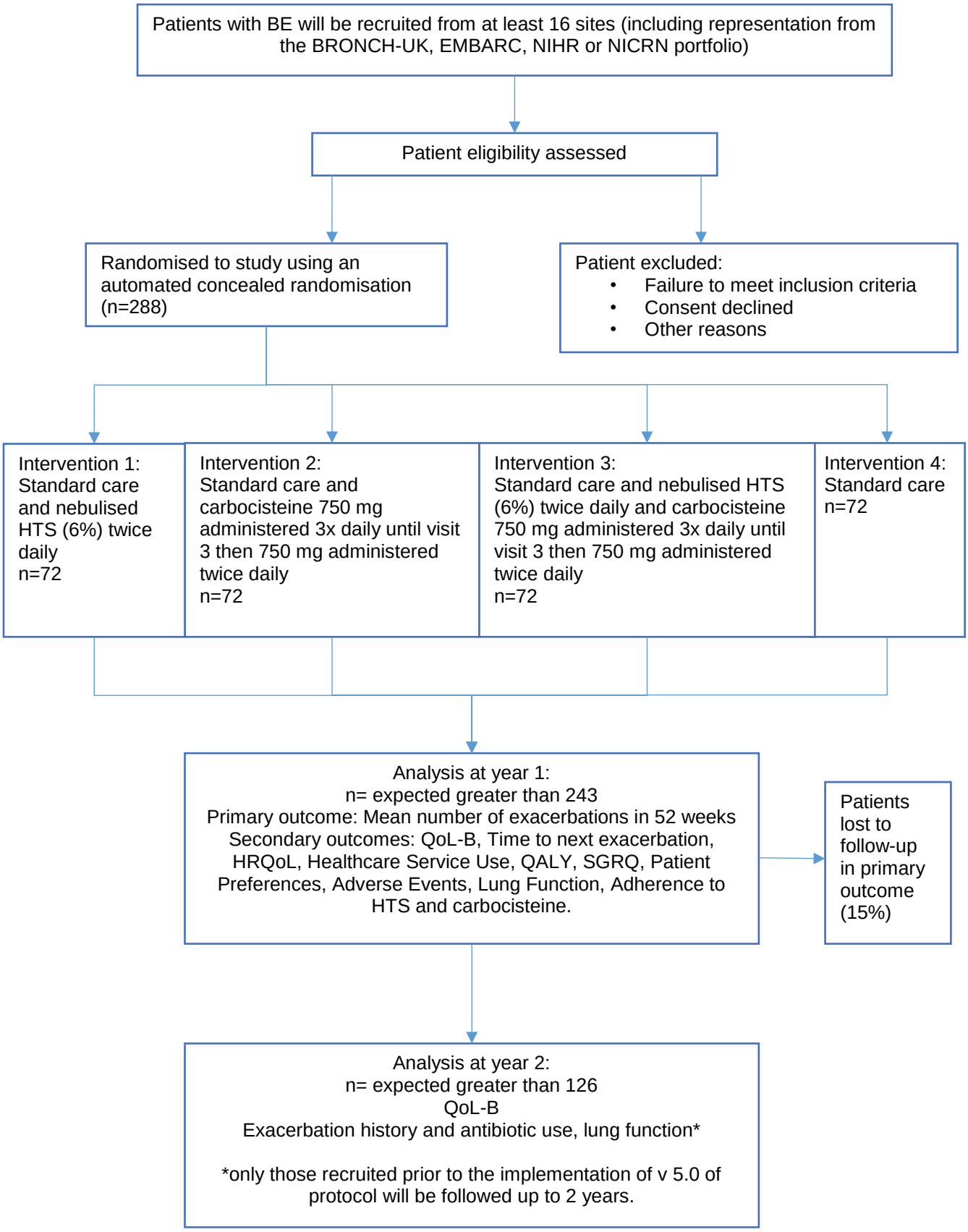
This is a multicentre, 2x2 factorial randomised open label trial in BE with a 12-month follow-up period.

In Population, Intervention, Comparison and Outcome(s) (PICO) terms:

Population:	Adults with a confirmed diagnosis on HRCT/CT of BE and 2 or more pulmonary exacerbations in the previous year requiring antibiotics.
Intervention 1:	Standard care and twice daily nebulised HTS (6%) over 52 weeks.
Intervention 2:	Standard care and carbocisteine (750 mg three times per day until visit 3* reducing to 750 mg twice per day) over 52 weeks.
Intervention 3:	Standard care and combination of twice daily nebulised HTS (6%) and carbocisteine (750 mg three times per day until visit 3* reducing to 750 mg twice per day) over 52 weeks.
Comparator:	Standard care over 52 weeks.
Outcome:	Number of exacerbations over 52 weeks post randomisation.

*Visit 3 occurs 8 weeks (+/- 7 days) post the baseline assessment.

1.8 Study Schematic



Full details of the background to the trial and its design are presented in the protocol.

2. OUTCOME MEASURES

2.1 Primary outcome measure

Mean number of exacerbations over 52 weeks

2.2 Secondary outcome measures

i. Disease specific HRQoL (respiratory symptoms of domain of QoL-B) at 52 weeks
ii. Time to next exacerbation post randomisation
iii. Number of days of antibiotics related to exacerbations over 52 weeks
iv. Generic HRQoL
v. Health Service use over 52 weeks
vi. Quality adjusted life year (QALY) over 52 weeks
vii. Measurement of health impairment using the Saint George's Respiratory Questionnaire (SGRQ)
viii. Patient preferences for treatment
ix. AEs over 52 weeks
x. Lung function over 52 weeks
xi. Adherence to HTS and carbocisteine over 52 weeks

3. DATA

3.1 CRF Forms and variables

Full details of the data to be collected and the timing of data collection are described in sections 11 and 12 of the trial protocol.

A copy of the Case Report Forms (CRFs) and questionnaires (e.g. Quality of Life (QoL) questionnaires) are presented in the protocol and/or the Trial Master File.

All data collected during study visits (including lung function data) and calls with the patient will be recorded in the source documents/electronic CRF for the study by the Principal Investigator (PI) or designee. Patient identification on the CRF will be through their unique participant study number, allocated at the time of recruitment. Data will be collected and recorded on the electronic CRF by the PI or designee as per the CRF entry timelines.

In addition, the eTrack will record nebuliser usage data. When patients bring their nebuliser to the research site, this data will be transferred to a central 'hub' at each site via Bluetooth, from where encrypted data will be transmitted to a secure cloud platform called PARITrack. The data will be pseudoanonymised using the nebuliser device serial number as a unique trial identifier and will not contain any patient identifiable information.

Lung function data will also be collected on the mySpiroSense when patients complete spirometry at home. When patients bring their spirometer to the research site the readings will be downloaded by site staff to a local computers/laptops with software for the SpiroSense system installed. The data downloaded by the site staff can be viewed locally. At different time points the local site staff will be asked to send pseudoanonymised spirometry data to PARI using a secure method. PARI will then provide the data to the CI and researchers at Queens University Belfast in excel or other format. In addition, at the end of the study the pseudoanonymised data saved on the laptops will be available to PARI.

Trial data including worksheet and questionnaire data will be entered onto the electronic CRF on a Clinical Trial Database (MACRO) by delegated site personnel and processed electronically as per CTU Standard Operating Procedures (SOPs) and the study specific Data Management Plan (DMP).

Data queries will be 'raised' electronically (MACRO) where clarification from site staff is required for data validations or missing data. Site staff will 'respond' electronically to data queries ensuring that amendments where applicable are made to the Clinical Trial Database.

The nebuliser usage data will be held in a secure cloud platform. The data can be accessed and viewed by authorised research personnel at each site for their patients and by the CTU and/or CI for all patients through a web based portal. Data for all patients will be provided to the CTU at the end of the treatment period in an agreed format for analysis.

When data is downloaded from SpiroSensePro spirometers and individual mySpiroSense (used by the patients at home) it can be viewed by the local research team on computers with the SpiroSense software installed. Research staff will record the required details from lung function readings taken during study visits directly into the source documents/electronic CRF for each patient. However, the data for the lung function readings completed by patients at home will be saved on computers/laptops at the site. At different time points the local site staff will be asked to send psuedoanonymised spirometry data to PARI using a secure method. PARI will then provide the data in excel or in another format to the CTU and/or Queens University Belfast research teams for analysis. In addition, at the end of the study the pseudoanonymised data saved on the laptops will be available to PARI.

All essential documentation and trial records will be stored securely and access will be restricted to authorised personnel.
All study documentation (including patient medical records) and data will be archived as per regulatory requirements and those responsible for archiving will be noted on the sponsor delegation framework/mCTA.

3.2 Management of datasets

At the time of analysis:
The Data Manager in collaboration with the Study Statistician will extract data from MACRO following procedures as detailed in the SOP DM09 Database Closure/Lock and the corresponding study Data Management Plan (DMP).

The following data will be collated by the Lead Applicant and Research Assistant using MS Excel and transferred via email directly to the NICTU Study Statistician. The data will be stored in the eTMF (Electronic Trial Master File).

- Lung function spirometry
- HTS adherence
- Drug Response Assessment
- Airway Clearance Record

3.3 Data completion schedule

3.3.1 Schedule of Assessments

All patients must be evaluated during the study according to the schedule of assessments outlined in below.

Study Visit Number		1	2*	3*	4*	5*	6*~+
Visit Schedule	Prior to entry	Base-line	Week 2	Week 8	Week 26	Week 52	Week 104
Visit Window		+ 14 days	+/- 3 days	+/- 7 days	+/- 14 days	+/- 14 days	+/- 14 days
Assessments							
Inclusion & Exclusion Criteria Review	x						
Informed consent	x						
Review Informed consent (if applicable)		x					
Demographics		x					
Patient BE Characteristics		x					
Assess Sputum colour from sample, if avaliable		x					
Patient Standard Care Review		x					
Medical History		x					
Review Medications		x	x	x	x	x	
Vital Signs		x	x	x	x	x	
Urine Pregnancy Test		x					
Physical Exam		x					
Confirmation of Eligibility		x					
Adverse Events		<----------					>
Respiratory and Systemic Symptoms Questionnaire (RSSQ) [&]		x	x	x	x	x	
Exacerbation/Antibiotic Use^			x	x	x	x	x
EME Sub Study							
Measure sputum elasticity (G') and viscosity (G'') (which combined represent the yield stress, T_c)		X	X				
EME Secondary Objectives							

Measure sputum elasticity (G') and viscosity (G'') (which combined represent the yield stress, T_c)				X			
Evaluate sputum inflammation as measured by IL-6, IL-8 and 8-isoprostane levels		X	X	X			
Evaluate sputum bacterial load/composition		X	X	X			
Patient Questionnaires							
Treatment Satisfaction Questionnaire			x	x	x	x	
QoL-B		x	x	x	x	x	x
SGRQ		x	x	x	x	x	
EQ-5D-5L		x	x	x	x	x	
Health Service Use Questionnaire		x	x	x	x	x	
Lung Function Tests		x	x	x	x	x	x
Randomisation & Treatment Allocation		x					
IMP prescribing & Dispensing		x		x	x		
Drug response assessment (for patients assigned any HTS group)		x					
Airway Clearance Record/Action Plan		x	x	x	x		
Patient Training on Usual care, spirometers and eFlow		x	x	x	x		
eFlow/mySpirosense Utility Questionnaire						x	
Spirometry (at home)[#]		<---------- -->					
Exacerbation Management^ Review duration, symptoms & antibiotic use Review spirometry RSSQ Review with Investigator or Designee		<---------- --> <----------> <----------> <----------> <----------> <---------->					

**Week 2-104 study visit schedule will be based on the completion of all Baseline study activities, when baseline activities occur over a number of different days.*
~It is planned that this data will be collected from the EMBARC or BRONCH-UK Registry. If this is not possible the participant will be asked to visit the research site for the data to be collected.
[&] If a participant's scheduled study visit corresponds with the start or end of an exacerbation the RSSQ that links to the exacerbation should be completed i.e. if it is the start of an exacerbation complete the RSSQ (symptoms of exacerbation version) instead of RSSQ (since last visit version). If it is at the end of an exacerbation complete the RSSQ (end of exacerbation version) instead of RSSQ (since last visit version). If the scheduled study visit falls in the middle of an exacerbation complete the RSSQ (since last visit version).
^The start date, associated symptoms, end dates (when symptoms resolved) and details of any antibiotics taken will be recorded. Data may be collected by telephone or during an unscheduled visit.

#Patients will be asked to complete spirometry at home on a weekly basis using the handheld spirometers provided. During weeks with study visits 2-5, the spirometry should be completed on the morning of their study visit.

+ Visit 6 at 104 weeks will only be completed for those patients recruited prior to the implementation of protocol v5.0. Those recruited after this will complete the study after visit 5 at 52 weeks

3.4 Data verification

Study specific data validation checks will be implemented. The process of data validation ensuring the accuracy and quality of the data will be carried out according to SOP DM04 Data Validation and Discrepancy Management.

3.5 Data coding

The variable codings will be as specified on the CRF.

4. DEFINITION OF TERMS

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td>Pulmonary Exacerbations</td><td>
<table>
<tr><th colspan="2">Criteria for the EMBARC definition</th></tr>
<tr><td colspan="2">The EMBARC definition consists of three parts that must all be satisfied for a fully qualifying exacerbation. If only two of the three parts of the definition are met, then it will be defined as a partially qualifying exacerbation (PQE).</td></tr>
<tr><td>Part 1- Symptoms</td><td>Patient must present with deterioration in 3 or more of the 6 following symptoms:
1. Cough
2. Sputum volume/consistency
3. Sputum purulence
4. Breathlessness/exercise tolerance
5. Fatigue and or Malaise
6. Haemoptysis</td></tr>
<tr><td>Part 2- Time</td><td>Symptoms must be present for at least 48 hours.</td></tr>
<tr><td>Part 3- Treatment</td><td>A change in bronchiectasis treatment not limited to antibiotics.</td></tr>
<tr><td colspan="2">For separate exacerbations there must be an unequivocal resolution of symptoms from the first event and >14 days to the commencement of a subsequent event. If this criterion is not met then the exacerbation is counted as a single continuous event.</td></tr>
</table>
</td></tr>
<tr><td>Fully Qualifying Exacerbation</td><td>Cases where a patient fulfils part 1, 2 and 3 of the EMBARC criteria.</td></tr>
<tr><td>Partially Qualifying Exacerbation</td><td>Cases where a patient fulfils either part 1 or 2 and part 3 of the EMBARC criteria.</td></tr>
<tr><td>Another form of exacerbation</td><td>Cases where a patient fulfils only part 3 of the EMBARC criteria.</td></tr>
<tr><td>Modified Intention to Treat Population</td><td>Randomised participants that have data from at least one post baseline efficacy assessment (week 8 or later)</td></tr>
<tr><td>Per Protocol Population</td><td>Randomised participants that have reached visit 5 (week 52) and attended visits 1-4.</td></tr>
<tr><td>HTS Adherence</td><td>Number of ampoules dispensed – Number of unused ampoules returned/Expected Dose</td></tr>
<tr><td>Carbocisteine Adherence</td><td>Number of capsules dispensed – Number of unused capsules returned/ Expected Dose</td></tr>
<tr><td>QOL-B Scoring</td><td>See appendix 2</td></tr>
<tr><td>Pre-pandemic</td><td>Participants recruited up to 11th March 2020</td></tr>
<tr><td>During pandemic</td><td>Participants recruited between 11th March 2020 and 01st October 2021</td></tr>
<tr><td>Post-pandemic</td><td>Participants recruited from 02nd October onwards</td></tr>
</table>

5. SAMPLE SIZE CALCULATIONS

The required sample size is 288 patients. Based on the primary outcome of mean exacerbations during 52 weeks, mean exacerbations in the control group of 0.7 and a pooled standard deviation (SD) of 0.9 exacerbations (RESPIRE2 - 20) 162 patients would be able to detect a mean difference between groups of 0.4 exacerbations with 80% power and at the 5% significance level. To allow for a potential interaction between the two interventions, 50% inflation has been included, to 243 patients. Assuming approximately 15% dropout gives a total of 288 patients (72 in each of the four groups).

The actual mean difference observed in the RESPIRE2 trial was 0.3 exacerbations for the 28 Day Cycle. The mean exacerbation rate observed in the RESPIRE2 placebo group was 0.7 exacerbations over 48 weeks which is lower than reported in other studies (BAT Trial - 21, BLESS Trial - 22, EMBRACE Trial - 23). It is postulated that new larger clinical trials may be reporting a lower rate of Protocol defined pulmonary exacerbation than in the previous literature potentially due to improvements in definitions of exacerbations and/or increased standardisation across centres in multi-centre studies.

This sample size would provide over 80% power to detect a minimally important difference of 8 points for the QoL-B scale (SD of 18) at the 5% significance level (8, 18). This sample size would also be sufficient to detect a 75% increase in median time to exacerbation at 94% power and a medium effect size for the other secondary outcomes at 88% power and 5% level of significance'

6. RANDOMISATION AND BLINDING

6.1 Randomisation

Intervention 1: Standard care and twice daily nebulised HTS (6%) over 52 weeks:
Intervention 2: Standard care and carbocisteine (750 mg three times per day until visit 3 reducing to 750 mg two times per day) over 52 weeks.
Intervention 3: Standard care and combination of twice daily nebulised HTS (6%) and carbocisteine (750 mg of three times per day until visit 3 reducing to 750 mg twice per day) over 52 weeks.
Control: Standard care over 52 weeks.

Intervention will be reported according to Tidier checklist (15).

Patients on the standard care arm will use airway clearance techniques in the management of their BE.

After 52 weeks all patients will revert to standard care and patients may/may not be prescribed an oral/nebulised mucolytic.

When the research team at each study site identifies a patient suitable for enrolment, they will obtain informed consent for participation in the trial. The randomisation service will allocate a unique trial identifier to each patient in accordance with the study randomisation schedule prepared prior to the start of the trial. The unique identifier allocated at the time of randomisation will be used throughout the trial for purposes of patient identification. Treatment allocation will be assigned using an automated randomisation process that each site research team will complete. Eligible participants will be allocated to one of the four treatment groups (three intervention groups or one standard care group) in a 1:1:1:1 ratio using a central randomisation system. Randomisation will be stratified by site, to minimise baseline imbalances in antibiotic use due to exacerbations in the last year (2-3 times, >3times) and based on current use of macrolides (yes, no).

6.2 Blinding and Allocation Concealment

This is an open label trial. Please see protocol for further details

7. ANALYSIS PRINCIPLES

Standard approaches will be used to detect patterns in missing data. Baseline characteristics, follow-up measurements, airway clearance, drug response assessment and safety data will be described using the appropriate descriptive summary measures depending on the scale of measurement.

Analysis will be conducted as for two separate comparisons: (i) participants who receive hypertonic saline compared to those who do not and (ii) participants who receive carbocisteine compared to those who do not, This is known as a factorial analysis (REF)

No interactions are anticipated between carbocisteine and hypertonic saline in the analysis of clinical endpoints. The presence and magnitude of an interaction between the two interventions will be formally investigated before testing their effects on the primary outcome.

The primary analysis will be conducted on a modified intention to treat basis. The modified intention-to-treat population will consist of randomised participants that have data from at least one post baseline efficacy assessment (week 8 or later). A per-protocol analysis may also be conducted which will involve a comparison of treatment groups that includes only those participants who completed all 5 visits.

Groups will be compared for the primary outcome (number of exacerbations over the 52 weeks – fully qualifying) and antibiotic use (number of days of antibiotic use over the 52 weeks) using Negative Binomial regression. The regression models will be used to adjust for macrolide use, site, antibiotic use and other covariates.

Groups will be compared for QoL-B and other continuous outcomes using analysis of covariance (ANCOVA). ANCOVA will be used to adjust for baseline characteristics and other covariates.

For time to next exacerbation, Kaplan-Meier curves will be prepared and the log-rank test calculated to compare the groups. A secondary analysis will be conducted for time to next exacerbation if the first exacerbation is within 28 days of randomisation then we will consider the 2nd exacerbation.

Secondary analyses for the primary outcome will include exacerbations coded as fully qualifying and partially qualifying and also all exacerbations (including full, partial, other and missed exacerbations captured from con-meds.

Sensitivity analyses will be performed for the primary outcome looking at the calendar effect by including season as a covariate.

Subgroup analyses (baseline) will be performed on the primary outcome measure for macrolide use, antibiotic use, age, season, site and SWAT C. A statistical interaction test will be used to assess differences in treatment effects between the subgroups and will be reported using 99% CI.

Subgroup analyses (post randomisation) will be performed on the primary outcome measure for macrolide use, covid-19, remote visits and changes in inclusion criteria. A statistical interaction test will be used to assess differences in treatment effects between the subgroups and will be reported using 99% CI.

The factorial design permits the separate testing of the effects of HTS and carbocisteine on HRQoL and the detection of any interaction between them. These tests will be implemented using three contrasts (representing HTS, carbocisteine, and the interaction) in the models.

The number of AEs, Adverse Reactions (AR), Serious Adverse Events (SAE), Serious Adverse Reactions (SARs), Suspected Unexpected Serious Adverse Reaction (SUSARs) and number (%) of patients experiencing the events will be reported. Chi-square test (or Fisher's exact test if appropriate) and proportion test will be used to check whether incidences of adverse events differ between the groups. Risk Ratio and 95% CI will be reported.

Analyses will be two-sided and tested at an a priori significance level of p=0.05. The primary time point has been defined as the 52-week time point. There is no adjustment for multiple testing at the different time points, as the primary outcome has been defined and prioritised.

A secondary analysis will be conducted which will focus on exploring the effect of adherence on the trial's primary (mean number of exacerbations at week 52) and secondary outcomes (QOL-B and time to next exacerbation). Patients will be included in this analysis if they have complete medication data between date of randomisation and date of drug termination.

Mean hypertonic saline adherence will be categorised in a four-level variable comprising: Good (>=79%); Moderate (<79% to >=50%); Low (>50% to >=21%) and Very Low (<21%). Carbocisteine adherence will be calculated based on the total number of tablets returned to sites by participants at study visits and categorised into a four-level variable comprising Good (>=79%); Moderate (<79% to >=50%); Low (>50% to >=21%) and Very Low (<21%).Kaplan-Meier curves will be generated to visualise differences in time to next exacerbation by level of adherence, hazard ratio and 95% CI from a cox proportional hazards model will be reported. A negative binomial regression will be used to investigate the possible relationship between adherence and mean number of exacerbations at week 52 and an ANCOVA model will be used to investigate the possible relationship between adherence and QOL-B.

The data will also be explored to ascertain whether there are any predictors of adherence

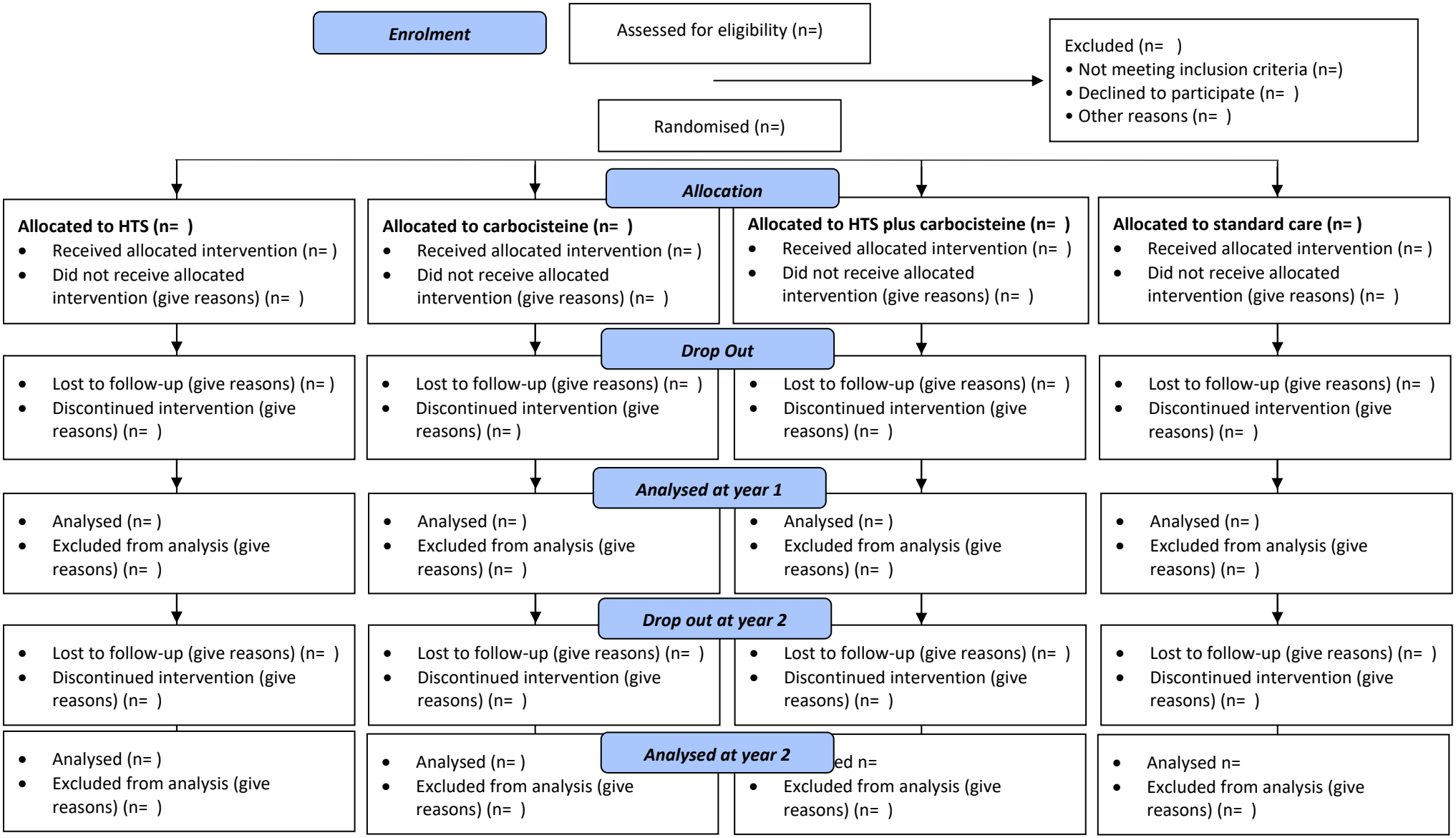
8. ANALYSIS DETAILS

The results of the analyses will be reported following the principles of the International Conference of Harmonisation (ICH) E3 guidelines on the Structure and Content of Clinical Study Reports.

8.1 Recruitment and follow-up patterns

- Recruitment by year, centre.
- Withdrawals by site - this should include the timing of withdrawals.

8.2 CONSORT Flow Diagram



8.3 Baseline Characteristics

- Gender, n(%) by treatment arm and by comparison
- Age, mean(sd) by treatment arm and by comparison
- Ethnicity, n(%) by treatment arm and by comparison
- Cigarette Use, n(%) by treatment arm and by comparison
- Pack Years, mean(sd) by treatment arm and by comparison
- E-cigarette use, n(%) by treatment arm and by comparison
- Height, mean(sd) by treatment arm and by comparison
- Weight, mean(sd) by treatment arm and by comparison
- Temperature, mean(sd) by treatment arm and by comparison
- Blood Pressure, mean(sd) by treatment arm and by comparison
- Pulse, mean(sd) by treatment arm and by comparison
- Respiratory Rate, mean(sd) by treatment arm and by comparison
- SpO2, mean(sd) by treatment arm and by comparison
- BSI Score, mean(sd) by treatment arm and by comparison
- Facet Score, mean(sd) by treatment arm and by comparison

Baseline characteristics will be presented for all patients and separately for patients recruited throughout COVID-19 (Pre-pandemic, during pandemic and post pandemic)

8.4 Trial treatment

- Study drug dispensed, n(%) by treatment arm and by comparison
- Time from randomisation to study drug termination (days), mean(sd) by treatment arm and by comparison
- No. of doses received, mean(sd) by treatment arm and by comparison
- Adherence(Good (>=79%); Moderate (<79% to >=50%); Low (>50% to >=21%) and Very Low (<21%)), n(%) by treatment arm and by comparison
- Did not receive allocated treatment, n(%) by treatment arm and by comparison
- Received treatment of other group, n(%) by treatment arm and by comparison
- Reasons for termination of study drug, n(%) by treatment arm and by comparison
- Post-randomisation withdrawal, n(%) by treatment arm and by comparison
- Protocol violations, no. events (%) by treatment arm, no. patients (%) by treatment arm and by comparison

8.5 Trial Outcomes

- **Primary Outcome (Modified ITT and Per Protocol)[a]**
    - Mean number of exacerbations (fully qualifying) over 52 weeks, mean(SD) by comparison, difference in mean with 95% CI.
    - **Subgroup Analyses[b]**
        - Macrolide Use (Yes/No), mean(SD) by comparison, difference in mean with 99% CI
        - Antibiotic Use (2-3, >3), mean(SD) by comparison, difference in mean with 99% CI
        - Age (Quartiles), mean(SD) by comparison, difference in mean with 99% CI
        - Study Site, mean(SD) by comparison, difference in mean with 99% CI
        - SWAT C (Generic thank you card, personalised thank you card, no thank you card), mean(SD) by comparison, difference in mean with 99% CI
    - **Secondary Analyses [a]**
        - Mean number of exacerbations (fully qualifying + partially qualifying) over 52 weeks, mean(SD) by comparison, difference in mean with 95% CI.
        - Mean number of exacerbations (All exacerbations) over 52 weeks, mean(SD) by comparison, difference in mean with 95% CI.
    - **Sensitivity Analyses:**
        - Calendar Effect i.e include season as a covariate
        - Fuch's definition
    - **Subgroup Analyses(Post Randomisation) [b]**

- COVID-19(Pre-pandemic, during pandemic and post pandemic)
- Change in inclusion criteria throughout the trial (Two or more pulmonary exacerbations in the last year requiring antibiotics*, 2 or more pulmonary exacerbations in a 1 year period in the past 2 years requiring antibiotics* and **One** or more pulmonary exacerbations in the last year requiring antibiotics.*.* This can included patient reported exacerbations)
- Remote visits (Good (>=79%); Moderate (<79% to >=50%); Low (>50% to >=21%) and Very Low (<21%))
- Macrolide use post randomisation (Yes/No)

- **Secondary Outcomes**
  - Disease specific HRQoL (respiratory symptoms of domain of QoL-B) at 52 weeks, mean(SD) by comparison, difference in mean with 95% CI. [b]
  - Time to next exacerbation post randomisation[d]
  - Number of days of antibiotics related to exacerbations over 52 weeks, , mean(SD) by comparison, difference in mean with 95% CI[a]
  - Measurement of health impairment using the SGRQ, mean(SD) by comparison, difference in mean with 95% CI. [c]
  - Patient preferences for treatment at weeks 2, 8, 26 and 52[c]
    - Treatment Satisfaction Questionnaire for Medication (TSQM) Effectiveness, mean(SD) by treatment arm, difference in mean with 95% CI[f]
    - TSQM Side Effects, mean(SD) by treatment arm, difference in mean with 95% CI[f]
    - TSQM Convenience, mean(SD) by treatment arm, difference in mean with 95% CI[f]
    - TSQM Global Satisfaction, mean(SD) by treatment arm, difference in mean with 95% CI[f]
  - Lung function over 52 weeks[c]
    - Change from baseline to 52 weeks in Forced Expiratory Flow in 1 second (FEV1) (L), mean(SD) by comparison, difference in mean with 95% CI
    - Change from baseline to 52 weeks in Forced Vital Capacity (FVC) (L) , mean(SD) by comparison, difference in mean with 95% CI
    - Change from baseline to 52 weeks in Forced Expiratory Flow in 1 second (FEV1) % predicted, mean(SD) by comparison, difference in mean with 95% CI
    - Change from baseline to 52 weeks in Forced Expiratory Flow (FEF) 25-75 (L/s) , mean(SD) by comparison, difference in mean with 95% CI
  - Adherence to HTS and carbocisteine over 52 weeks, mean(SD) by treatment arm, difference in mean with 95% CI. [c]
  - Generic HRQoL[e]
  - Health Service use over 52 weeks[e]
  - QALY over 52 weeks[e]

[a]Groups will be compared for the primary outcome (number of exacerbations over the 52 weeks) and antibiotic use (number of days of antibiotic use over the 52 weeks) using Negative Binomial regression. The regression models will be used to adjust for macrolide use, site, antibiotic use and other covariates..

[b] A statistical interaction test will be used to assess differences in treatment effects between the subgroups and will be reported using 99% CI.

[c]Groups will be compared for QoL-B and other continuous outcomes using analysis of covariance (ANCOVA). ANCOVA will be used to adjust for macrolide use, site, antibiotic use and other covariates.

[d]Groups will be compared for time to next exacerbation post randomisation using survival methods, Kaplan-Meier curves will be prepared and the log-rank test calculated to compare the groups. A secondary analysis will be conducted for time to next exacerbation if the first exacerbation is within 28 days of randomisation then we will consider the 2nd exacerbation.

[e]Outcomes will be analysed as per the Health Economics Analysis Plan (HEAP)

[f]Difference in mean (95% CI) only presented for week 52 (one year)..

8.6 Toxicity/ Symptoms

- Adverse Events (AEs), no. events (%) by treatment arm and by comparison, no. patients (%) by treatment arm, risk ratio and 95% CI*
- Adverse Reactions (ARs), no. events (%) by treatment arm, no. patients (%) by treatment arm and by comparison, risk ratio and 95% CI
- Serious Adverse Events (SAEs), no. events (%) by treatment arm and by comparison, no. patients (%) by treatment arm, risk ratio and 95% CI
- Serious Adverse Reactions (SARs), no. events (%) by treatment arm and by comparison, no. patients (%) by treatment arm, risk ratio and 95% CI
- Suspected Unexpected Serious Adverse Reactions (SUSARs), no. events (%) by treatment arm and by comparison, no. patients (%) by treatment arm, risk ratio and 95% CI Death,n(%) by treatment arm, risk ratio and 95% CI
  **Secondary Outcome*

8.7 Drug Response Assessment (Hypertonic Saline comparison only)

- Test dose administered; no. (%) by comparison
  - Pre test BD, no. (%) by comparison
  - Post test BD, no. (%) by comparison
- Spirometry appropriate; no. (%) by comparison
  - Pre test FEV1 (L/min), mean(SD) by comparison Post test FEV1 (L/min), mean(SD) by comparison
  - % change, mean(SD) by comparison
- SP02 pre (%), mean(SD) by comparison
- SP02 post (%), mean(SD) by comparison
- HR pre(bpm), mean(SD) by comparison
- HR post(bpm), mean(SD) by comparison
- Symptoms;
  - None, no. (%) by comparison
  - Light headed, no. (%) by comparison
  - Chest tightness, no. (%) by comparison
  - Wheeze, no. (%) by comparison Salty taste, no. (%) by comparison
  - Throat irritation/tickle/dry, no. (%) by comparison
  - Cough, no. (%) by comparison
- 10 mins post tests needed, no. (%) by comparison 10 mins post FEV1 (L/min), mean(SD) by comparison
- 10 mins post % change, mean(SD) by comparison
- Inhalation technique discussed, no. (%) by comparison
- Explained potential AEs, no. (%) by comparison
- Safe for HTS use;
  - Yes, Repeat DRA and Failed DRA, no. (%) by comparison
- Pre Repeat Tests;
  - Repeat DRA on same day, no. (%) by comparison
  - Pre repeat test BD, no. (%) by comparison
  - Repeat test % change, mean(SD) by comparison
- Proceed to trial inclusion; no. (%) by comparison

8.8 Airway Clearance

- Adjunct;
  - Acapella, no. (%) by comparison
  - Aerobika, no. (%) by comparison
  - Flutter, no. (%) by comparison
  - Cough assist device, no. (%) by comparison
  - NIV device, no. (%) by comparison
  - PEP mask, no. (%) by comparison
  - HFCWO device, no. (%) by comparison
- Non-adjunct;
  - ACBT, no. (%) by comparison

- Huffing, no. (%) by comparison
- Exercise and/or physical activity, no. (%) by comparison
- Coughing, no. (%) by comparison
- Postural drainage, no. (%) by comparison
- Clapping/Percussion, no. (%) by comparison
- Autogenic drainage, no. (%) by comparison
- Singing, no. (%) by comparison
- ELTGOL, no. (%) by comparison

- Use of reminders;
  - Electronic/alarm, no. (%) by comparison
  - Family, no. (%) by t comparison
  - Follow visable record/ACR, no. (%) by comparison
  - Carry on person, no. (%) by comparison
  - Medication organiser used, no. (%) by comparison
  - Follow routine, no. (%) by comparison
  - Chest tightness, no. (%) by comparison
  - None, no. (%) by comparison

8.9 Additional Analyses

- Mean number of exacerbations at 52 weeks, mean(SD) by level of adherence (Good ≥79%, Moderate <79% and ≥50%, Low <50% and ≥21%, Very Low <21%), difference in mean with 95% CI[a].
- Time to next exacerbation, mean(SD) by level of adherence (Good ≥79%, Moderate <79% and ≥50%, Low <50% and ≥21%, Very Low <21%), hazard ratio with 95% CI[b]
- QOL-B, mean(SD) by level of adherence (Good ≥79%, Moderate <79% and ≥50%, Low <50% and ≥21%, Very Low <21%), difference in mean with 95% CI[c].
-

[a]Negative Binomial regression. The regression models will be used to adjust for macrolide use, site, antibiotic use and other covariates..
[b].Cox proportional hazards model
[c] ANCOVA

9. ADDITIONAL INFORMATION

9.1 Trial Steering Committee (TSC)

A group of experienced clinicians, trialists and lay people will act as a TSC. The TSC will provide oversight with respect to the conduct of the study on behalf of the Funder and Sponsor.

The TSC will have at least 75% independent member ship. It will include the CI, independent clinicians (1 of whom will act as chair) and lay representatives. The TSC will meet during the course of the trial and observers may be invited and be in attendance at TSC meetings, such as the Sponsor or Funder representatives or the Trial Manager to provide input on behalf of the CTU.

A TSC charter will be drawn up to detail the terms of reference of the TSC including membership and roles/responsibilities.

9.2 Data Monitoring and Ethics Committee (DMEC)

The role of the DMEC is to safeguard the rights, safety and wellbeing of trial participants, monitor data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue and monitor the overall conduct of the study to ensure the validity and integrity of the study findings. The DMEC will meet annually.
The DMEC will comprise independent members with at least one statistician and two respiratory specialists.
A DMEC charter will be drawn up to detail the terms of reference of the DMEC including membership and roles/responsibilities.

10. REFERENCES

List any references used.

11. SIGNATURES OF APPROVAL

Date: 13th December 2024
Version: 1.0
This document has completed a final review and is understood and approved by the following:
See attached email

Professor Stuart Elborn Chief Investigator Name	*Chief Investigator Signature*	Date dd/mm/yyyy
Clíona McDowell Senior Statistician or designee Name	C. Mc Dowell *Senior Statistician or designee Signature*	16/12/2024 Date dd/mm/yyyy
Clíona McDowell Study Statistician Name	C. Mc Dowell *Study Statistician Signature*	16/12/2024 Date dd/mm/yyyy

APPENDIX 1: EXAMPLE SUMMARY TABLES

- Put Intervention on left and Control on right.
- No hard spaces or hard returns (create new rows in tables)
- Use superscript letters for footnotes and list in order in footers as they appear in the table
- When reporting n(%) for a variable – list in descending order from largest to smallest as per intervention
- Include the primary /secondary outcomes in one table making clear what is primary and what is secondary

Table x.x.x. Screening & recruitment summary

Site No	Site	Date Opened	No. Screened	No. Recruited	No. Withdrawals	Time on study*
1	Altnagelvin Area Hospital	19.06.2018				
2	Royal Free Hospital	23.10.2018				
3	Royal Infirmary of Edinburgh	03.09.2018				
4	Freeman Hospital	16.10.2018				
5	Royal Brompton Hospital	04.09.2018				
6	Belfast City Hospital	17.06.2018				
7	Ninewells Hospital	25.10.2018				
8	Princess Alexandra Hospital	18.07.2018				
10	Southampton General Hospital	03.07.2018				
11	Craigavon Area Hospital	10.10.2018				
12	Morcambe (Formally Royal Lancaster Infirmary)	07.08.2019				
14	Queen Elizabeth Birmingham	23.10.2019				
15	Churchill Hospital Oxford	20.06.2019				
16	Royal Gwent Hospital	30.08.2019				
20	Blackpool Victoria Hospital	19.10.2021				
25	Stoke Mandeville Hospital	15.03.2022				
19	Cardiff & Vale - Llandough	03.02.2022				
21	North Tyneside General Hospital - Northumbria	07.04.2022				
35	Omagh & SWAH	09.08.2022				
22	Bradford Royal Infirmary	N/A				
34	Sandwell & West Birmingham	N/A				
26	Milton Keynes University Hospital	N/A				
38	Liverpool Heart & Chest Hospital	N/A				

***Withdrawn patients only**

Figure x.x.x Recruitment

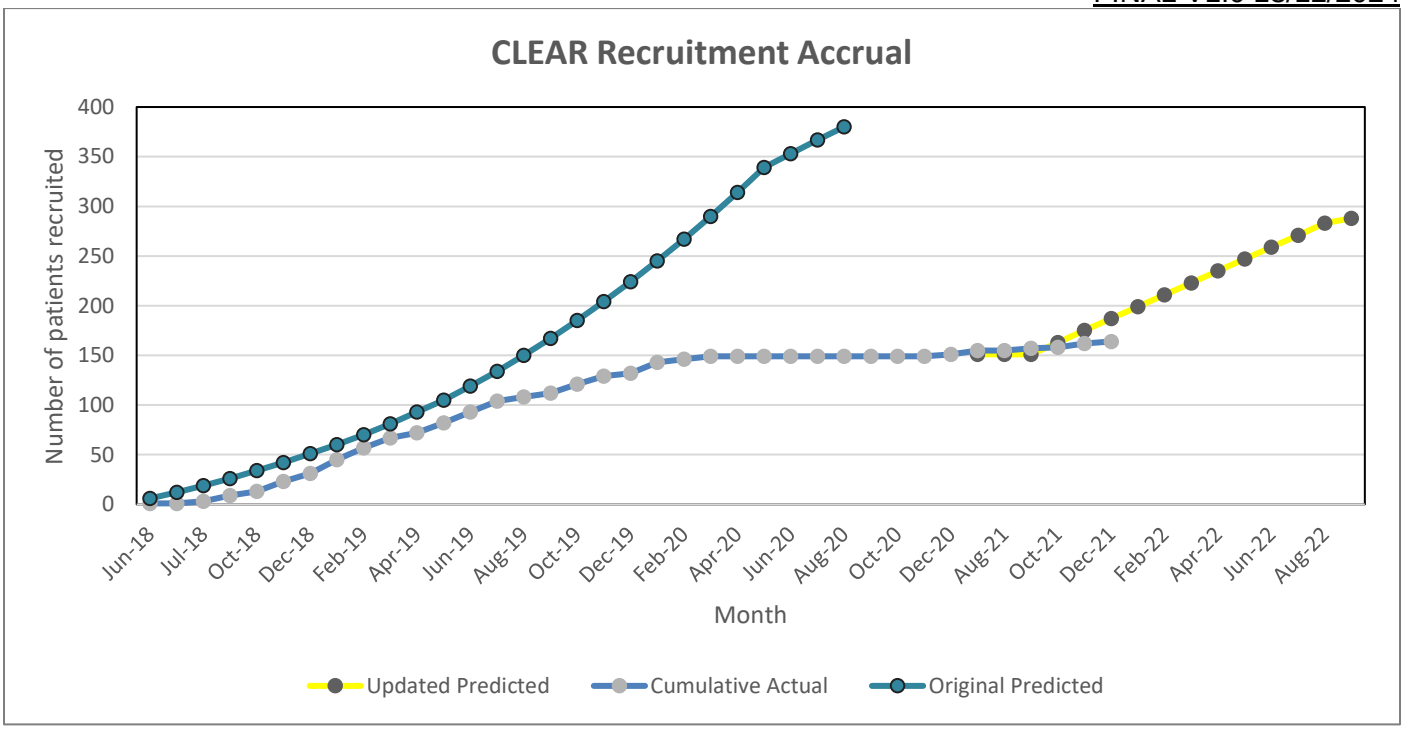


Table x.x.x. Baseline Characteristics at trial entry (All participants)

Baseline Characteristics			Treatment Group			
			HTS	Carbocisteine	HTS plus Carbocisteine	Standard Care
			n=<n>	n=<n>	n=<n>	n=<n>
Gender	Male		n(%)	n(%)	n(%)	n(%)
	Female		n(%)	n(%)	n(%)	n(%)
Age (years)			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Ethnicity	White		n(%)	n(%)	n(%)	n(%)
	Non-White		n(%)	n(%)	n(%)	n(%)
Cigarette Use	Never Smoked		n(%)	n(%)	n(%)	n(%)
	Ex-Smoker					
		Cigarettes	n(%)	n(%)	n(%)	n(%)
		No. smoked per day	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		No. years smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		Pack years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		No. years stopped	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		Pipe	n(%)	n(%)	n(%)	n(%)
		No. smoked per day	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		No. years smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		Pack years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		No. years stopped	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
E-cigarette use	Never vaped		n(%)	n(%)	n(%)	n(%)
	Ex-vaper		n(%)	n(%)	n(%)	n(%)
	Current Vaper		n(%)	n(%)	n(%)	n(%)
Height (m)			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Weight (kg)			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Temperature (°C)			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Blood Pressure			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Pulse			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Respiratory Rate			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

SpO2	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
BSI Score	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Facet Score	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Mean (SD) (or median[IQR] if appropriate) presented for continuous variables and no. (%) for all categorical variables.
Note: Table will also be presented by comparison (i.e. HTS vs No HTS and Carbocisteine vs No Carbocisteine)

Table x.x.x. Baseline Characteristics at trial entry (Pre-pandemic)

Baseline Characteristics			**Treatment Group**			
			HTS	**Carbocisteine**	**HTS plus Carbocisteine**	**Standard Care**
			n=<n>	**n=<n>**	**n=<n>**	**n=<n>**
Gender	**Male**		n(%)	n(%)	n(%)	n(%)
	Female		n(%)	n(%)	n(%)	n(%)
Age (years)			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Ethnicity	**White**		n(%)	n(%)	n(%)	n(%)
	Non-White		n(%)	n(%)	n(%)	n(%)
Cigarette Use	**Never Smoked**		n(%)	n(%)	n(%)	n(%)
	Ex-Smoker					
		Cigarettes	n(%)	n(%)	n(%)	n(%)
		No. smoked per day	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		No. years smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		Pack years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		No. years stopped	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		Pipe	n(%)	n(%)	n(%)	n(%)
		No. smoked per day	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		No. years smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		Pack years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
		No. years stopped	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
E-cigarette use	**Never vaped**		n(%)	n(%)	n(%)	n(%)
	Ex-vaper		n(%)	n(%)	n(%)	n(%)
	Current Vaper		n(%)	n(%)	n(%)	n(%)
Height (m)			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Weight (kg)			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Temperature (°C)			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Blood Pressure			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Pulse			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Respiratory Rate			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
SpO2			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
BSI Score			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Facet Score			xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Mean (SD) (or median[IQR] if appropriate) presented for continuous variables and no. (%) for all categorical variables.
Note: Table will also be presented by comparison (i.e. HTS vs No HTS and Carbocisteine vs No Carbocisteine)

Table x.x.x. Baseline Characteristics at trial entry (During pandemic)

Baseline Characteristics		**Treatment Group**			
		HTS	**Carbocisteine**	**HTS plus Carbocisteine**	**Standard Care**
		n=<n>	**n=<n>**	**n=<n>**	**n=<n>**
Gender	**Male**	n(%)	n(%)	n(%)	n(%)
	Female	n(%)	n(%)	n(%)	n(%)
Age (years)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Ethnicity	**White**	n(%)	n(%)	n(%)	n(%)
	Non-White	n(%)	n(%)	n(%)	n(%)
Cigarette Use	**Never Smoked**	n(%)	n(%)	n(%)	n(%)
	Ex-Smoker				
	Cigarettes	n(%)	n(%)	n(%)	n(%)
	No. smoked per day	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	No. years smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Pack years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	No. years stopped	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Pipe	n(%)	n(%)	n(%)	n(%)
	No. smoked per day	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	No. years smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Pack years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	No. years stopped	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
E-cigarette use	**Never vaped**	n(%)	n(%)	n(%)	n(%)
	Ex-vaper	n(%)	n(%)	n(%)	n(%)
	Current Vaper	n(%)	n(%)	n(%)	n(%)
Height (m)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Weight (kg)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Temperature (°C)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Blood Pressure		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Pulse		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Respiratory Rate		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
SpO2		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
BSI Score		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Facet Score		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Mean (SD) (or median[IQR] if appropriate) presented for continuous variables and no. (%) for all categorical variables.
Note: Table will also be presented by comparison (i.e. HTS vs No HTS and Carbocisteine vs No Carbocisteine)

Table x.x.x. Baseline Characteristics at trial entry (Post pandemic)

Baseline Characteristics		**Treatment Group**			
		HTS	**Carbocisteine**	**HTS plus Carbocisteine**	**Standard Care**
		n=<n>	**n=<n>**	**n=<n>**	**n=<n>**
Gender	**Male**	n(%)	n(%)	n(%)	n(%)
	Female	n(%)	n(%)	n(%)	n(%)
Age (years)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Ethnicity	**White**	n(%)	n(%)	n(%)	n(%)
	Non-White	n(%)	n(%)	n(%)	n(%)
Cigarette Use	**Never Smoked**	n(%)	n(%)	n(%)	n(%)
	Ex-Smoker				
	Cigarettes	n(%)	n(%)	n(%)	n(%)
	No. smoked per day	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	No. years smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Pack years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	No. years stopped	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Pipe	n(%)	n(%)	n(%)	n(%)
	No. smoked per day	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	No. years smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Pack years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	No. years stopped	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
E-cigarette use	**Never vaped**	n(%)	n(%)	n(%)	n(%)
	Ex-vaper	n(%)	n(%)	n(%)	n(%)
	Current Vaper	n(%)	n(%)	n(%)	n(%)
Height (m)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Weight (kg)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Temperature (°C)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Blood Pressure		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Pulse		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Respiratory Rate		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
SpO2		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
BSI Score		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Facet Score		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Mean (SD) (or median[IQR] if appropriate) presented for continuous variables and no. (%) for all categorical variables.
Note: Table will also be presented by comparison (i.e. HTS vs No HTS and Carbocisteine vs No Carbocisteine)

Table x.x.x. Treatment after Trial Entry

	Treatment Group			
	HTS	**Carbocisteine**	**HTS plus Carbocisteine**	**Standard Care**
	n=<n>	**n=<n>**	**n=<n>**	**n=<n>**
Treatment Adherence				
Study drug given	n(%)	n(%)	n(%)	n(%)
Time from randomisation to study drug termination (days)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Patient has completed 52 weeks of intervention	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
Adverse Event	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
Serious Adverse Event	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
Protocol violations or non compliance as determined by the PI	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
Intercurrent significant illness	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
Occurrence of intolerable side effects	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
Patient request	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
Decision by the PI the study drug should be discontinued on safety grounds	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
Death	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
Complexity of study	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*

Increased hypertonic intolerance		*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
Other		*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*	*xx.x (xx.x)*
No. of doses received*		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Adherence	**Good (≥79%)**	n(%)	n(%)	n(%)	n(%)
	Moderate (<79% and ≥50%)	n(%)	n(%)	n(%)	n(%)
	Low (<50% and ≥21%)	n(%)	n(%)	n(%)	n(%)
	Very Low (<21%)	n(%)	n(%)	n(%)	n(%)
Did not receive allocated treatment		n(%)	n(%)	n(%)	n(%)
Received treatment of other group		n(%)	n(%)	n(%)	n(%)
Reasons for termination of study drug					
Patient has completed 52 weeks of intervention		n(%)	n(%)	n(%)	n(%)
Adverse Event		n(%)	n(%)	n(%)	n(%)
Serious Adverse Event		n(%)	n(%)	n(%)	n(%)
Protocol violations or non compliance as determined by the PI		n(%)	n(%)	n(%)	n(%)
Intercurrent significant illness		n(%)	n(%)	n(%)	n(%)
Occurrence of intolerable side effects		n(%)	n(%)	n(%)	n(%)
Patient request		n(%)	n(%)	n(%)	n(%)
Decision by the PI the study drug should be discontinued on safety grounds		n(%)	n(%)	n(%)	n(%)
Death		n(%)	n(%)	n(%)	n(%)
Complexity of study		n(%)	n(%)	n(%)	n(%)
Increased hypertonic intolerance		n(%)	n(%)	n(%)	n(%)
Other		n(%)	n(%)	n(%)	n(%)
Post-randomisation withdrawal					
Withdrawal of consent		n(%)	n(%)	n(%)	n(%)

Refused use of data already collected	n(%)	n(%)	n(%)	n(%)
Refused data collection from NHS records	n(%)	n(%)	n(%)	n(%)

*Patients are expected to receive 728 doses of Hypertonic Saline and/or 1568 doses of Carbocisteine as per treatment allocation
Note: Table will also be presented by comparison (i.e. HTS vs No HTS and Carbocisteine vs No Carbocisteine)

Table x.x.x. Treatment after Trial Entry – Protocol Deviations
Note: Table will also be presented by comparison (i.e. HTS vs No HTS and Carbocisteine vs No Carbocisteine)

	Number of Events					Number of Patients				
	Total	**HTS**	**Carbocisteine**	**HTS plus Carbocisteine**	**Standard Care**	**Total**	**HTS**	**Carbocisteine**	**HTS plus Carbocisteine**	**Standard Care**
	n= <n>	**n= <n>**	**n= <n>**	**n= <n>**	**n= <n>**	**n= <n>**	**n= <n>**	**n= <n>**	**n= <n>**	**n= <n>**
Eligibility	n	n(%)	n(%)	n(%)	n(%)	n	n(%)	n(%)	n(%)	n(%)
Study drug administration	n	n(%)	n(%)	n(%)	n(%)	n	n(%)	n(%)	n(%)	n(%)
Exacerbation phone call not done	n	n(%)	n(%)	n(%)	n(%)	n	n(%)	n(%)	n(%)	n(%)
Study visit not completed within protocol window	n	n(%)	n(%)	n(%)	n(%)	n	n(%)	n(%)	n(%)	n(%)
Other	n	n(%)	n(%)	n(%)	n(%)	n	n(%)	n(%)	n(%)	n(%)
Total	n	n	n	n	n	n	n	n	n	n

Table x.x.x Primary Outcome - Mean number of exacerbations over 52 weeks (Modified ITT)

Mean number of exacerbations over 52 weeks (NB fully qualifying exacerbations as classified by an independent panel)		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms Results from negative binomial regression presented

Table x.x.x Primary Outcome - Mean number of exacerbations over 52 weeks (Per Protocol)

Mean number of exacerbations over 52 weeks (NB fully qualifying exacerbations as classified by an independent panel)		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

Mean (SD) presented for treatment arms

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms Results from negative binomial regression presented

Table x.x.x Primary Outcome Subgroups

		Treatment Group				Difference (99% CI)	Interaction Term
		HTS	No HTS	Carbocisteine	No Carbocisteine		
		n=<n>	n=<n>	n=<n>	n=<n>		
Macrolide use	**Yes**	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx
	No	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
Antibiotic use due to exacerbations in the last year	**2-3 times**	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx
	>3 times	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
Age	**Quartile 1**	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx
	Quartile 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
	Quartile 3	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
	Quartile 4	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
Study Site	**S01**	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx
	S02	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
	S03	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
	S04	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
	Etc….	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
SWAT C	**Generic thank you card**	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx
	Personalised thank you card	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
	No thank you card	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
COVID-19	**Pre-pandemic (prior to 12/03/2020)**	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
	During pandemic (12/03/2020 – 30/09/2021)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
	Post pandemic (01/10/2021 onwards)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
Change in inclusion criteria throughout the trial	**Two or more pulmonary exacerbations in the last year requiring antibiotics***	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx
	2 or more pulmonary exacerbations in a 1 year period in the past	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	

	2 years requiring antibiotics*(Protocol V5.0 Implemented 09/11/2021)						
	One or more pulmonary exacerbations in the last year requiring antibiotics.*(Protocol V6.0 Implemented 20/09/2022)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
Remote visits	**Very Low (<21%)**	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx
	Low (>50% to >=21%)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
	Moderate (<79% to >=50%)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
	Good (>=79%)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	
Macrolide use post randomisation	**Yes**	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	x.xxx
	No	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	

A statistical interaction test will be used to assess differences in treatment effects between the subgroups and will be reported using 99% CI.

* This can included patient reported exacerbations

Table x.x.x Primary Outcome Sensitivity Analyses - Mean number of exacerbations over 52 weeks (Modified ITT)

Mean number of exacerbations over 52 weeks (NB fully qualifying and partially qualifying exacerbations as classified by an independent panel)		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean number of exacerbations over 52 weeks (NB all exacerbations)		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms Results from negative binomial regression presented

Table x.x.x Secondary outcome (Disease specific HRQoL (respiratory symptoms of domain of QoL-B) at 52 weeks)

Disease specific HRQoL (respiratory symptoms of domain of QoL-B) at 52 weeks		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms
P-value from ANCOVA adjusted for baseline characteristics and other covariates

Table x.x.x Secondary outcome (Time to next exacerbation post randomisation)

Time to next exacerbation post randomisation		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms

Groups will be compared for time to next exacerbation post randomisation using survival methods, Kaplan-Meier curves will be prepared and the log-rank test calculated to compare the groups. A secondary analysis will be conducted for time to next exacerbation if the first exacerbation is within 28 days of randomisation then we will consider the 2nd exacerbation.

Table x.x.x Secondary outcome (Number of days of antibiotics related to exacerbations over 52 weeks)

Number of days of antibiotics related to exacerbations over 52 weeks		HTS		Total
		No	Yes	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	No HTS	Carbocisteine	No Carbocisteine
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms
P-value from negative binomial regression

Table x.x.x Secondary outcome (Measurement of health impairment using the SGRQ)

Measurement of health impairment using the SGRQ		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms
P-value from ANCOVA adjusted for baseline characteristics and other covariates

Table x.x.x Secondary outcome (Adherence to HTS and carbocisteine over 52 weeks)

Adherence to HTS and carbocisteine over 52 weeks		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms
P-value from ANCOVA adjusted for baseline characteristics and other covariates

Table x.x.x Secondary outcome (Lung Function Over 52 Weeks - Change from baseline to 52 weeks in FEV_1 (L))

Change from baseline to 52 weeks in FEV_1 (L)		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms
P-value from ANCOVA adjusted for baseline characteristics and other covariates.

Table x.x.x Secondary outcome (Lung Function Over 52 Weeks - Change from baseline to 52 weeks in FVC (L))

Change from baseline to 52 weeks in FVC (L)		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms
P-value from ANCOVA adjusted for baseline characteristics and other covariates.

Table x.x.x Secondary outcome (Lung Function Over 52 Weeks - Change from baseline to 52 weeks in FEV_1 % predicted)

Change from baseline to 52 weeks in FEV_1 % predicted		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms
P-value from ANCOVA adjusted for baseline characteristics and other covariates.

Table x.x.x Secondary outcome (Lung Function Over 52 Weeks - Change from baseline to 52 weeks in FEF_{25-75} (L/s))

Change from baseline to 52 weeks in FEF_{25-75} (L/s)		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
No. Exacerbations	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms
P-value from ANCOVA adjusted for baseline characteristics and other covariates.

Table x.x.x Secondary outcome (Patient preferences for treatment)

	Treatment Group		Difference (95% CI)	P-value
	HTS	Carbocisteine		
	n=<n>	n=<n>		
Visit 2 (Week 2)				
TSQM Effectiveness	xx.x(xx.x)	xx.x(xx.x)		
TSQM Side Effects	xx.x(xx.x)	xx.x(xx.x)		
TSQM Convenience	xx.x(xx.x)	xx.x(xx.x)		
TSQM Global Satisfaction	xx.x(xx.x)	xx.x(xx.x)		
Visit 3 (Week 8)				
TSQM Effectiveness	xx.x(xx.x)	xx.x(xx.x)		
TSQM Side Effects	xx.x(xx.x)	xx.x(xx.x)		
TSQM Convenience	xx.x(xx.x)	xx.x(xx.x)		
TSQM Global Satisfaction	xx.x(xx.x)	xx.x(xx.x)		
Visit 4 (Week 26)				
TSQM Effectiveness	xx.x(xx.x)	xx.x(xx.x)		
TSQM Side Effects	xx.x(xx.x)	xx.x(xx.x)		
TSQM Convenience	xx.x(xx.x)	xx.x(xx.x)		
TSQM Global Satisfaction	xx.x(xx.x)	xx.x(xx.x)		
Visit 5 (Week 52)				
TSQM Effectiveness	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx
TSQM Side Effects	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx
TSQM Convenience	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx
TSQM Global Satisfaction	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x to xx.x)	x.xxx

Table x.x.x Secondary outcome (Adherence to HTS and carbocisteine over 52 weeks)

Adherence to HTS and carbocisteine over 52 weeks		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (Standard Care)	xx.x(xx.x) (HTS)	xx.x(xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (Carbocisteine)	xx.x(xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (Carbocisteine)
Total		xx.x(xx.x) (no HTS)	xx.x(xx.x) (HTS)	

	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
Adherence	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value	0.xxx		0.xxx	

Mean (SD) presented for treatment arms
P-value from ANCOVA adjusted for baseline characteristics and other covariates.

Table x.x.x Additional Analysis Airway Clearance

	Treatment Group			
	HTS	**No HTS**	**Carbocisteine**	**No Carbocisteine**
	n=<n>	n=<n>	n=<n>	n=<n>
Adjunct				
Acapella	n (%)	n (%)	n (%)	n (%)
Aerobika	n (%)	n (%)	n (%)	n (%)
Flutter	n (%)	n (%)	n (%)	n (%)
Cough assist device	n (%)	n (%)	n (%)	n (%)
NIV device	n (%)	n (%)	n (%)	n (%)
PEP mask	n (%)	n (%)	n (%)	n (%)
HFCWO device	n (%)	n (%)	n (%)	n (%)
Non-adjunct				
ACBT	n (%)	n (%)	n (%)	n (%)
Huffing	n (%)	n (%)	n (%)	n (%)
Exercise and/or physical activity	n (%)	n (%)	n (%)	n (%)
Coughing	n (%)	n (%)	n (%)	n (%)
Postural drainage	n (%)	n (%)	n (%)	n (%)
Clapping/Percussion	n (%)	n (%)	n (%)	n (%)
Autogenic drainage	n (%)	n (%)	n (%)	n (%)
Singing	n (%)	n (%)	n (%)	n (%)
ELTGOL	n (%)	n (%)	n (%)	n (%)
Use of reminder *				
Electronic/alarm	n (%)	n (%)	n (%)	n (%)
Family	n (%)	n (%)	n (%)	n (%)
Follow visable record/ACR	n (%)	n (%)	n (%)	n (%)
Carry on person	n (%)	n (%)	n (%)	n (%)
Medication organiser used	n (%)	n (%)	n (%)	n (%)
Follow routine	n (%)	n (%)	n (%)	n (%)
Chest tightness	n (%)	n (%)	n (%)	n (%)
None	n (%)	n (%)	n (%)	n (%)

*Yes results presented

Table x.x.x Additional Analysis Drug Response Assessment

	HTS	**No HTS**
	n=<n>	n=<n>
Test dose administered (Y/N)*	n (%)	n (%)
Pre test BD (Y/N)*	n (%)	n (%)
Post test BD (Y/N)*	n (%)	n (%)
Spirometry appropriate (Y/N)*	n (%)	n (%)
Pre test FEV1 (L/min)	xx.x(xx.x)	xx.x(xx.x)
Post test FEV1 (L/min)	xx.x(xx.x)	xx.x(xx.x)
% change	xx.x(xx.x)	xx.x(xx.x)
SPO2 pre (%)	xx.x(xx.x)	xx.x(xx.x)
SPO2 post (%)	xx.x(xx.x)	xx.x(xx.x)
HR pre(bpm)	xx.x(xx.x)	xx.x(xx.x)
HR post(bpm)	xx.x(xx.x)	xx.x(xx.x)
None	n (%)	n (%)
Light headed	n (%)	n (%)
Chest tightness	n (%)	n (%)
Wheeze	n (%)	n (%)
Salty taste	n (%)	n (%)
Throat irritation/tickle/dry	n (%)	n (%)
Cough	n (%)	n (%)
10 mins post tests needed (Y/N)*	n (%)	n (%)
10 mins post FEV1 (L/min)	xx.x(xx.x)	xx.x(xx.x)
10 mins post % change	xx.x(xx.x)	xx.x(xx.x)
Inhalation technique discussed (Y/N)*	n (%)	n (%)
Explained potential AEs (Y/N)*	n (%)	n (%)
Yes	n (%)	n (%)
Repeat DRA	n (%)	n (%)
Failed DRA	n (%)	n (%)
Repeat DRA on same day (Y/N)*	n (%)	n (%)
Pre repeat test BD (Y/N)*	n (%)	n (%)
Repeat test % change	xx.x(xx.x)	xx.x(xx.x)
Proceed to trial inclusion (Y/N)*	n (%)	n (%)

*Yes results presented

Table x.x.x Additional Analysis Descriptive Statistics for QOL-B domains at each visit

Domain	Visit	HTS	No HTS	Carbocisteine	No Carbocisteine
		n=<n>	n=<n>	n=<n>	n=<n>
Role functioning	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Vitality	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Emotional functioning	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Social functioning	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Treatment burden	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Health perceptions	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Respiratory symptoms	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)

Mean (SD) presented for treatment arms

Table x.x.x Additional Analysis Descriptive Statistics for SGRQ domains at each visit

Domain	Visit	HTS	No HTS	Carbocisteine	No Carbocisteine
		n=<n>	n=<n>	n=<n>	n=<n>
Symptoms	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Activity	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Impacts	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
Total	Baseline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 8	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 26	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Week 52	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)

Table x.x.x Additional Analysis Descriptive Statistics for mySpirosense satisfaction questionnaire at week 52

		HTS	No HTS	Carbocisteine	No Carbocisteine
		n=<n>	n=<n>	n=<n>	n=<n>
Myspirosense					
What is your overall satisfaction with the myspirosense device?	**Very satisfied**	n (%)	n (%)	n (%)	n (%)
	Satisfied	n (%)	n (%)	n (%)	n (%)
	Neutral	n (%)	n (%)	n (%)	n (%)
	Unsatisfied	n (%)	n (%)	n (%)	n (%)
	Not satisfied at all	n (%)	n (%)	n (%)	n (%)
If you have the chance to use myspirosense again, would you do so?	**Very likely**	n (%)	n (%)	n (%)	n (%)
	Likely	n (%)	n (%)	n (%)	n (%)
	Maybe	n (%)	n (%)	n (%)	n (%)
	Unlikely	n (%)	n (%)	n (%)	n (%)
	Never, ever	n (%)	n (%)	n (%)	n (%)
Would you recommend the myspirosense device to other family members or friends?	**Very likely**	n (%)	n (%)	n (%)	n (%)
	Likely	n (%)	n (%)	n (%)	n (%)
	Maybe	n (%)	n (%)	n (%)	n (%)
	Unlikely	n (%)	n (%)	n (%)	n (%)
	Never, ever	n (%)	n (%)	n (%)	n (%)
Did you already use a peak flow meter device in order to measure lung function parameters at home?	**Yes, a mechanical Peak Flow Meter**	n (%)	n (%)	n (%)	n (%)
	Yes, an electronic Peak Flow Meter	n (%)	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)	n (%)
How was the overall handling of the myspirosense device?	**Very easy**	n (%)	n (%)	n (%)	n (%)
	Easy	n (%)	n (%)	n (%)	n (%)
	Neutral	n (%)	n (%)	n (%)	n (%)
	Difficult	n (%)	n (%)	n (%)	n (%)
	Very difficult	n (%)	n (%)	n (%)	n (%)
eFlow Nebulizer System with eTrack Controller					
What is your overall satisfaction with the eflow Nebulizer System?	**Very satisfied**	n (%)	n (%)	n (%)	n (%)
	Satisfied	n (%)	n (%)	n (%)	n (%)
	Neutral	n (%)	n (%)	n (%)	n (%)
	Unsatisfied	n (%)	n (%)	n (%)	n (%)
	Not satisfied at all	n (%)	n (%)	n (%)	n (%)
Were the displayed symbols and information on the etrack Controller clearly understandable?	**Very clear**	n (%)	n (%)	n (%)	n (%)
	Clear	n (%)	n (%)	n (%)	n (%)
	Neutral	n (%)	n (%)	n (%)	n (%)
	Unclear	n (%)	n (%)	n (%)	n (%)
	Very unclear	n (%)	n (%)	n (%)	n (%)
Did the etrack Controller menu allow an easy use of the device?	**Very easy**	n (%)	n (%)	n (%)	n (%)
	Easy	n (%)	n (%)	n (%)	n (%)
	Neutral	n (%)	n (%)	n (%)	n (%)
	Difficult	n (%)	n (%)	n (%)	n (%)
	Very difficult	n (%)	n (%)	n (%)	n (%)
Was it easy to start nebulization	**Very easy**	n (%)	n (%)	n (%)	n (%)
	Easy	n (%)	n (%)	n (%)	n (%)

		HTS	No HTS	Carbocisteine	No Carbocisteine
		n=<n>	n=<n>	n=<n>	n=<n>
with the etrack Controller?	Neutral	n (%)	n (%)	n (%)	n (%)
	Difficult	n (%)	n (%)	n (%)	n (%)
	Very difficult	n (%)	n (%)	n (%)	n (%)

Table x.x.x Additional Analysis (Effect of adherence on number of exacerbations)

Mean number of exacerbations	Good	Moderate	Low	Very Low	p-value
Hypertonic Saline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	**0.xxx**
Carbocisteine	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	**0.xxx**

p-value from negative binomial regression

Table x.x.x Additional Analysis (Effect of adherence on time to next exacerbation)

Time to next exacerbation	Good	Moderate	Low	Very Low	p-value
Hypertonic Saline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	**0.xxx**
Carbocisteine	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	**0.xxx**

p-value from cox proportional hazards model

Table x.x.x Additional Analysis (Effect of adherence on QOL-B Respiratory Symptoms

QOL-B Respiratory Symptoms	Good	Moderate	Low	Very Low	p-value
Hypertonic Saline	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	**0.xxx**
Carbocisteine	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	**0.xxx**

p-value from ancova

Table x.x.x. Safety by Treatment Group

		No. Events				No. Patients				
		HTS	**Carbocisteine**	**HTS plus Carbocisteine**	**Standard Care**	**HTS**	**Carbocisteine**	**HTS plus Carbocisteine**	**Standard Care**	**Risk Ratio (95% CI)**
AEs, SAEs and SUSARs	**Total SAES**	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Related to study drug	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Related to study drug and unexpected	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Total AES*	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Related to study drug	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Total Deaths	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
SAEs	**Cardiac Arrhythmia**	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Cardiac General	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Gastrointestinal	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Etc…..	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
AEs	**Cardiac Arrhythmia**	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Cardiac General	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Gastrointestinal	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
	Etc…..	n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
Adverse Reactions		n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)
Serious Adverse Reactions		n	n	n	n	n(%)	n(%)	n(%)	n(%)	xx.x (xx.x – xx.x)

*Secondary Outcome

Note: Table will also be presented by comparison (i.e. HTS vs No HTS and Carbocisteine vs No Carbocisteine)

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APPENDIX 2: QOL-B SCORING

Manual Scoring Instructions for QOL-B Version 3.1

Step 1: Item-by-item responses

The values assigned to participants' responses for each question are listed below. Enter them on the Item-by-Item Worksheet.

For questions 1 – 4: A lot of difficulty = 1, Moderate difficulty = 2, A little difficulty = 3, No difficulty = 4
For questions 5 – 11: Always = 1, Often = 2, Sometimes = 3, Never = 4
For questions 12 – 15: Use the assigned number designated for each specific response
For questions 16 – 26: Completely true = 1, Mostly true = 2, A little true = 3, Not at all true = 4
For question 27: Use the assigned number designated for each specific response
For question 28: Always = 1, Often = 2, Sometimes = 3, Never = 4
For questions 29 – 31: A lot = 1, A moderate amount = 2, A little = 3, Not at all = 4
For question 32: Clear = 1, Clear to yellow = 2, Yellowish-green = 3, Brownish-dark = 4, Green with traces of blood = 4, Don't know = 6
For questions 33 – 37: Always = 1, Often = 2, Sometimes = 3, Never = 4

Step 2: Scoring multiple responses or skipped questions

If two responses are marked and there is no opportunity to ask the respondent which one is correct, the **worst response** should be selected for data entry and scoring. This provides a conservative estimate of their response to this item. For example, item #29 asks: "Have you felt congestion in your chest?" The response choices range from "A lot" to "Not at all." If the respondent marks "a lot" and "a moderate amount" you should enter "a lot" for this question.

Please note that some items are reverse-keyed and therefore, the worst response is not necessarily the lower number.

If participants skip a question, do not assign a response value (i.e. leave it blank).

Step 3: Scaling item 32 and reverse coding
Item 32 (resp32) has 5 possible answers that are scored and all other items on the QOL-B questionnaire have only 4 possible answers. Possible scores for resp32 are 1, 2, 3, 4, 5 and 6, whereas for other questions the possible scores are 1, 2, 3, and 4.
Resp32 and eight other items are also reverse coded; because of the wording for these particular items, reverse coding is necessary to make higher scores correspond to better health outcomes. Reverse coding is conducted for resp32, and for health5, vital8, treat12, treat14, health15, role20, health24, and role27. These items are marked with an asterisk on the Item-by-Item Worksheet and the reverse-coded values are shown in the box on the worksheet.

For item 32:
Original value = Reverse-coded value
1 = 4
2 = 3
3 = 2
4 = 1
6 = Not scored

For item 19:
"doesn't apply" = Not scored

For items 5, 8, 12, 14, 15, 20, 24, 27:
Original value = Reverse-coded value
1 = 4
2 = 3
3 = 2
4 = 1

Step 4: Preparing to calculate scaled scores and missing values

Transfer the values from the Item-by-Item Worksheet to the Scaled Score Worksheet. For reverse-coded items, use the reverse-coded values. Do not enter any values for missing responses; leave the line blank. If the responses are missing for more than half the items in a scale, the score for that scale should not be calculated. Missing values are not imputed. Note that missing responses within a scale will change the number of points corresponding to a change of one answer category for one item for that respondent.

Step 5: Calculate the scaled scores
Calculate scores for the eight QOL-B domains using the formulas on the Scaled Score Worksheet. Note that a total QOL-B score is not calculated.

Item-by-Item Worksheet
Numbers correspond to items on the QOL-B Version 3.1 questionnaire. Fill in the values using the scoring rules described in steps 1 – 3.

1. _____
2. _____
3. _____
4. _____
5.* _____=_____
6. _____
7. ____
8.*_____=_____
9. _____
10. ____
11. ____
12.*____=_____
13. ____
14.*____=_____
15.*____=_____
16. ____
17. ____
18. ____
19. ____
20.*____=_____
21. ____
22. ____
23. ____
24.*____=_____
25. ____
26. ____
27.*____=_____
28. ____
29. ____
30. ____
31. ____
32.*____=_____
33. ____
34. ____
35. ____
36. ____
37. ____

***Reverse-Coded Values**

For items 5, 8, 12, 14, 15, 20, 24, 27:

Original Value = Reverse-Coded Value 1 =
4
2 = 3
3 = 2
4 = 1

For item 32:

Original Value = Reverse-Coded Value 1 =
4
2 = 3
3 = 2
4 = 1
6 = Not scored

Scaled Scores Worksheet – Page 1 of 3

Enter the values from the Item-by-Item Worksheet. Use the reverse-coded values, if applicable. Do not enter any values for missing responses; leave the line blank.
Assess the number of missing values and calculate scores as described in Steps 4 and 5 (see page 2).

Physical Functioning Domain (5 items)
1. ____
2. ____
3. ____
4. ____
16. ___

If 3 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _
mean of responses

Role Functioning Domain (5 items)
17. ___
20. ___
25. ___
27. ___
28. ___

If 3 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _
mean of responses

Vitality Domain (3 items) 6. ___
8._____
9. ____

If 2 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _
mean of responses

Scaled Scores Worksheet – Page 2 of 3

Emotional Functioning Domain (4 items) 7. __
10. ___
11. ___
23. ___

If 3 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _ mean of responses

Social Functioning Domain (4 items)
18. ___
19.____(* “doesn’t apply” = Not scored)
22. ___
26. ___

If 3 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _ mean of responses

Treatment Burden Domain (3 items)
12. ___
13. ___
14. ___

If 2 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _ mean of responses

Health Perceptions Domain (4 items) 5. _____
15. ___
21. ___
24. ___

If 3 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _ mean of responses

Scaled Score Worksheet – Page 3 of 3

Respiratory Symptoms Domain (9 items)
29. ___
30. ___
31. ___
32. ___
33. ___
34. ___
35. ___
36. ___
37. ___

If 5 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = __ mean of responses

Note: No total score is calculated.