Supplementary Online Content 1

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Study Protocol

PROTOCOL TITLE '**Effectiveness of routine nebulisation of mucolitycs and bronchodilators in mechanically ventilated intensive care patients**'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS	
ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
ARDS	**Acute Respiratory Distress Syndrome**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
CVVH	**Continuous Veno-Venous Hemofiltration**
DSMB	**Data Safety Monitoring Board**
GCP	**Good Clinical Practice**
IC	**Informed Consent**
ICU	**Intensive Care Unit**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NAC	**N-Acetylcysteine**
PEEP	**Positive End Expiratory Pressure**
(S)AE	**(Serious) Adverse Event**
SDD	**selective digestive tract decontamination**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
VAP	**Ventilator Associated Pneumonia**

VFDs	**Ventilator Free Day's**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

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SUMMARY

Rationale: Routine nebulisation of mucolytics and bronchodilators is a frequently used preventive strategy in intubated and mechanically ventilated intensive care unit (ICU) patients. The aim of routine nebulisation of mucolytics and bronchodilators is to prevent sputum plugging and as such atelectasis. It is highly uncertain whether this expensive strategy is effective, and whether we should restrict nebulisation of mucolytics and bronchodilators to those patients in whom sputum plugging is a problem.

Hypothesis: We hypothesize that a strategy restricting nebulisation to patients with sputum plugging is as effective as, but cheaper and safer than, a strategy using routine nebulisation in all intubated and mechanically ventilated ICU patients.

Objective: The primary objective of this study is to determine the effectiveness of a strategy using routine nebulisation of mucolytics and bronchodilators as compared to a strategy that uses nebulisation only on clinical indication in intubated and ventilated ICU patients. In addition we aim to compare safety, and related health care costs of both strategies.

Study design: This study is an investigator initiated multicenter randomized controlled non-inferiority trial in intubated and ventilated ICU patients.

Study population: Consecutive intubated and ventilated adult ICU patients with an anticipated duration of ventilation > 24 hours.

Intervention: Routine nebulisation of mucolytics and bronchodilators administered every 6 hours (i.e., in all patients for the complete duration of intubation and mechanical ventilation) is compared to nebulisation of mucolytics and bronchodilators on strict clinical indication (i.e., only if a patient shows to have problems with sputum clearance or bronchospasm).

Main study parameters/endpoints: The primary endpoint is the number of ventilator-free days (VFDs), defined as the number of days from day 1 to day 28 after ICU admission and start of mechanical ventilation. Secondary endpoints include ICU and hospital length of stay and mortality, incidence of secondary ARDS, ventilator-associated pneumonia, atelectasis and side effects of nebulisation of mucolytics and bronchodilators. Also, related health care costs will be estimated with a cost benefit – and budget impact analysis.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Benefits and risks of routine nebulisation of mucolytics and

bronchodilators in mechanical ventilated patients are unknown. This procedure is suggested to prevent endotracheal tube occlusion and sputum plugging, by diluting sputum, although no solid research is conducted. Nebulisation of acetylcysteine could induce bronchospasm while nebulisation of salbutamol may be associated with tachycardia, tachyarrhythmia, tremor and agitation.

1. INTRODUCTION AND HYPOTHESIS

1.1 Routine nebulisation in mechanical ventilated patients:

Routine nebulisation of mucolytics and bronchodilators is a frequently used preventive strategy in intubated and mechanically ventilated intensive care unit (ICU) patients[1–3] This strategy is suggested to dilute pulmonary secretions and as such to prevent sputum plugging in sedated and paralyzed patients who are less able to clear their airways through coughing[1–4].

1.2 Uncertainty over the effectiveness and side effects:

Whether this preventive strategy truly benefits ICU patients is highly unknown. There is no evidence that the routine nebulisation of mucolytica and bronchodilators reduces the risk of tube obstruction, duration of ventilation or the risk of ventilator induced pneumonia. Randomized controlled trials have addressed neither the clinical efficacy nor the economic consequences of routine nebulisation of mucolytics and bronchodilators in intubated and ventilated ICU patients. Notably, as with every pharmacological intervention, nebulisation of mucolytics and bronchodilators carries risks of side effects. First, there is the risk for pulmonary related adverse effects, including increased airway resistance due to bronchoconstriction [1] and increased risk for development of ventilator–associated pneumonia[5]. Second, nebulisation interferes with the patient-ventilator interaction, which may lead to hypoventilation, decreased oxygenation and anxiety[6]. Additionally, nebulizing mucolytics and bronchodilators is associated with systemic effects and may contribute to the generation of tachycardia, tachyarrhythmia -especially in patients with underlying cardiac disorders, although results are inconclusive-, tremor, and agitation[1,7–10].

1.3 Rational for this study:

The care for ventilated ICU patients has changed fundamentally. Indeed, while deep hypnosedation and neuromuscular blocking agents were used in almost all intubated and ventilated ICU patients in the early years of ICU medicine, nowadays these patients preferably receive analogo-sedation and almost never neuromuscular blocking agents. While deep hypno-sedation and paralysis could promote stasis of airway secretions, analgo–sedation increasingly allows patients to cough and as

such clear the airways from sputum themselves. Also, ICU patients are mobilized more early in the course of disease[11], which could prevent atelectasis.

We hypothesize that a strategy restricting nebulisation to patients with sputum plugging is as effective as, but cheaper and safer than a strategy using routine nebulisation in all intubated and mechanically ventilated ICU patients.

2. OBJECTIVES

2.1 Primary Objective:

The primary objective of this study is to determine whether a strategy using nebulisation of mucolytics and bronchodilators on strict clinical indication has equal effectiveness compared to routine nebulisation in intubated and ventilated ICU patients, in terms of number of ventilator-free days.

2.2 Secondary Objectives

Secondary objectives are to compare the effects of both nebulisation strategies on ICU- and hospital length of stay, mortality, incidence of secondary ARDS, ventilator-associated pneumonia, atelectasis, and side effects of nebulisation of mucolytics and bronchodilators. Also, related health care costs will be estimated.

3. STUDY DESIGN

This will be an investigator–initiated, multi–center, randomized, controlled, parallel two group, non-inferiority trial in intubated and ventilated adult ICU patients. A total of 950 patients in 6 participating centers will be included.

4. STUDY POPULATION

4.1 Population

Consecutive intubated and ventilated adult intensive care patients with an anticipated ventilation duration of minimal 24 hours will be recruited at onset of ventilation. Patients are recruited in the ICUs of 6 centers in The Netherlands. We will randomize a total of 950 patients. It is expected that each participating center will randomize approximately 160 patients.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

- Age 18 year or older;
- Expected duration of intubation and ventilation > 24 hours, as judged by the ICU staff at time of admission;
- Written informed consent.

4.3 Exclusion criteria

A patient who meets any of the following criteria will be excluded from participation in this study:

- Age less than 18 years;
- Ventilation before present ICU admission (though short-term ventilation in the emergency room or in the operation room for general anesthesia during surgery is allowed);
- Suspected or confirmed pregnancy;
- Diagnosed with lung diseases for which inhalation therapy and/or oral steroids are used;
- Diagnoses of: Guillain-Barré syndrome, complete spinal cord lesion or amyotrophic lateral sclerosis, Multiple Sclerosis, Myasthenia Gravis
- Known allergy for acetylcysteine or salbutamol

4.4 Sample size calculation

Group size calculation is focused on demonstrating non-inferiority. When the sample size in each group is 445 (890 patients in total), an one-sided non-inferiority test (targeted at 0.05) for log-transformed normalized data has 80% power to reject the null hypothesis that the number of ventilator-free days (VFDs) in the intervention group (nebulisation on strict clinical indication) is inferior to the number of VFDs in the control group (routine nebulisation) by a margin of 10% and a coefficient of variation of 0.70, in favor of the alternative hypothesis that the number of VFDs in the intervention group is non-inferior. The choice for a margin of 10% is motivated by what we consider acceptable from a clinical point of view as the maximal acceptable reduction of the ventilator-free period for non-inferiority. Clinically this margin means that an increase of > 10% in the duration of mechanical ventilation will reduce the ventilator free days with > 12 hours (calculated over the mean duration of mechanical ventilation of 5 days) which will be considered inferior, assuming that the data will be analyzed in the log scale using t-test for differences in means at the 5% level. To allow for an anticipated drop out of approximately 5%, a number of 475 (950 in total) patients will be included in each group.

R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/. Sample size is calculated in R (package PowerTost)

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Patients will be randomized in a 1:1 ratio to receive either:

- 'routine nebulisation', i.e. nebulisation of mucolytics and bronchodilators, administered every 6 hours (i.e., 4 times per day) for the complete duration of ventilation, or
- 'nebulisation on strict clinical indications only', i.e.nebulisation of mucolytics in case of occurrence of persistent thick and tenacious sputum (Suzakawa criteria class 3[13]), and only after active humidification is set. Nebulisation of bronchodilators in case of occurrence of brochospasm and only when signs and symptoms of bronchospasm (wheezing, increased airway pressures, increasing airway resistance, up sloping curve of de end tidal CO_2 monitoring) are confirmed. The decision to start nebulisation on strict clinical indications will be made by the attending ICU–physician and should be evaluated daily. In case the clinical indication no longer exists, the therapy should be stopped (appendix 3).

Each routine nebulisation contains of a 3 mL-solution of acetylcysteine (fluimucil 100mg/ml, a mucolytic) and a 2.5 mL solution containing salbutamol (ventolin 2.5 Nebules 2.5mg/2.5 ml, a bronchodilator).

Each nebulisation on strict indication contains of a 3 mL-solution of acetylcysteine (fluimucil 100mg/ml, a mucolytic) and/or a 2.5 mL solution containing salbutamol (ventolin 2.5 Nebules 2.5mg/2.5 ml, a bronchodilator).

The solutions are nebulized using a jet nebulizer or a vibrating mesh nebuliser depending on local standard in the participating center,which is attached to the ventilator circuit with a T-piece adaptor. Jetebulizers will be operated synchronized with the ventilator in case of an internal nebulizer or with pressured gas or oxygen from an external source in case of a ventilator without an internal nebuliser, with a flow of 3-5 L/min. If oxygen saturation is insufficient during nebulisation, pressured gas is replaced by oxygen. The nebulizer will be placed in front of the Y-piece or betweenthe Y-piece and the circuit prior to the heated humidifier or HME filter. Each nebulisation session lasts about 20 minutes. If a patient becomes able to breathe

without assistance for at least 24 hours but subsequently requires additional mechanical ventilation within a period of 28 days, the same nebulisation strategy is resumed.

5.2 Concomitant medication:

If indicated, nebulisation of other aerosol agents (antibiotics, antimycotics, ilomedine or iloprost), is allowed in both treatment groups. These agents should be administered preferably prior to the nebulisation of acetylcysteine and salbutamol, or otherwise afterwards.

5.3 Standard procedures

5.3.1 Mechanical ventilation

Attending physicians are advised to use lung–protective ventilation strategies, including the use of lower tidal volumes (≤ 6 mL/kg predicted body weight) and/or lower airway pressures (≤ 30 cmH2O). Levels of positive end–expiratory pressure (PEEP) and inspired oxygen (FiO2) are titrated on PaO2, preferably using a PEEP/ FiO2–table, and according to local guidelines. If spontaneous ventilation is well tolerated it is used from then till the end of ventilation. Thereafter, weaning from ventilation is performed by stepwise lowering of pressure–support level. Daily assessment of the patient's readiness to wean will be performed. As soon as patients are ready to be weaned from the ventilator, the pressure–support level is lowered stepwise to 5 cmH2O. A patient is assumed to be ready for extubation when the following criteria are met:

- Responsive and cooperative;
- Adequate cough reflex;
- PaO2/FiO2 of > 200 mmHg with FiO2 ≤ 40%;
- Respiratory rate of 8 to 30/minute;
- No signs of respiratory distress (i.e., marked accessory muscle use, abdominal paradox, diaphoresis, marked dyspnea);
- Pressure support level < 7 cm H2O;
- Hemodynamically stable (systolic blood pressure 80 to 160 mmHg and heart rate 40 to 130/min) and no uncontrolled arrhythmia;

- Rectal temperature > 36.0°C and < 38.0°C.

5.3.2 Tracheostomy:

Early tracheostomy has no advantage over late tracheostomy[14]. Tracheostomy is only to be performed on strict indications and preferably not earlier than 10 days after intubation.

Indications for tracheostomy are assumed:

- Failure to intubate;
- Expected duration of ventilation > 14 days;
- Glasgow Coma Score < 7 and/or inadequate swallow or cough reflex with retention of sputum;
- Severe ICU–acquired weakness;
- Prolonged or unsuccessful weaning;
- Repeated respiratory failure after extubation.

Readiness for weaning with a tracheostomy follows the same criteria as those in patients with an endotracheal tube. Although this is applied by a weaning schedule for unassisted ventilation with a tracheostomy according to the local standard of the participating centers.

5.3.3 Airway Care:

Endotracheal suction will be provided according to the local guidelines. Concomitant normal saline installation will not be applied.

The choice of method of the inhaled air humidification is left to the discretion of the participating center. Active humidification of the air inhaled will be supplied by the use of an electrically powered humidifier. Passive humidification of the air inhaled will be supplied by the use of a heat and moisture exchange (HME) filter. In case of a (relative) contra-indication for passive humidification, such as lung edema, lung bleeding or thick and tenacious secretions (Suzukawa classification[13]),active humidification will be applied. Oral care consist of combining tooth brushing and rinsing of the oral cavity every 6 hours. Head-of-bed elevation is pursued according to the IHI ventilator bundle[15], to prevent ventilator associated pneumonia.

5.3.4 Sedation and comfort protocol:

Primary goals of sedation are patient comfort, i.e. to reduce agitation, discomfort and pain, and to reduce oxygen consumption and physical resistance against daily care and examination. Insufficient sedation is associated with discomfort, pain, agitation, delirium and autodetubation[16,17]. In this matter, an analgo-sedative approach is favored over hypno-sedation, and use of bolus is favored over continuous infusion of sedating agents. Level of sedation will be determined using the Richmond Agitation Sedation Scale (RASS) [18]. Pain levels are monitored using the Numeric Rating Scale (NRS), Visual Analogue Scale (VAS), Critical Care Pain Observation Tool (CCPOT) or Behavorial Pain Scale (BPS) [19–21].

Delirium is assessed daily using a standardized tool i.e Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Checklist Screening (ICDCS) [22].

5.3.5 Fluid management:

Fluid management will be according to local guidelines. In general, patients are resuscitated using saline solutions, targeting a urine output of 0.5 – 1.0 ml/kg/hr. After the first 24 hours, fluid administration is dictated by clinical needs. Blood transfusions and blood products will be provided if necessary following local guidelines of the participating centers.

5.3.6 Nutrition

Nutrition management will be following local guidelines. Feeding will be started immediately after admission to achieve an optimal nutritional balance, based on nutritional status and BMI, with respect to sufficient protein and calorie intake. Enteral feeding will be performed using a gastric feeding tube. If retention occurs persistently, a postpyloric feeding tube will be provided. Enteral feeding is preferable to parenteral feeding.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational products:

Acetylcysteine (a mucolytic): a registered inhalation solution for disorders of the respiratory tract in which a reduction of the viscosity of the bronchial secretion is required in order to facilitate expectoration and removal of the secretion, such as bronchitis, emphysema, cystic fibrosis, and bronchiectasis [23] .

Salbutamol (a bronchodilator): a registered inhalation solution for treatment of bronchospasms, exacerbations and routine maintenance therapy in asthma and COPD[24].

6.2 Summary of findings from non-clinical studies

Little research is published about the effectiveness and safety of nebulized acetylcysteine. Despite in vitro mucolytic activity, there are no data demonstrating that nebulized acetylcysteine is an effective therapy for any lung disease [25]. Significantly increased airway resistance, excessive airway secretions and spontaneous cough where found after aerosol delivery of acetylcysteine (400mg cumulative dose) through an endotracheal tube in six mechanical ventilated cats with experimental induced asthma[26]. In addition in a rat model, administration of acetylcysteine was found to attenuate the inflammatory responses, apoptosis and ventilator induced lung injury[27]. Described observations of preclinical studies suggested reductions of pulmonary edema and alveolar clearance in ADRS with treatment of nebulized beta 2-agonists in rat models and ex vivo human lung tissue[28].

6.3 Summary of findings from clinical studies

There are no data demonstrating that nebulized acetylcysteine is an effective therapy for any lung disease[25]. Bronchodilator therapy is frequently administered in mechanically ventilated ICU patients with the aim to resolve bronchoconstriction, decrease work of breathing and relieve dyspnea. Beta-agonists enhance mucociliary clearance in normal subjects, although this advantage seems to be diminished during mechanical ventilation[10]. No significant differences were found in the number of ventilator free days between patients with ARDS/ALI who received aerosolized albuterol (salbutamol) versus placebo[29]. The assumption is that nebulisation of

bronchodilators is often performed in spite of the absence of an obvious clinical response in patients without asthma or COPD[10,30–32]

Nebulizing mucolytics and bronchodilators in mechanical ventilated patients carry the risk of side-effects. First, mucolytic drugs have been reported to provoke bronchoconstriction[1]. This risk can be reduced by pre-treatment with a bronchodilator[1]. Nausea or vomiting may be provoked by the bad odor of Acetylcysteine which is due to the release of hydrogen sulfide[33,34]. Other side effects include urticarial, pruritis, stomatitis, rhinorroe, irritation of the airways and hypersensitivity reactions, although frequencies of occurrence are not available[22]. Second, nebulizing bronchodilators is associated with adverse effects on the myocardium in COPD patients suffering from preexisting arrhythmias and hypoxemia[9]. In a study in patients with ALI/ARDS who received albuterol, modest elevated heart rates were found accompanied with a tendency towards more fluid resuscitation. Evidence of serious adverse effects including arrhythmias have not been demonstrated[28]. Other side effects of bronchodilators include, tremor, muscle cramps, headache, tachycardia and palpitations[7,23]. In addition, nebulisation interferes with the patient-ventilator interaction, which may lead to hypoventilation, decreased oxygenation and anxiety[6].

6.4 Summary of known and potential risks and benefits

Acetylcysteine reduces viscosity of mucus. A more liquid state of mucus may facilitate aspiration of secretions with suction catheters, which may be useful in intubated patients. Bronchodilators resolve bronchoconstriction, decrease work of breathing and relieve dyspnea. However, there is actually no evidence that the use of nebulized mucolytica and bronchodilators is useful in reducing the risk of tube obstruction, the duration of mechanical ventilation, or the risk of ventilator associated pneumonia. Nebulisation of acetylcysteine is associated with increased airway resistance due to bronchoconstriction [1]. Nebulisation of bronchodilators is associated with systemic effects and could contribute to the generation of tachycardia, tachyarrhythmias, tremor and agitation[7,23]. Additionally, nebulisation of aerosols in general interferes with the patient-ventilator interaction, which may lead to hypoventilation, decreased oxygenation and anxiety[6].

6.5 Description and justification of route of administration and dosage

Acetylcysteine and salbutamol will be nebulized using a jet nebulizer or a vibrating mesh nebuliser, depending on local standard in the participating center. The nebuliser is attached to the ventilator circuit with a T-piece adaptor. Jet nebilisers will be operated with pressured gas or oxygen at a flow of 3-5 L/min or with an inline flow synchronized with ventilator. The nebulizer will be placed in front of the Y-piece or between the Y-piece and the circuit prior to the heated humidifier or HME filter. Each nebulisation session lasts about 20 minutes. These two types of nebulisers were chose since we want to study current nebulisation practice but avoid additional risks by introducing a new procedure with potential serious outcomes. As a consequence we decided that, although jet nebulizers are most commonly used for nebulizing mucolytics and bronchodilators during mechanical ventilation, nebulising with a vibrating mesh nebuliser is allowed in the participating centers were this is standard practice.

6.6 Dosages, dosage modifications and method of administration

Nebulisation of mucolytics (acetylcysteine) and bronchodilators (salbutamol): a 3 mL-solution of acetylcysteine (fluimucil 100mg/ml)[23] and a 2.5 mL solution of salbutamol (Ventolin 2.5 Nebules 2.5mg/2.5 ml)[24] will be nebulised using a jet nebuliser or vibrating mesh nebuliser, which is attached to the ventilator circuit with a T-piece adaptor. These dosages are currently used in Intensive Care practice. The jet nebuliser will be operated with pressured gas at a flow of 3-5 L/min. The nebulizer will be placed in front of the Y-piece or between the Y-piece and the circuit prior to the heated humidifier or HME filter. Each nebulisation session lasts about 20 minutes.

6.7 Drug accountability

Flasks of acetylcysteine and salbutamol are provided by the pharmacy of the participating center. Both agents are widely used and, therefore, are available in each participating center. Since no placebo will be used, labeling of drugs is not necessary.

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

Not applicable.

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

Not applicable.

7.4 Summary of known and potential risks and benefits

Not applicable.

7.5 Description and justification of route of administration and dosage

Not applicable.

7.6 Dosages, dosage modifications and method of administration

Not applicable.

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable.

7.8 Drug accountability

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary endpoint is the number of ventilator-free days (VFDs), defined as the number of days from day 1 to day 28 after ICU admission and start of mechanical ventilation on which a patient breathes without assistance of the ventilator if the period of unassisted breathing lasted at least 24 consecutive hours. Patients who die or are mechanically ventilated longer than this period are assigned zero ventilator-free days.

8.1.2 Secondary study parameters/endpoints

The study will focus on the following secondary outcomes:

- Side effects of nebulisation of mucolytics and/or bronchodilators (due to nebulisation itself, or as a result of exposure to the nebulized agents);
- ICU and hospital stay till day 90;
- ICU and hospital mortality;
- Incidence of secondary ARDS using consensus criteria[35];
- Clinical defined ventilator-associated pneumonia according to the VAP criteria of the CDC 2014 (see Appendix 1);
- Atelectasis (lung opacification on chest radiograph with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory over inflation in the adjacent non-atelectatic lung);
- Health care related costs, including costs of ventilation, stay in ICU and/or hospital, cumulative use of sedative drugs and neuromuscular blocking agents, use of tracheostomies, and costs of ventilator-associated pneumonia.

8.2 Randomisation, blinding and treatment allocation

Patients will be randomly assigned in a 1:1 ratio to one of both nebulisation strategies within 24 hours after intubation, after informed consent is signed by the patient or the patient's legal representative. Randomization will be performed using a dedicated, password protected, SSL-encrypted website. Randomization sequence is generated by a dedicated computer randomization software program using random block sizes

and is stratified per center. Due to the nature of the intervention blinding of the caregivers is not possible. Data analysis will be performed blinded for the type of intervention.

8.3 Study procedures

Patients will be randomly assigned, after written informed consent is obtained, in a 1:1 ratio to one of the following two nebulisation strategies:

1. Routine nebulisation: Nebulisation of mucolytics and bronchodilators, administered every 6 hours (i.e., 4 times per day) within 24 hours after initiation of ventilation continuing until tracheal extubation.

2. Nebulisation on clinical indication only: Nebulisation is performed incidentally in case of a clinical indication according to the same procedure applied in the routine nebulisation group. Clinical indications are defined as:

- Occurrence of persistent thick and tenacious secretions following the Suzakawa criteria[13] (for which nebulisation of mucolytics can be started) and only after active humidification of the ventilator circuit is set.
- Occurrence of bronchospasm (for which nebulisation of bronchodilators can be started) and only when signs and symptoms of bronchospasm (wheezing, increased airway pressures, increasing airway resistance, up sloping curve of de end tidal CO2 monitoring) are confirmed.

The decision to nebulize mucolytics and/or bronchodilators is to be made on a daily basis by the attending ICU–physician. As soon as the clinical indication no longer exists, the therapy should be stopped (appendix 3).

8.4 Data to be collected

An overview of the type and timing of data to be collected is given in Appendix 2.

8.4.1 On admission and on the ICU:

- gender and age
- height and weight
- reason for ICU admission
- reason for ventilation

- cause of respiratory failure
- APACHE II score and SAPS II
- Comorbidity (heartfailure, arrhythmia, pulmonic comorbidity, immune status)
- Substance abuse
- Non-invasive ventilation at home
- Treatment limitation at admission to ICU

8.4.2 Baseline parameters 1 hour after intubation:

- Mechanical ventilation parameters:
  - tube size;
  - tidal volume;
  - respiratory rate (breath/minute);
  - level of positive end– expiratory pressure;
  - peak and plateau pressures, or level of pressure support (level above PEEP, and maximal airway pressure, cmH2O);
  - inspiration to expiration ratio;
  - inspired oxygen fraction;
  - minute volume (liters/minute);
  - pulmonary compliance;
  - Lung Injury Score [36] and Oxygenation Index[37]
- Respiratory parameters:
  - peripheral oxygen saturation (%);
  - end–tidal fractions of CO2; PaO2; PaCO2; arterial bicarbonate;
  - arterial pH: arterial base excess.
- Chest ray (if available)
- Non respiratory parameters
  - Heart rate, mean arterial pressure, central venous pressure
  - Laboratory (if available): Hemoglobin, leukocytes, Potassium

8.4.3 Daily from day 1 till detubation*

- Mechanical ventilation parameters:
  - tube size;
  - tidal volume;

- respiratory rate (breath/minute);
- level of positive end– expiratory pressure;
- peak and plateau pressures, or level of pressure support (level above PEEP, and maximal airway pressure, cmH2O);
- inspiration to expiration ratio;
- inspired oxygen fraction;
- minute volume (liters/minute);
- pulmonary compliance;
- Lung Injury Score [36] and Oxygenation Index[37]

- Respiratory parameters:
  - peripheral oxygen saturation (%);
  - end–tidal fractions of CO2; PaO2; PaCO2; arterial bicarbonate;
  - arterial pH: arterial base excess.
- Chest ray (if available)
- Respiratory status
  - intubation status
  - tracheostomy status
  - invasiveness of ventilation (invasive, non–invasive, intermittent via tracheostomy)
  - Type of airway humidification (passive, active)
- Endo tracheal suctioning
  - Cumulative endotracheal suction procedures
  - Consistency of tracheal aspirate[13]
  - Sputum culture (if available)
- Non respiratory parameters
  - Heart rate, mean arterial pressure, central venous pressure
  - Laboratory (if available): Hemoglobin, leukocytes, Potassium
- Location of patient (in ICU, hospital, other facility, or home)
- Life status (alive or deceased and cause of dead)
- Non-respiratory parameters:
  - cumulative fluid balance (ml);
  - cumulative urine output (ml);
  - Sequential Organ Failure Assessment score (SOFA) score[38];

- blood transfusions (type and ml);
- infusion of (artificial) colloids (type and ml);
- extra pulmonic infection, sepsis, re-operation, cardiac arrest

- Pulmonary complications:
  - presence of ARDS (yes or no; derived from other data),
  - pneumonia (yes or no; derived from other data),
  - atelectases (yes or no; derived from other data)
- Cumulative use of nebulized
  - acetylcysteine
  - salbutamol
  - other medication
- Mode of nebulisation (with pressured gas from an external source or synchronized with inspiratory airflow from the ventilator)
- Cumulative use and duration of
  - Sedatives
  - analgetics
  - neuromuscular blocking agents
- Side-effects associated with:
  - nebulisation
  - the administration of acetylcysteine
  - the administration of salbutamol
- Tube obstruction:
  - A CT scan of the endotracheal tube will be performed to assess tube obstruction.

8.4.4 Data collected daily from extubation* till discharge from the hospital:

- Location of patient (ICU, hospital ward)
- Life status (alive or deceased and cause of dead)

*in patients with a tracheostomy, detubation is defined as the moment when a patient has been free from the ventilator for at least 24 hours.

8.4.5 Data collected at day 90 of follow up:

- Location of patient (in ICU, hospital, other facility, or home)
- Life status (alive or deceased and cause of dead)

8.4.6 Data to be collected for the economic evaluation

The economic evaluation incorporates health care costs that will be estimated from a health system perspective over the time horizon of this study. Costs will be determined for both intervention groups during a 28-days follow-up period after initial ICU admission. The costs of medical care will be calculated, divided into direct medical and direct non-medical and indirect costs, if applicable. The direct costs include the costs of (a) ventilation and (b) stay in ICU and/or hospital; (c) costs of cumulative use of sedatives, and (e) neuromuscular blocking agents, (f) the use of tracheostomies, and (g) ventilator-associated pneumonia.

8.5 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.5.1 Specific criteria for withdrawal

A specific reason for withdrawal of a participating patient is translocation of the patient to another hospital that does not participate in this study before discharge from the ICU. If the patient is transferred to another hospital after discharge from the ICU there is no reason for withdrawal.

8.6 Replacement of individual subjects after withdrawal

Subjects who are withdrawn from the study will not be replaced. In the sample size calculation a dropout rate of 5% has been taken into account. Analysis will be according to the intention-to-treat principle.

8.7 Follow-up of subjects withdrawn from treatment

Reason for withdrawal from nebulisation will be recorded and follow up of subjects will be continued.

8.8 Premature termination of the study

A concern regarding safety could be the occurrence of occlusion of the endotracheal tube due to less administration of mucolytica. To date, data on side effects of nebulisation of mucolytica and bronchodilators are limited. For mucolytica, bronchospasms are a well-known side effect. Arrhythmia may be of major concern in the administration of bronchodilators. An independent Data Safety Monitoring Board (DSMB) will monitor the study on safety aspects and if necessary recommend termination of the study.

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 AEs, and SAEs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational intervention judged by the attending ICU physician. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

The investigator will appreciate the severity of an event and give his opinion on whether the event is related or not to the study procedures. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the study procedures will be considered and investigated.

Adverse events that are considered related to the study procedures include, but are not limited to, development of bronchospasm, dyspnea, development of hypoxemia, hypercapnia and the development of tachycardia, tachyarrhythmia.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;

- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- Any other important medical event that may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

SAEs, that are considered related to study procedures, include, but are not limited to, development of ventilator-associated pneumonia, development of ARDS, new onset ventricular tachyarrhythmia with hemodynamic instability wherefore an intervention is indicated and the development of endotracheal tube occlusion. SAEs considered (possibly) to be related to a study procedure will be reported by the Coordinating PI to the CCMO and central METC using the CCMO module "ToetsingOnline". The reporting will occur within 15 days after the investigator has first received information on the SAE. For fatal of life-threatening cases a preliminary report will be offered within 7 days followed by a complete report within 8 days.

The local site investigator is responsible to report a SAE within 24 hours of the first knowledge of the event to the Coordinating PI.

SAEs that are considered unrelated to a study procedure by the PI, will be recorded and reported in an overview list (line-listing) that will be submitted once every half year to the METC.

Documentation

All adverse events have to be documented in the participant's chart and in the CRF. Cases of misuse, or deviations in the administration of the study intervention have to be documented even when there is no adverse event. In case the AE results in a persistent disease, the AE has to be classified as a SAE and to be documented at the end of the trial.

9.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.4 Data Safety Monitoring Board (DSMB)

An DSMB will be installed to monitor safety parameters and the overall conduct of the study. The DSMB consists of 3 experts of critical care and mechanical ventilated patients, one of them will be the chairman. They will be supported by an independent statistician experienced in the statistical methods for clinical research.
The composition, tasks, responsibilities, and working procedures of the DSMB are elaborated in the DSMB Charter (K5. DSMB charter Nebulae versie 2, d.d. 28-07-2014), which is attached.
Following each DSMB meeting, the DSMB will send a confidential report to the Principal Investigator of each meeting. The report does not include unblinded data and contains sufficient information to explain the rationale behind any specific recommendation by the DSMB. Should the Coordinating PI decide not to fully implement the advice of the DSMB, the Coordinating PI will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be follow.

10.STATISTICAL ANALYSIS

10.1 General considerations

All analyses will be performed according to the intention-to-treat principle. In addition, per protocol analyses will be done to check for robustness of results, considering the trial being a non-inferiority trial. The intention-to-treat analysis considers all patients as randomized regardless of whether they received the randomized treatment, The "per protocol" group considers only those patients who complete the treatment according to the originally allocated protocol. In this non-inferiority trial we include a hierarchical, superiority, primary efficacy analysis. If the non-inferiority criterion is satisfied, a secondary analysis for superiority for the primary endpoint will be conducted. When appropriate, statistical uncertainty will be expressed by the 95% confidence levels. All statistical analyses will be performed with the R language and environment for statistical computing[39].

10.2 Primary study parameter(s)

The main analysis will compare the number of ventilator free days between the two treatment groups to evaluate the non-inferiority hypothesis. The null hypothesis entails that the nebulisation on indication group is inferior by a margin of 10%to the routine nebulisation group. If the 95% CI upper bound for inferiority of the nebulized-on-indication group is < 10%, the null hypothesis of inferiority is rejected. If the non-inferiority criterion is satisfied, then superiority for the primary endpoint, the number of ventilator free days will be tested.

In addition to the parametric analysis (t-test) of the normalized log data of the mean duration from the ventilator free days between the two groups, we will use a nonparametric analysis method to test the confidence interval of the difference between the two medians of the ventilator free days from both groups.

Additionally, time to freedom from mechanical ventilation is expressed with Kaplan-Meier curves. Differences between groups will be tested by the log-rank test. As this is a RCT, we expect that randomization in this study population will sufficiently balance patients' baseline characteristics. However if imbalances occur

between groups, a Cox proportional hazard model will be used and adjusted accordingly. The effect of nebulisation on the primary outcome will be investigated in pre-specified subgroups based on humidification method (active or passive), type of nebuliser (jet nebuliser or vibrating mesh) and type of flow used for nebulisation (continues with external source or breath synchronised with an inline flow from the ventilator).

10.3 Secondary study parameters

Continuous normally distributed variables will be expressed by their mean and standard deviation or when not normally distributed as medians and their interquartile ranges. Categorical variables will be expressed as counts (n) and percentages (%). To analyze differences in continuous variables between groups the two test groups Students's t test will be used, or in case continuous data is not normally distributed, the Mann-Withney U test will be used. Categorical variables will be compared with the Chi-square test or Fisher's exact tests. The ICU mortality, hospital mortality, the length of ICU stay, and the length of hospital stay will be expressed with Kaplan-Meier curves.

10.4 Interim analysis

An interim analysis for safety will be performed after the first one third (317) and two thirds (634) of the study population, respectively are included and have completed follow up for the primary outcome. The main concern is the occurrence of tube related incidents in the non-nebulized group, development of ventilator associated pneumonia in the nebulisation group. Serious adverse events (SAEs) such as death, ventilator associated pneumonia, ARDS, new onset ventricular tachyarrhythmia with hemodynamic instability wherefore an intervention is indicated or tube occlusion that are possibly related to study intervention will be compared.

10.5 Economic Evaluation

Alongside the proposed RCT a prospective economic study will be performed. The main question in the economic evaluation is whether the costs of preventive nebulisation are justified by their beneficial effects compared to nebulisation only on strict indication. Based on a non-inferior assumption we expect no differences in

outcomes. Therefore this prospective cost study is set-up as a cost-benefit analysis (CBA).

Cost Benefit Analysis

The cost benefit analysis (CBA) incorporates health care costs that will be estimated from a health system perspective over the time horizon of this study. In this economic evaluation costs will be determined for both intervention groups during a 28-days follow-up period after initial ICU admission and start of mechanical ventilation. The costs of medical care will be calculated, divided into direct medical and direct non-medical and indirect costs if applicable. Costs are defined as the volumes of used resources multiplied by calculated unit prices. No discounting of costs and effects will be applied. Although if any difference of interest in primary and/or secondary outcomes is observed, registered resource use and related costs will be compared between both intervention groups. In addition a cost-effectiveness analysis, to calculate incremental cost ratio's (ICER) will be performed.

Cost analysis

In this economic evaluation costs associated with 28-days follow-up will be prospectively determined for 950 intubated and ventilated ICU patients included in both study groups. Cost-calculations will be set up to reflect a hospital perspective and will be based on actual resource use in routine care. The direct costs of follow-up of the study population include the costs of (a) ventilation and (b) stay in ICU and/or hospital; (c) costs of cumulative use of sedatives, and (e) neuromuscular blocking agents, (f) the use of tracheostomies, and and (g) ventilator-associated pneumonia. Initially costs will be estimated for the short term (1 year). Additional costs as a result of co-morbid conditions will be excluded.

Costs are defined as the volumes of used resources multiplied by calculated unit prices. Unit costs, if available, of used resources will be determined based on standard current Dutch costing guidelines[40] and market prices. Data on resources used are collected from the hospital information system (with continuous registration), the case record form (CRF) and financial reports. Protocol driven costs will be excluded from the calculations.

Budget Impact Analysis (BIA):

Next to the economic evaluation a budget impact analysis (BIA) will be performed according to the ISPOR Task Force principles[40,41]. The purpose of this BIA is to estimate the financial impact of the adoption of nebulisation on strict clinical indication at the national level in the future. The analysis will be based on the decrease in ICU costs of not applying nebulisation in ventilated assisted patients as estimated during the study, and the expected number of patients eligible for this treatment in the Netherlands. Overall costs of the treatment, side effects and other consequences of both interventions (e.g. follow-up treatment) will be included in the BIA. These registered data reflect the eligible ICU population. The BIA will be conducted from the perspective of the different health care payers (i.e. health care providers: the hospital). The following scenarios will be compared: (a) the intervention change is not yet implemented, (b) the intervention change is implemented in 100% of the target group, (c) the intervention change is gradually introduced over a period of two years. Sensitivity analyses will be performed on the price of the intervention and the diffusion rate from the hospital perspective. Factors that determine the budget impact will be determined (clinical outcomes and costs).

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (Forteleza, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO), Good Clinical Practice Guidelines (ICH-GCP) and with local guidelines.

11.2 Recruitment and consent

Consecutive intubated and ventilated ICU patients with an anticipated duration of ventilation > 24 hours will be screened whether they meet the inclusion criteria. Patients will be recruited by the executive investigator or the attending ICU-physician. If the patient is awake and able to judge about his or her situation properly, information is provided and written informed consent is asked and signed by the patient within 24 hours after intubation. If a patient is not able to judge about his or her situation properly, information is provided to the legal representative and written informed consent is asked and signed by the legal representative within 24 hours after intubation. A second informed consent is asked from the patient in retrospect, at the moment the patient is awake and able to judge about his or her situation properly. Information on the study is then provided and written informed consent is asked and signed by both the executive investigator and the patient. If a patient declines consent, all collected study data on this patient will be destroyed.

11.3 Benefits and risks assessment, group relatedness

Both nebulisation strategies of mucolytics and bronchodilators are frequently used therapies in Intensive Care Units nationwide. Benefits and risks of both strategies are uncertain. Since the nebulisation procedures are the same as those in current standard practice and no additional investigations or intervention will be administered, the study does not pose an extra burden on patients. The risks of the patients in the routine nebulisation group include possible occurrence of adverse reactions due to nebulisation of mucolytics and bronchodilators. These risks are the same as in current standard clinical practice. Patients randomized to the ‘nebulisation on indication only’ group will be less exposed to the possible adverse reactions of nebulisation itself or the drugs nebulized. The risks of the patients in the

only on indication nebulisation group include possible occurrence of tube occlusion. However, the nebulisation treatment will not be withheld if a clinical indication is present.

Patients needing mechanical ventilation are often considered incapacitated due to their severe illness. Since the strategies to compare in this study are only used in severely ill mechanical ventilated patients, we consider it inevitable to include these patients.

11.4 Compensation for injury

In this study two standard treatment strategies will be compared. As a consequence there are no additional risks of participation in this study. Therefore, exemption of insurance for additional harm was granted by the Medical Ethical Research Committee of the Academic Medical Center for participants in this study. A liability insurance will be present in every participating center.

11.5 Incentives

Enrolled patients will not receive any special incentives, compensation or treatment through participation in this trial.

12.ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be handled confidentially and anonymously. To ensure data security and to protect the subjects privacy, data on individual subjects will be encoded according to a subject identification code list. Patient data will be entered by way of an eCRF in a central GCP proof internet based database to facilitate on-site data-entry. All patients will be addressed to the interventions with a random patient identification code. Security is guaranteed with login names, login codes and encrypted data transfer. The executive investigator safeguards the code and has access to the source data at any time. All other investigators will have access to source data as well. When necessary for monitoring of the study, access will be granted to the Health Inspectors of the Dutch Government (Inspectie voor de Gezondheidzorg) and the members of the sponsors of this study; the Academic Medical Center in case of an internal audit. Data will be stored in a secure place during a period of 20 years, in the archives of the Academic Medical Center, Amsterdam.

12.2 Monitoring and Quality Assurance

The study will be monitored according to ICH-GCP guidelines throughout its duration by a GCP-certified monitor according to the Monitoring Plan (K6. Monitoringplan Nebulae, versie 1).

On-site monitoring will be conducted to evaluate the progress of the study, ensure the rights and wellbeing of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments, GCP and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical study documents as well as discussion on the conduct of the study with the investigator and staff. Every participating center will be visited at least once every year.

12.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

12.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study to the accredited METC.

12.6 Public disclosure and publication policy

The study protocol and analysis plan will be published before start of the study on Clinicaltrials.gov and trialregister.nl. The results of the study will find their way into (inter-)national scientific journals and guidelines. We will submit analyses to scientific journals in the field of intensive care medicine as well as anesthesiology, since both ICU physicians and anesthesiologists apply ventilation in the ICU setting.

13.STRUCTURED RISK ANALYSIS

13.1 Synthesis

Nebulisation solution for both acetylcysteine and salbutamol are registered in The Netherlands for disorders of the respiratory tract. In this study both drugs will only be applied within this indication. Standard ICU care will be provided in both groups and procedures will be performed by experienced trained ICU physicians and nurses. An independent Data Safety Management Board (DSMB) will be installed to monitor safety parameters and the overall conduct of the study.

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Appendix 1.

CDC criteria for Clinically defined Ventilator Associated Pneumonia (2014)
One or more serial X-rays with one of the following (two or more serial X-rays in patients with underlying disease): - New or progressive and persistent infiltrate - Consolidation - Cavitation - Pneumatoceles, in ≤1 y.o.
AND
At least one of the following: - Fever (>38°C/100.4°F) - Leukopenia (<4,000 WBC/mm³) OR leukocytosis (>12,000 WBC/mm³) - Altered mental status with no other cause, in >70 y.o.
AND
At least two of the following: - New onset of purulent sputum OR change in character of sputum OR ↑respiratory secretions OR ↑suctioning requirements - New onset or worsening cough OR dyspnea OR tachypnea - Rales OR bronchial breath sounds - Worsening gas exchange (e.g., O2desats [e.g., PaO2/FiO2<240],7↑O2req, OR ↑ventilation demand)

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Appendix 2

Data collection

		Baseline (<24 hr)	At randomization	Daily (day 0-28)	Day 90
Baseline	Gender	x			
	Age	x			
	High	x			
	Weight	x			
	BMI	x			
	Reason admission icu	x			
	Reason ventilation	x			
	Cause respiratoir failure	x			
	APACHE II score	x			
	SAPS score	x			
	Cardiac comorbidity	x			
	Pulmonal comorbidity	x			
	Medication	x			
	Respiratory parameters		x	x	
MV parameter	MV parameters		x	x	
Location	ICU/hospital/facility/home			x	x
Life status	Alive/deceased			x	x
	Pulmonary complications			x	
	Medication use			x	
Other	Cumulative fluid balance			x	
	Cumulative urine output			x	
	SOFA score			x	
	Blood transfusions			x	
	Colloid infusion			x	
Side effects	Nebulisation			x	
	Acetylcysteine			x	
	Salbutamol			x	

Abbreviations: BMI: body mass index; MV: mechanical ventilation;NIV: non-invasive mechanical ventilation; APACHE II: Acute Physiology and Chronic Health Evaluation II;SAPS II: Simplified acute physiology score II;PEEP: positive end expiratory pressure; IE ratio: inspiratory expiratory ratio; Fi02: Fraction inspired oxygen; MV: minute volume; SOFA score: sequential Organ Failure Assessment

Appendix 3.

Protocol: Nebulisation in the "nebulisation on clinical indication only" arm:

Nebulisation is performed incidentally in case of a clinical indication according to the same procedure applied in the routine nebulisation group.

Clinical indications are defined as:

Mucolytics:

In case of ccurrence of persistent thick and tenacious secretions, following the Suzakawa criteria* observed during daily care by nurse or physician, the attending ICU-physician starts the following protocol:

1. Start active humidification of the ventilator circuit
2. In case of persistent tick and tenacious secretions prescribe four times daily nebulization of 3 mL-solution of acetylcysteine (fluimucil 100mg/ml) and record indication in the medical chart.
3. Reconsider daily whether this indication is still present or whether nebulisation can be withdrawn again and record in the medical chart.

Bronchodilators:

In case of occurrence of bronchospasm, defined as occurrence of at least one of following signs and symptoms of bronchospasm: wheezing, increased airway pressures, increasing airway resistance, up sloping curve of de end tidal CO2 monitoring, the attending ICU-physician starts the following protocol:

1. Prescribe four times daily nebulization of 2.5 mL solution of salbutamol (Ventolin 2.5 Nebules 2.5mg/2.5 ml) and record indication in the medical chart.
2. Reconsider daily whether this indication is still present or whether nebulisation can be withdrawn again and record in the medical chart.

*Suzukawa criteria secretion :

Class 1- aqueous: no secretion remains behind on the inside of the suction catheter

Class 2- sticky: some secretion remains behind on the inside of the suction catheter, simply removable with rinsing fluid

Class 3- thick/tenacious: secretion remains behind on the inside of the suctioning catheter, which cannot be flushed away after two times of rinsing with fluid