MucAct

What is the clinical effectiveness and cost-effectiveness of nebulised 7% sodium chloride in patients with chronic obstructive pulmonary disease?

**Statistical Analysis Plan**

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|---|---|
| **SAP Version No** | 1.0 |
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| Number | Name | Date involvement started | Date involvement finished | Notes (optional) |
|---|---|---|---|---|
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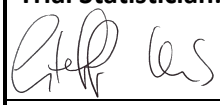
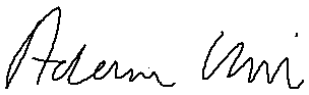
| SAP Approval Signatures | |
|---|---|
| **Trial Statistician:**  | **Date Approved:** 22-May-2025, 10:05 |
| **Chief Investigator:**  | **Date Approved:** 22-May-2025, 10:05 |

| **SAP Document History** | | |
|---|---|---|
| **Version No** | **Date** | **Summary of Revisions** |
| 1.0 | 22May2025 | Initial Creation |
| | | |

# Table of Contents

## List of Abbreviations

| Abbreviation | Full name |
|---|---|
| ACBT | Active Cycle Breathing Technique |
| ACCORD | Academic and Clinical Central Office for Research and Development |
| AE | Adverse Event |
| CAT | COPD Assessment Test |
| cm | Centimetres |
| COPD | Chronic Obstructive Lung Disease |
| ECTU | Edinburgh Clinical Trials Unit |
| FEV | Forced Expiratory Volume |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| HR | Hazard Ratio |
| ITT | Intention to Treat |
| Kg | Kilogramme |
| L | Litres |
| LCQ | Leicester Cough Questionnaire |
| Mg | Metre |
| MucAct | Trial acronym for 'What is the clinical effectiveness and cost-effectiveness of nebulised 7% sodium chloride in patients with chronic obstructive pulmonary disease?' |
| QC | Quality Control |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software |
| SD | Standard Deviation |
| SGRQ | St George's Respiratory Questionnaire |
| SOP | Standard Operating Procedure |
| URTI | Upper Respiratory Tract Infection |
| WURSS-24 | Wisconsin Upper Respiratory Symptom Survey-24 |
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# 1. Introduction

This document details the criteria to be used for the definition of the analysis population and the statistical methodology for analysis for the MucAct trial, a 2-arm 1:1-randomised parallel-group multicentre prospective open-label trial of nebulised 7% sodium chloride plus Active Cycle Breathing Technique (ACBT) compared with carbocisteine plus ACBT in patients with Chronic Obstructive Lung Disease (COPD) that have either chronic bronchitis and/ or associated bronchiectasis, who have self-reported difficulty self-expectorating. The aim was to recruit 860 patients, but the study closed early due to slow recruitment, having recruited 206 participants. The randomisation system was stratified by current smoking status (never smoked and ex-smoker versus current smoker) and COPD severity classified by Global Initiative for Chronic Obstructive Lung Disease (GOLD, classes 1 and 2 versus 3 and 4). Randomisation was by variable blocks of sizes 4, 6 and 8. The probability of each of these block sizes occurring was a third.

This document has been compiled according to the Edinburgh Clinical Trials Unit (ECTU) standard operating procedure (SOP) "Statistical Analysis Plans" ECTU_ST_04 and has been written based on information contained in the study protocol version 5.0, dated 1 May 2023.

# 2. Statistical Methods section from the protocol

*The primary analysis of the primary outcome will be based on an intention-to treat population and will use linear regression (with appropriate transformations to achieve Normality) to compare the 12-month CAT scores between allocated treatment groups, adjusting for baseline CAT score and stratification variables. Statistical significance will be at $p \leq 0.05$, and tests will be 2-sided tests for a difference. The adjusted difference in the mean CAT scores between treatment groups, plus its 95% confidence interval will be presented. If the level of missing data is high enough that the method of accounting for it might influence the results, then we will use multiple imputation, assuming data are missing at random. Similar methods will be used for continuous secondary outcome measures. Time to event will be analysed using Cox proportional hazards, if the assumptions of proportionality hold. All statistical analyses will be fully specified in a comprehensive Statistical Analysis Plan, authored by statisticians blind to accruing unblinded results and signed off prior to database lock. The choice of methods in this plan will consider the accruing blinded data (e.g. whether scales are Normally distributed, whether missingness requires accounting for in analysis). Processes will follow relevant ECTU and ACCORD Standard Operating Procedures and Working Practice Documents for Clinical Trials of an Investigational Medicinal Product, including involving sufficient statisticians in the study to allow for appropriate blinding where needed.*

# 3. Overall Statistical Principles

## 3.1 General principles

Categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, median, standard deviation (SD), minimum, maximum, lower and upper quartiles and number of patients with an observation (N). Data will be split by intervention arm and time-point where applicable.

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level. 95% (2-sided) confidence intervals will be presented. All analyses are testing superiority, rather than equivalence or non-inferiority.

Where there is missing data for an outcome variable, in the first instance, those records will be removed from any formal statistical analysis relating to that outcome variable (complete case analysis), unless otherwise specified. If the level of missing data is high enough that the method of accounting for it might influence the results, then we will use multiple imputation ('*proc mi'* in SAS), assuming data are missing at random and including the same variables as in the complete case analysis.
In tabulations, numbers of missing observations will be provided, but percentages will not include them.

For time-to-event analyses, the date that the patient was followed up to (i.e. date used for patients who do not have an event), will be taken as the latest date available, taken from the available dates in the database.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots. If the distributional assumptions for the parametric approach are not satisfied, further data transformation (to alleviate substantial skewness (i.e. normalizing) or to stabilise the variance), or other suitable methods will be considered. This will be documented in the statistical results report together with the reasoning supporting the action taken, if applicable.

All analyses and data manipulations will be carried out using the most up to date version of SAS available.

## 3.2 Adjustment for covariates

Where possible, analyses of primary and secondary outcomes will be adjusted for the randomisation stratification variables: smoking status and GOLD class. Smoking status will be adjusted for as never smoked and ex-smoker versus current smoker, and COPD severity classified by GOLD class as classes 1 and 2 versus 3 and 4).

Where appropriate, and where possible, analyses will be adjusted for baseline measurement of the outcome being analysed.

If an adjusted model does not converge due to the number of adjustment variables, then the adjustment variables will be added in the following order until no more can be added: baseline value, GOLD class, smoking status.

Unadjusted analyses will also be presented.

## 3.3 Analysis populations

The analysis populations defined for the statistical reporting of the trial is as follows:

| | |
|---|---|
| **All screened** | All screened patients. |
| **Intention to treat (ITT)** | All randomised patients, analysed according to the trial arm to which they were originally assigned. |
| **Safety** | The safety population will include all patients who were randomised and had at least one dose of IMP or placebo. Patients will be summarised according to treatment received. |

# 4. List of Analyses

***Note: Unless otherwise specified, no formal statistical testing will be performed and data summaries and analyses will be presented overall and by the allocated intervention arm.***

## 4.1 Recruitment and retention

Analysis population = All screened

Graph of cumulative number of patients allocated to a trial arm over time, showing total trial [both randomised arms combined].
Numbers of patients at each stage of the study, will be tabulated, to enable presentation in a flow chart. We will report the number of patients allocated to each trial arm, and present both arms combined.

We will report:

- number of patients screened;
- Number of participants eligible to take part in the study.
- number of patients in whom full consent was obtained;
- number of patients who were allocated to any trial arm
- number of allocated patients who withdrew consent including to use of data;
- number of patients allocated to each trial arm;
- number of patients included in analysis of primary outcome at 6 and 12 months, by allocated trial arm, with reason for not being included in the primary outcome analysis.

We will also report the date of first and last patient allocated to a trial arm. We will produce a tabulation of numbers of patients allocated to any trial arm by study site.

## 4.2 Baseline characteristics

Analysis population = ITT.

The following baseline characteristics are to be tabulated by allocated trial arm, and overall, as follows. No formal statistical testing of the baseline characteristics will be performed. The first relevant observation will be presented if more than one observation was collected.

Demographics
Age at randomisation (years, continuous)
Age at randomisation (years, categorised: 18-64, 65-84, >=85)
Sex at birth [Male, Female]

Medical History
Asthma [Yes/No/ Unknown]
Bronchiectasis [Yes/No/Unknown]
Interstitial Lung Disease [Yes/No/Unknown]
Peripheral Vascular Disease [Yes/No/Unknown]
Hypertension [Yes/No/Unknown]
Diabetes mellitus [Yes/No/Unknown]
Ischaemic heart disease [Yes/No/Unknown]
Stroke [Yes/No/Unknown]
Rheumatological disease requiring disease modifying therapy [Yes/No/Unknown]

Inflammatory bowel disease [Yes/No/Unknown]

Smoking History
Smoking History [Current, Ex-smoker, Never]
Years smoked
Average cigarettes per day
No of packs
Pack years
Length of time since stopped smoking (years]

GOLD Classification
GOLD Classification [Class I, Class II, Class III, Class IV]

Physical Measurements
Height (cm)
Weight (kg)
BMI (kg/m2) – to be calculated

Baseline measurements of outcomes
CAT score (no units, continuous)
LCQ (no units, continuous)
SGRQ (no units, continuous)
FEV1 (% of predicted, continuous)
FEV1 (actual, L, continuous)
FEV1 (predicted, L, continuous)
FEV6 (same description as FEV1)
Ratio of FEV1/FEV6, for all 3 types of measure

## 4.3 Trial intervention details, and adherence

Analysis population = ITT.
No formal statistical testing will be performed. The following will be presented:

**Adherence**
By trial arm, N got carbocysteine (any dose), N got no carbocysteine but got saline, N got no treatment.

Table of adherence over time: so that each timepoint adds to 206, and we indicate N still in the trial and took all med, N in the trial and took some med, N in trial but had stopped med permanently, N had left the trial.

Table: Missed doses – tabulate n and % of randomised participants with missed doses at each time point – Combine ‘Missing’, ‘Unavailable’ and ‘Unknown’ into ‘Unknown’, so we have Yes/No/Unknown.

Table: Number of doses missed, for those who said they had missed a dose – tabulate n and % of randomised participants who had 1, 2, 3, 4, or 5 or more missed doses at each time point – Combine ‘Missing’, ‘Unavailable’ and ‘Unknown’ into ‘Unknown’, so we have 1/2/3/4/>=5/Unknown.

Table: Has the participant permanently stopped taking their medication? tabulate n and % of randomised participants with missed doses at each time point – Combine 'Missing', 'Unavailable' and 'Unknown' into 'Unknown', so we have Yes/No/Unknown.

## 4.4 Primary outcome.

Analysis population = ITT.

The primary outcome is the COPD Assessment Test (CAT), measured at 12 months after randomisation.

Table: CAT scores at baseline, 12 months, and the change from baseline to 12 months [continuous]

***Principal analysis***

The primary analysis of the primary outcome will use linear regression (with appropriate transformations to achieve Normality, if necessary) to compare the 12-month CAT scores between allocated treatment groups, adjusting for baseline CAT score and stratification variables. Statistical significance will be at p≤0.05, and tests will be 2-sided tests for a difference. If the level of missing data is high enough that the method of accounting for it might influence the results, then we will use multiple imputation ('*proc mi'* in SAS), assuming data are missing at random and including the same variables as in the primary outcome model.

An analysis adjusting for baseline CAT score only will also be presented, as a sensitivity analysis.

The number of patients with outcome measured (by trial arm) will be tabulated, and the following statistics will be presented: adjusted difference in the mean CAT scores between treatment groups (and 95% confidence interval, p value), unadjusted difference in the mean CAT scores between treatment groups (and 95% confidence interval, p value).

## 4.5 Secondary outcomes

4.5.1. COPD Assessment Test (CAT), measured at 6 months after randomisation.

Table: CAT scores at baseline, 6 months, and the change from baseline to 6 months [continuous]

Analysis will use linear regression (with appropriate transformations to achieve Normality, if necessary) to compare the 6-month CAT scores between allocated treatment groups, adjusting for baseline CAT score and stratification variables. Statistical significance will be at p≤0.05, and tests will be 2-sided tests for a difference. If the level of missing data is high enough that the method of accounting for it might influence the results, then we will use multiple imputation ('*proc mi'* in SAS), assuming data are missing at random and including the same variables as in the original COPD assessment model.

An analysis adjusting for baseline CAT score only will also be presented, as a sensitivity analysis.

The number of patients with outcome measured (by trial arm) will be tabulated, and the following statistics will be presented: adjusted difference in the mean CAT scores between treatment groups (and 95% confidence interval, p value), unadjusted difference in the mean CAT scores between treatment groups (and 95% confidence interval, p value).

4.5.2. Leicester Cough Questionnaire.

Leicester Cough Questionnaire at 6 months and 12 months. We will assess the mean change from baseline to 6 months and baseline to 12 months between total LCQ scores between groups but also compare the number that have a 1.3 unit or more improvement in total LCQ scores.

Leicester Cough Questionnaire at 12 months:
Table: scores at baseline, 12 months, and the change from baseline to 12 months [continuous]

An analysis will be performed using linear regression (with appropriate transformations to achieve Normality, if required) to compare the 12-month LCQ scores between allocated treatment groups, adjusting for baseline LCQ score and stratification variables. Statistical significance will be at p≤0.05, and tests will be 2-sided tests for a difference. If the level of missing data is high enough that the method of accounting for it might influence the results, then we will use multiple imputation ('*proc mi'* in SAS), assuming data are missing at random and including the same variables as in the original 12 month LCQ assessment model.
An analysis adjusting for baseline LCQ score only will also be presented, as a sensitivity analysis.

The number of patients with outcome measured (by trial arm and by time point) will be tabulated, and the following statistics will be presented: adjusted difference in the mean LCQ scores between treatment groups (and 95% confidence interval, p value), unadjusted difference in the mean LCQ scores between treatment groups (and 95% confidence interval, p value).

Leicester Cough Questionnaire at 6 months:
Table: scores at baseline, 6 months, and the change from baseline to 6 months [continuous]

An analysis will be performed using linear regression (with appropriate transformations to achieve Normality) to compare the 6-month LCQ scores between allocated treatment groups, adjusting for baseline LCQ score and stratification variables. Statistical significance will be at p≤0.05, and tests will be 2-sided tests for a difference. If the level of missing data is high enough that the method of accounting for it might influence the results, then we will use multiple imputation ('*proc mi'* in SAS), assuming data are missing at random and including the same variables as in the original 6 month LCQ assessment model.

An analysis adjusting for baseline LCQ score only will also be presented, as a sensitivity analysis.

The number of patients with outcome measured (by trial arm) will be tabulated, and the following statistics will be presented: adjusted difference in the mean LCQ scores between treatment groups (and 95% confidence interval, p value), unadjusted difference in the mean LCQ scores between treatment groups (and 95% confidence interval, p value).

Leicester Cough Questionnaire binary assessment:
The number and percentage of patients with a >=1.3 unit improvement between baseline and outcome time point will be presented; separately for 6 month and 12 month outcomes. This will be presented by treatment group, and overall. No formal statistical testing will be performed.

4.5.3. St George's Respiratory Questionnaire.
St. George's Respiratory Questionnaire at 6 months and 12 months. We will assess the mean change from baseline to 6 months and baseline to 12 months between total SGRQ scores between groups but also compare the number that have a 4 unit or more improvement in SGRQ scores between groups.

St George's Respiratory Questionnaire at 12 months:
Table: scores at baseline, 12 months, and the change from baseline to 12 months [continuous]

An analysis will be performed using linear regression (with appropriate transformations to achieve Normality, if required) to compare the 12-month SGRQ scores between allocated treatment groups, adjusting for baseline SGRQ score and stratification variables. Statistical significance will be at p≤0.05, and tests will be 2-sided tests for a difference. If the level of missing data is high enough that the method of accounting for it might influence the results, then we will use multiple imputation ('*proc mi'* in SAS), assuming data are missing at random and including the same variables as in the original 12 month SGRQ assessment model.
An analysis adjusting for baseline SGRQ score only will also be presented, as a sensitivity analysis.

The number of patients with outcome measured (by trial arm) will be tabulated, and the following statistics will be presented: adjusted difference in the mean SGRQ scores between treatment groups (and 95% confidence interval, p value), unadjusted difference in the mean SGRQ scores between treatment groups (and 95% confidence interval, p value).

St George's Respiratory Questionnaire at 6 months:
Table: scores at baseline, 6 months, and the change from baseline to 6 months [continuous]

An analysis will be performed using linear regression (with appropriate transformations to achieve Normality) to compare the 6-month SGRQ scores between allocated treatment groups, adjusting for baseline SGRQ score and stratification variables. Statistical significance will be at p≤0.05, and tests will be 2-sided tests for a difference. If the level of missing data is high enough that the method of accounting for it might influence the results, then we will use multiple imputation ('*proc mi'* in SAS), assuming data are missing at random and including the same variables as in the original 6 month SGRQ assessment model.
An analysis adjusting for baseline SGRQ score only will also be presented, as a sensitivity analysis.

The number of patients with outcome measured (by trial arm) will be tabulated, and the following statistics will be presented: adjusted difference in the mean SGRQ scores between treatment groups (and 95% confidence interval, p value), unadjusted difference in the mean SGRQ scores between treatment groups (and 95% confidence interval, p value).

St George's Respiratory Questionnaire binary assessment:
The number and percentage of patients with a ≥4 unit improvement between baseline and outcome time point will be presented; separately for 6 month and 12 month outcomes. This will be presented by treatment group, and overall. No formal statistical testing will be performed.

4.5.4. Leicester Cough Questionnaire and St George's Respiratory Questionnaire combined assessment.
The number and percentage of patients with a ≥1.3 unit improvement in the Leicester Cough Questionnaire or a ≥4 unit improvement in the St George's Respiratory Questionnaire between baseline and outcome time point will be presented; separately for 6 month and 12 month outcomes. This will be presented by treatment group, and overall. No formal statistical testing will be performed.

4.5.5. Number of exacerbations over a 12 month period requiring antibiotic therapy and/or systemic steroid treatment.

A table of the number of exacerbations split by treatment group and overall shall be presented as categories (for example: 0 exacerbations; 1; 2; 3 or more exacerbations) along with a Chi-square test for trend.

4.5.6. Time to first exacerbation requiring antibiotic therapy and/or systemic steroids over 12 months
The outcome will be measured as the time between allocation to trial arm and the first relevant event. Patients discontinuing the study (for any reason) prior to reaching the outcome will have their time to outcome censored at the last contact date or date of death.
If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and the primary outcome will be analysed using Cox proportional hazard regression. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The principal analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.
The number of patients with an outcome event (by trial arm) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% confidence interval, p value), unadjusted HR (and 95% confidence interval, p value). A Kaplan-Meier plot will be produced, showing results by allocated trial arm - The p-value on the plot will be the p-value from the adjusted Cox regression analysis above.

4.5.7 Proportion of exacerbations needing antibiotic therapy over 12 months
Table: Split by randomised treatment. [continuous]
For each person, will have n exacerbations over a 12 month period requiring antibiotic therapy (from 4.5.5), and n exacerbations over a 12 month period. Divide the former by the latter to get a proportion.
Tabulate: N with no exacerbations, N with ≥1 exacerbation
Tabulate: For those with ≥1 exacerbations, tabulate the proportion of those needing antibiotic therapy over 12 months.
A first examination on these results will determine what analysis is appropriate. If there is enough data for the data to be treated continuously then linear regression may be appropriate, however if it is more appropriate for the data to be grouped into categories then a chi-square test for trend or a comparison of proportions analysis may be more appropriate.

4.5.8. Number of upper respiratory tract infections over 12 months assessed using the Wisconsin Upper Respiratory Symptom Survey-24 (WURSS-24)

Tabulate: N with no URTI, N with ≥1 UTRI
Tabulate: Number of UTRIs per participant
A first examination on these results will determine what analysis is appropriate. If there is enough data for the data to be treated continuously then linear regression may be appropriate, however if it is more appropriate for the data to be grouped into categories then a chi-square test for trend or a comparison of proportions analysis may be more appropriate.

4.5.9. Overall and COPD related hospital attendances/admissions over 12 months

Each tabulation is presented by treatment group and overall:

- Tabulate: N with at least one instance of hospital attendance/admission over 12 months.
- Tabulate: Of those with at least one instance, number of instances of reported hospital attendances/admissions over 12 months.

- Tabulate: Of the number of hospital attendances/admission, number of these that are recorded to be COPD related.
- Tabulate: Total number of COPD hospital attendances/admissions.

4.5.10. Frequency of use of nebulised 7% sodium chloride in exacerbations.
Referring to the concomitant medications table, tabulate the number of participants who used nebulised 7% sodium chloride in exacerbations by treatment group and overall. Numbers are expected to be low here so analysis shall be decided at the final analysis.

4.5.11. Proportion being infected with a potential pathogenic organism and viruses at 6 months and 12 months (from sputum samples and combined nose and throat swabs (if taken as part of standard care))
Depending on the data available at the time of analysis:
Tabulate: Proportion of participants with a positive swab or sputum sample at each timepoint (i.e. baseline, 6m, 12m). A logistic regression analysis shall be performed to look at the change from baseline at 6 months and 12 months separately.

4.5.12. Viral transmissibility (household contacts to participant and participant to household contacts)

The following shall be tabulated:

- Number of participants who have completed the viral transmissibility form
- Total number of viruses recorded
- Number of participants with at least one virus
- Number of viruses that are linked with an exacerbation

No formal statistical analysis shall be performed on this data.

4.5.13. Stable or improved Forced Expired Volume in 1 second (FEV1) and Forced Expired Volume in 6 seconds (FEV6), at 6 months and 12 months

The following shall be performed for both FEV1 and FEV6 separately:

To examine the change in baseline to 6 and 12 months separately, a linear regression (with appropriate transformations to achieve Normality) to compare the 6 and 12-month FEV1 Actual scores between allocated treatment groups, adjusting for baseline FEV1 Actual score and stratification variables. Statistical significance will be at $p \leq 0.05$, and tests will be 2-sided tests for a difference.

Health economic analyses will not be performed by the ECTU statistical team, and are not described in this SAP.

## 4.6 Safety.

Analysis population = safety.
Total N AEs, N patients with at least 1 AE, N AEs per participant. Summarise causality, severity, seriousness. N SAEs, patients with at least 1 SAE, N SAEs per participant. Line listing.

## 5. Validation and QC

The following will be done by a second statistician:

1. Separate programming and checking of primary outcome results and conclusions.

2. The statistical report will be read and sense-checked for accuracy and consistency.

## 6. Data sharing

A file, or set of files, containing the final data will be prepared, along with a data dictionary. These will be made available to the Chief Investigator after the primary results paper based on the final statistical report has been published.

Note that if any participants have opted out of sharing anonymised data, then their data must not be included in any dataset for sharing. This is an option for this study so must be checked.

# MucAct_SAP v1.0 22May2025

Final Audit Report 2025-05-22

| | |
|---|---|
| Created: | 2025-05-22 (British Summer Time) |
| By: | Steff Lewis (Steff.Lewis@ed.ac.uk) |
| Status: | Signed |
| Transaction ID: | CBJCHBCAABAAta3J3z92nkNJUhHGcK1fDMmRAqRq3YC_ |

## "MucAct_SAP v1.0 22May2025" History

Document created by Steff Lewis (Steff.Lewis@ed.ac.uk)
2025-05-22 - 09:58:57 GMT+1- IP address: 192.41.125.254

Document emailed to Steff Lewis (Steff.Lewis@ed.ac.uk) for signature
2025-05-22 - 10:01:32 GMT+1

Document e-signed by Steff Lewis (Steff.Lewis@ed.ac.uk)
Signature Date: 2025-05-22 - 10:02:14 GMT+1 - Time Source: server- IP address: 192.41.125.254

Document emailed to adam.hill@nes.scot.nhs.uk for signature
2025-05-22 - 10:02:15 GMT+1

Email viewed by adam.hill@nes.scot.nhs.uk
2025-05-22 - 10:02:39 GMT+1- IP address: 77.101.234.155

Signer adam.hill@nes.scot.nhs.uk entered name at signing as Professor Adam Hill
2025-05-22 - 22:17:36 GMT+1- IP address: 77.101.234.155

Document e-signed by Professor Adam Hill (adam.hill@nes.scot.nhs.uk)
Signature Date: 2025-05-22 - 22:17:38 GMT+1 - Time Source: server- IP address: 77.101.234.155

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