EFFICACY OF INSTILLED SALINE IN CONJUNCTION WITH CHEST PHYSIOTHERAPY ON SECRETION CLEARANCE IN ADULTS DIAGNOSED WITH A VENTILATOR ACQUIRED PNEUMONIA: A FEASIBILITY STUDY

By

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Abstract

Introduction

Chest physiotherapy is routinely provided to intubated and mechanically ventilated patients in intensive care units (ICUs) to aid secretion clearance. If pulmonary secretions are thick, physiotherapists will often use normal saline instillation (NSI) as part of a multimodal intervention. However, evidence on the benefits of NSI during chest physiotherapy is limited. This trial aimed to evaluate the feasibility of delivering a definitive trial to examine the efficacy of NSI during chest physiotherapy on secretion yield for patients with ventilator acquired pneumonia (VAP).

Methods

Patients admitted to a large West Midlands ICU and diagnosed with VAP were included in the trial. A randomised crossover feasibility design was employed for the intervention (twice daily chest physiotherapy). On day one patients were randomised to receive either chest physiotherapy with NSI or without NSI during the morning treatment session. Physiotherapy treatment then alternated between NSI and non-saline sessions for three days or until extubated, whichever sooner. Primary outcomes were feasibility measures: patient recruitment, retention, and protocol fidelity. Secondary outcomes included physiological parameters, sputum weight and safety of NSI.

Results

Of 32 eligible patients, 94% (n=30) consented to participate. Of these, 28 (93%) completed the study intervention with only two (7%) patients' next of kin withdrawing consent during the intervention. Of patients surviving to hospital discharge who regained capacity (n=9), 100% provided consent for ongoing participation. Protocol fidelity was at 100% with no missing data or adverse events related to NSI. NSI was associated with a significant drop in SpO_2 two minutes post intervention ($p<0.05$) and higher sputum pellet weight ($p<0.001$).

Adjusted wet sputum weight is not a reliable outcome measure for measuring secretion clearance when NSI is used.

Conclusion

A trial looking at the effect of NSI during chest physiotherapy on secretion yield for mechanically ventilated patients with VAP is feasible to conduct and acceptable to participants. However, validation of the methodology for processing sputum samples and determining sputum pellet weight is required before proceeding to a definitive trial.

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Frequent Abbreviations

AARC	American Association for Respiratory Care
ACPRC	Association of Chartered Physiotherapists in Respiratory Care
AMs	Alveolar macrophages
APACHE	Acute Physiology and Chronic Health Evaluation
BMI	Body Mass Index
BP	Blood pressure
CWV	Chest wall vibrations
CPIS	Clinical Pulmonary Infection Score
CRF	Case report form
CRP	C-reactive Protein
CV	Cardiovascular
ETS	Endotracheal suction
ETT	Endotracheal Tube
GCP	Good Clinical Practice
HR	Heart rate
ICU	Intensive Care Unit
ICUAW	Intensive Care Unit Acquired Weakness
IL	interleukin
MRC	Medical Research Council
MV	Mechanical Ventilation
NETS	neutrophil extracellular traps
NHS	National Health Services
NOK	Next of Kin
HRA	Health Research Authority
NSI	Normal Saline Instillation
PPI	Patient and Public Involvement
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SOFA	Sequential Organ Failure Assessment
SpO_2	Peripheral oxygen saturations

TNF-a	Tumour necrosis factor
VAP	Ventilator acquired pneumonia
V_t	Tidal volumes

CHAPTER 1 – Introduction

Approximately 200,000 adults are admitted to general intensive care units (ICUs) in England, Wales and Northern Ireland annually (ICNARC, 2019). Of these, 40% require invasive MV as part of their medical management to treat airway disease, hypoxemic or respiratory pump failure, or to support with the increased ventilatory demand imposed by sepsis (ICNARC, 2019). Although a life-saving intervention, mechanical ventilation (MV) is associated with a sequalae of complications including the development of ventilator acquired pneumonia (VAP) (Wu et al., 2019).

1.1 Ventilator acquired pneumonia.

Ventilator acquired pneumonia is defined as a pneumonia that manifests 48 hours after initiating MV, and is the most common nosocomial infection in adult ICUs, occurring in approximately 9% to 27% of patients (O'Grady et al., 2012). It is characterised by the presence of fever, leucocytosis, radiographic changes on chest x-ray and increase in purulent secretions. VAP is associated with prolonged MV, increased lengths of ICU and hospital stay, and increased risk of mortality (Fàbregas et al., 1999; Hadda et al., 2014; Luo et al., 2021). In addition, VAP is estimated to increase healthcare costs by £9000 per patient, representing a significant financial burden (Safdar et al., 2005).

1.2 Pathobiology of VAP

The placement of an endotracheal tube (ETT) and initiation of MV breaches the upper airway's natural protective barriers, allowing direct communication between the oropharynx and nasal sinus and the tracheobronchial tree (Hunter, 2012). Although the ETT cuff allows effective delivery of positive pressure ventilation and minimises gross aspiration (Mietto et al., 2013), the loss of cuff pressure and ETT movement means secretions pooled in the oropharynx, nasal sinuses and stomach are susceptible to leaking below the cuff, resulting in silent micro-aspirations and VAP (Craven & Hjalmarson, 2010; Zolfaghari & Wyncoll, 2011).

Ventilator acquired pneumonia is also related to bacterial biofilm formation, found on the ETT surface of 95% of mechanically ventilated patients and occurring within hours of intubation (Deem & Treggiari, 2010; Morris, 2018). The biofilm acts as a reservoir for infective microorganisms which can lead to VAP; with associations found between pathogens identified in tracheal secretions and the ETT biofilm (Deem & Treggiari, 2010; Morris, 2018). *(Figure 1).*

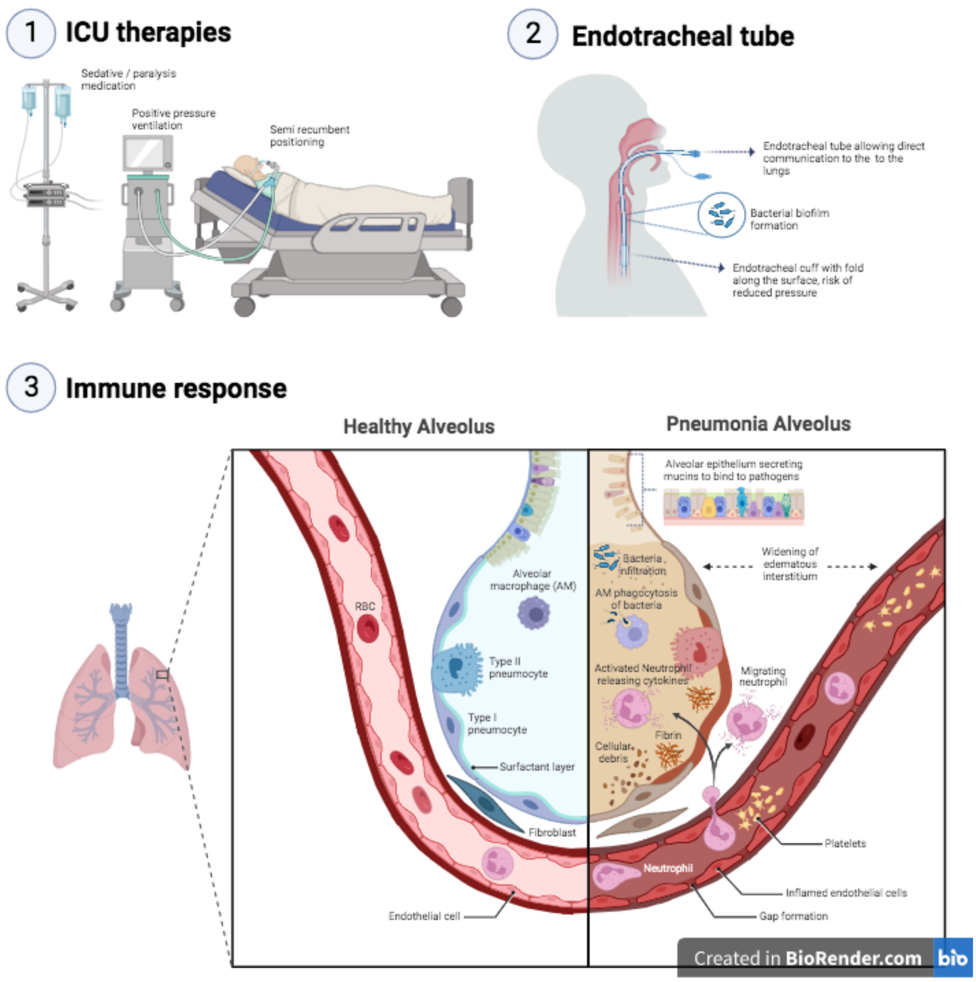

Figure 1: *Mechanisms of ventilator-acquired pneumonia; 1. External factors associated with ICU therapies including MV, sedation and paralysis agents and semi recumbent positioning; 2. Endotracheal tube which prevent glottis closure and provides direct communication to the lungs allowing microaspiration of secretions from the nasal sinuses and oropharynx. The endotracheal cuff is at risk of deflation, movement and small folds which allow leakage of pooled secretions. A bacterial biofilm can form around the endotracheal tube which can then become dislodged with movement or suctioning; 3. Immune responses local to the alveoli of the lung in response to invading pathogen, leading to inflamed, oedematous and infected alveoli.*

1.2 Microbiology, local innate immunity and inflammation associated with VAP

1.3.1 Microbiology of VAP

Increasing prevalence of antibiotic resistant bacteria means VAP is often polymicrobial (Lynch, 2001). However, the primary pathogens responsible for VAP development are gram-negative bacteria, including *Pseudomonas spp, Klebsiella spp, Escherichia coli Acinetoacter spp,* and other Enterobacteriaceae, along with some gram-positive species such as *Staphylococcus aureus* and Enterococci (Delle Rose et al., 2016; Hellyer et al., 2015). Candida colonization is also common and poses a risk of fungal VAP (Azoulay et al., 2006).

1.3.2 Innate immune response of the lung parenchyma

For VAP to develop, microbes must first overcome the body's natural mechanical barriers i.e. cough, swallow and mucociliary escalator (Morris, 2018), before colonising the tracheobronchial tree and proliferating until they exceed the lungs ability to maintain immune resistance (Quinton et al., 2018). Alveolar macrophages (AMs), found in the lower respiratory tract serve as the body's frontline defence against invading respiratory pathogens through phagocytosis and apoptosis of microbes. If the innate immune system becomes overwhelmed by pathogenic microbes, AMs co-ordinate the release of cytokines through NF-kB transcription, including interleukins (IL) (IL-1α, IL-1β, IL-6, IL-8) and tumour necrosis factor (TNF-a). Cytokines facilitate migration of neutrophils to the infection site which have antimicrobial roles including phagocytosis and degranulation. Additionally, neutrophils cause the release of reactive oxygen species and formation of neutrophil extracellular traps (NETs) which contain histone and antimicrobial peptides to eradicate microbes (Cheng & Palaniyar, 2013; Mikacenic et al., 2018; Porto & Stein, 2016). This immune response causes localised inflammation within the lungs. Additionally, AMs act as antigen presenting cells, activating lymphocyte cells triggering cellular and humoral responses; subsequently leading to further inflammation of the lung parenchyma, leaking capillaries and exudative congestion (Quinton et al., 2018; Torres et al., 2021). This inflammation, coupled with the presence of microbes, results in the excessive production of purulent mucus from goblet and epithelium cells in the respiratory tract.

1.3.3 Localised inflammation

Critical illness represents a complex state characterized by proinflammation and immune suppression (Muszynski et al., 2016). Moreover, positive pressure ventilation can trigger a localised inflammatory response in the lungs, known as biotrauma (Halbertsma et al., 2005). Biotrauma involves the upregulation of pulmonary cytokines, perpetuates local inflammation and may consequently heighten the vulnerability to VAP (Halbertsma et al., 2005). Identifying the precise inflammatory mediators and their respective contributions to VAP poses clinical challenges. Nevertheless, recent research has highlighted significant elevations in pulmonary biomarkers such as interleukin-1 beta, IL-8, matrix metalloproteinase-8, MMP-9, and human neutrophil elastase, as well as serum markers like CRP and IL-6 in VAP cases (Grover et al., 2014; Hellyer et al., 2015). While neutrophils are crucial role to the innate immune response to VAP, the release of NETs can contribute to sustained local inflammation, precipitating lung injury and patient mortality (Horn et al., 2023; Mikacenic et al., 2018).

1.4 ICU factors Impacting on respiratory secretion clearance

The increase in purulent tracheobronchial secretions associated with VAP poses significant challenges in mechanically ventilated patients, where the normal physiological mechanisms for clearing secretions become impaired. In healthy individuals the mucociliary transport and gas liquid interaction, which includes flow bias and cough is responsible for expelling mucus from peripheral and small airways; whilst coughing, an augmentation of the gas-liquid interaction is the principal method for clearing large central airway secretions (Button & Button, 2013). However, in clinical manifestations that result in a loss of a cough reflex, flow bias also becomes integral to clearing upper airways.

The impairment in the normal mechanisms for secretion clearance observed in mechanically ventilated patients is multifactorial and related to therapeutic interventions employed in the management of critical illness which compromise the functionality of the mucociliary escalator, affect flow bias and diminish cough effectiveness (Kenaley et al., 2018; Marini & Formenti, 2016) (Figure 2).

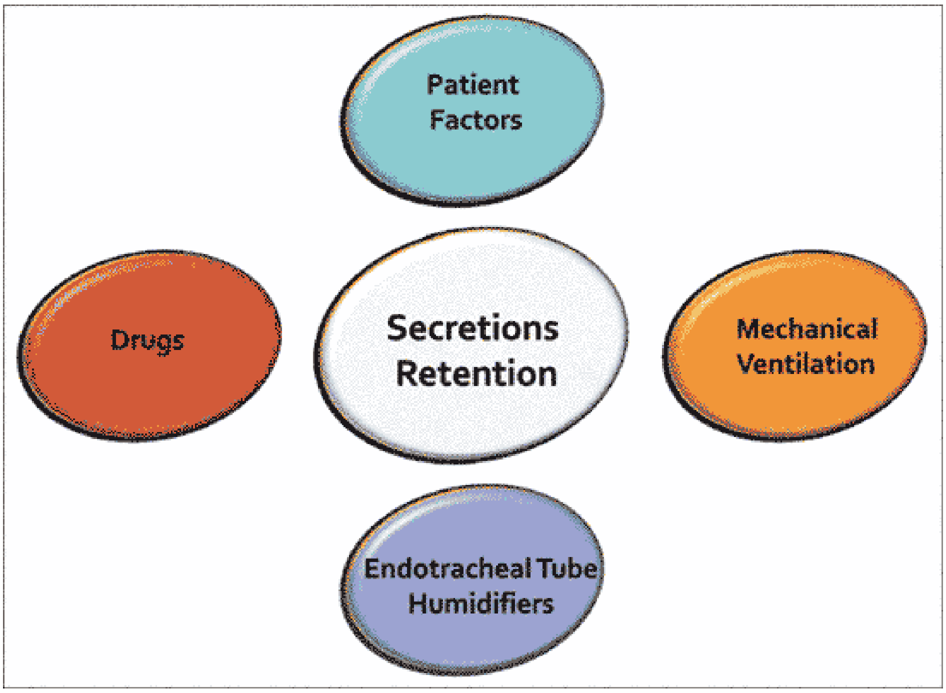

Figure 2. Mechanisms of secretion retention in mechanically ventilated patients

1.4.1 Mechanical Ventilation and ETT

The insertion of an ETT through the vocal cords prevents the normal sphincteric action of the larynx, leading to incomplete closure of the glottis and a reduction in the initial build-up of pressure necessary for an effective cough (Gal, 1980). The ETT also narrows the diameter of the main bronchi, resulting in increased total airway resistance, diminished expiratory flows rates and reduced cough effectiveness (Li et al., 2022). Additionally, inflation of the ETT cuff causes localised mucosal inflammation which impedes the function of the mucociliary escalator that normally aids secretion clearance (Li Bassi et al., 2008).

MV also influences airflow bias within the airway. In patients on pressure control or pressure control mandated ventilation, peak inspiratory flow has been shown to exceed peak expiratory flow, creating an inspiratory flow bias (Ntoumenopoulos et al., 2011). Such bias results in caudad movement of secretions, which then become embedded in distal airways. This is supported by Konrad et al, (1994) who demonstrated a significant reduction in bronchial transport velocity within three days of commencing MV.

Insufficient humidification within the tracheobronchial tree caused by inspiring un-humidified gas during MV can increase mucus viscosity (Hill et al., 2022). Increased mucus viscosity interferes with the gas-liquid interaction and reduces mucociliary clearance (Kim et al., 1987). Kelly et al. (2021) also demonstrated exposing the tracheal epithelium to non-humidified, room temperature air, reduces mucus transport velocity and cilia beat frequency.

1.4.2 Patient factors.

Patient position

Guidelines for the prevention of VAP advocate positioning MV patients with the head of the bed elevated to 30–45 degrees to reduce gastroesophageal reflux (Tablan et al., 2004). Subsequently patients are positioned for prolonged periods in a semi-recumbent position. Animal studies comparing the effects of head up or down positioning on tracheal mucous transport velocity in MV sheep showed that only sheep nursed in a semi-recumbent position developed VAP (Li Bassi et al., 2008). In addition, video fluoroscopy showed that mucus distal to the proximal trachea travelled towards the lungs in sheep nursed in a semi recumbent position as opposed to towards the airway in those nursed head down, suggesting the semi recumbent position could augment sputum being embedded and colonised in distal airways (Li Bassi et al., 2008). These findings were supported by a randomised control trial (RCT) in mechanically ventilated patients which demonstrated significantly lower rates of microbiologically confirmed VAP with head down position (Li Bassi et al., 2017). However, clinical adoption of head down positioning on ICU has been limited due to serious adverse events such as acute desaturation, accidental extubation and cardiovascular instability (Li Bassi et al., 2017).

Intensive Care Unit Acquired Weakness

ICU-acquired weakness (ICUAW) affects approximately 40% of ICU patients and involves peripheral and respiratory muscle weakness including the diaphragm and accessory respiratory muscles (Appleton et al., 2015; Smith et al., 2012). Patients with ICUAW therefore experience difficulty in expectorating secretions due to a reduced cough effort, leading to the accumulation of airway secretions, airway collapse, delayed respiratory weaning and extubation failure (Thille et al., 2020). Neuromuscular disorders, spinal cord injury, and restrictive lung disease are also associated with respiratory muscle weakness, reduced peak cough flow and cough effectiveness (Voulgaris et al., 2019).

1.4.3 ICU medications

Sedation and analgesia commonly used for ICU patients requiring MV, have widespread inhibitory effects on the central nervous system that help prevent pain and anxiety, permit invasive procedures, reduce stress and oxygen consumption, and improve synchrony with MV (Hughes et al., 2012). However, sedation and analgesia diminish airway reflexes, reduce patient alertness, and cause paralysis of peripheral and respiratory muscles (Paul & Paul, 2013; Zhang et al., 2023). This leads to patient immobility, reduced or absent cough, inability to co-operate in cough augmentation interventions and impaired secretion clearance (Volpe & Guimarães, 2021). Endotracheal suction (ETS) can be performed to void proximal airway secretions, however ETS is ineffective at clearing peripheral airways in the absence of a cough (American Association for Respiratory Care, 2010)

1.5 Chest physiotherapy in ICU

Reduced airway clearance can result in secretion retention, airway collapse, impaired gas exchange and delayed weaning from MV (Ntoumenopoulos, 2014). Consequently, chest physiotherapy is routinely provided to mechanically ventilated patients, including those who develop a VAP (Pathmanathan et al., 2014). Chest physiotherapy is an umbrella term used to describe a variety of interventions including positioning, manual techniques (expiratory vibrations and percussion) and manual hyperinflation. Chest physiotherapy aims to simulate a cough or huff, increasing expiratory flow to augment cephalad movement of secretion towards the larynx where they can then be cleared by coughing or ETS (Shannon et al., 2010). Evidence demonstrates chest physiotherapy can improve clearance of airway secretions, reduce airway collapse and improve lung compliance (Berney et al., 2004; Stiller et al., 1990; van der Lee et al., 2021).

If pulmonary secretions are thick and tenacious, physiotherapists may use normal saline instillation (NSI) (0.9% sodium chloride) directly down a patient's ET or tracheostomy tube as part of a multimodal intervention. A survey of 68 respiratory physiotherapists from the Association of Chartered Physiotherapists in Respiratory Care (ACPRC) reported 96% of physiotherapists would use NSI during ETS if secretions were thick and other secretion clearance techniques were ineffective to increase the volume of secretions removed during suction (Roberts, 2009). The theoretical rationale for using NSI includes several key factors. Firstly, direct instillation of saline into the lungs can trigger a cough reflex, aiding in the clearance of airway secretions. This may be particularly advantageous for patients with a diminished cough reflex due to neurological conditions or those with altered consciousness who cannot cough voluntarily. Additionally, saline instillation may help “shear” or loosen secretions adhered to the bronchial tree, an effect that can be further enhanced when combined with physiotherapy techniques, such as chest wall vibrations (Bostick & Wendelgass, 1987). Moreover, saline instillation may alter sputum rheology by mixing with sputum, potentially changing its viscoelastic properties and making it more amenable to clearance via suctioning (Raymond, 1995). However, studies by Demers and Saklad (1973) and Hanley et al. (1978) indicate that sputum and 0.9% saline are largely immiscible, even under vigorous agitation, providing limited evidence to support this hypothesis. Nonetheless, given the theoretical basis, NSI remains a widely used technique among healthcare professionals (Reeve et al., 2007).

1.6 Normal saline instillation

There is very limited evidence regarding the use of NSI during chest physiotherapy when saline is the controlled variable and in particular with regards to sputum yield (Paratz & Stockton, 2009). In the few studies reporting the effect of NSI on secretion yield, the volume of saline instilled during ETS is not accounted for (Bostick & Wendelgass, 1987), hence future studies should correct to recording dry sputum weight.

Studies investigating the effect of NSI, as part of a pulmonary lavage (without chest physiotherapy), on outcomes such as SpO^2, oxygen consumption, and risk of infection suggest it may not be advantageous (Ackerman & Mick, 1998; Akgül & Akyolcu, 2002; Hagler & Traver, 1994; Ji et al., 2002; Kinloch, 1999). However, the cohort of patients in these studies were unlikely to have a high secretion burden due to the short duration of MV. In addition, some studies lacked methodological rigour, calling into question the validity and reliability of their results. Interestingly, the largest RCT by Caruso et al. (2009) looking at NSI use and incidence of VAP reported no adverse events with the instillation of 8mls of saline prior to ETS with comparable levels of lobular atelectasis and ETT occlusion between groups. A 54% relative risk reduction in incidence of VAP was observed with NSI (Caruso et al., 2009). However, a failure to report sedation levels between groups and cough effort is a confounder that needs to be considered when interpreting results.

The most recent meta-analysis of RCTs by Wang et al. (2017) concluded NSI did not affect cardiovascular stability, but it was associated with significantly lower SpO_2 5 minutes post suction. However, it represented a mean reduction in SpO_2 of <2%. The acceptance of statistically significant changes in SpO_2 without reference to a clinically meaningful difference is important to acknowledge i.e., a reduction in SpO_2 from 100% to 98% is described by Wang et al. (2017) as an 'adverse effect'. A lack of standardisation and reference to pre-ETS oxygenation and post-ETS O_2 requirements are acknowledged methodological weaknesses, reducing reliability of findings. Wang et al. (2017) concluded further larger RCTs are required.

The use of NSI is therefore debatable. Current literature and clinical guidelines including The American Association for Respiratory Care (AARC) (Blakeman et al., 2022) dissuade from the use of NSI during ETS, citing risk of harm, VAP and short-term cardio-respiratory decline as potential adverse effects. Despite its wide use by physiotherapists during treatment of patients requiring MV, there are no national physiotherapy guidelines on NSI use or evidence regarding potential benefits of NSI as part of chest physiotherapy on secretion clearance. Literature published within the nursing field have used physiological outcome measures to report the impact of NSI (Ackerman & Mick, 1998; Akgül & Akyolcu, 2002; Hagler & Traver, 1994; Ji et al., 2002; Kinloch, 1999). However, these are not pertinent to reviewing the primary reason physiotherapists use NSI i.e. secretion clearance. NSI during chest physiotherapy aims to improve secretion yield and lung compliance. Hence, there is a need to inform physiotherapy practice by evaluating whether treatment effectiveness and patient outcomes are improved by the addition of NSI in conjunction with chest physiotherapy by undertaking a RCT. However, a feasibility study would be required to ascertain the acceptability and deliverability of such a trial.

The thesis introduction has identified a void of research investigating NSI practice amongst physiotherapists, particularly related to outcomes such as sputum yield. Due to limited robust evidence, a systematic review and meta-analysis was not possible. A scoping review of NSI practice was therefore undertaken and presented in chapter 2. Chapter 3 presents the aim, objectives and methods used for the feasibility study reported in this thesis, with study findings reported in Chapter 4. Chapter 5 discusses the results and future research recommendations. Chapter 6 provides a conclusion around the feasibility of a definitive RCT looking at the efficacy of NSI on secretion clearance in patients MV with VAP.

CHAPTER 2. Scoping review

This chapter presents the findings of a scoping review related to the available evidence around the use of NSI during ETS in MV patients. The methodology of the scoping review is described, findings are presented in narrative and tabular format and discussed briefly. The findings of the scoping review will be further discussed in Chapter 5 (Discussion) in relation to the findings from the feasibility study.

2.1 Aim

To report the extent, scope and nature of the existing literature on the use of NSI during ETS and to identify research gaps within this literature.

2.2 Objectives

- To systematically search, identify and gather literature relevant to the use of NSI during ETS in the last 10 years.
- To identify and collate relevant information from studies meeting the eligibility criteria.
- To summarise and synthesise the information extracted from the relevant papers.

2.3 Design

A scoping search of Pubmed, Google Scholar and EMBASE looking specifically at NSI use as part of chest physiotherapy yielded no studies in which NSI was the controlled variable. Since NSI use as part of chest physiotherapy is not a topic that has been investigated comprehensively it was not possible to undertake a systematic review, as systematic reviews focus on a well-defined research question and require an appropriate number of methodologically rigorous studies to be identified (Pollock & Berge, 2018). A scoping review to map the key concepts and research underpinning the use of NSI during ETS in adult patients who are MV in critical care was therefore employed. Although scoping reviews do not provide a robust and reliable summary of evidence like systematic reviews, they aim to map the volume, nature and characteristics of primary research within the existing field of literature, enabling research gaps to be identified (Arksey & O'Malley, 2005; Levac et al., 2010).

2.4 Methods

The review was conducted adhering to scoping review guidelines and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews (PRSIMA-SCR) guidelines to ensure a reproducible, reliable and meaningful review (Arksey & O'Malley, 2005; Peters et al., 2015; Tricco et al., 2018). The study protocol was registered on Open Science Framework (OSF) and made available on the OSF website (https://osf.io/z43we/). Ethics approval was not required for this scoping review. After manuscript publication, all review data will be publicly available at Open Science Framework.

2.5 Search strategy

To reduce reporting bias, six medical and allied health professionals electronic publication databases were searched to ensure papers pertinent to the review topic were identified. These databases included ‘Pubmed’, ‘EMBASE’, ‘MEDLINE’, ‘Cochrane’, ‘Pedro’, and

‘CINAHL’. These databases were used as they are the most prominent and widely used within healthcare research, with robust governance (Oermann et al., 2021). Pedro was utilised due to its specificity within the field of physiotherapy (Stevens et al., 2016).

To ensure literature saturation around the use of NSI and to identify unpublished work, relevant national organisations including The Association of Chartered Physiotherapists in Respiratory Care and prominent academic physiotherapists within the field of critical care were contacted to ascertain if they were aware of any additional studies not identified during the database search. EndNote (Version 20) reference management software was utilised to store and organise references of articles meeting the eligibility criteria.

2.5.1 Key Words

To identify the keywords for the database searches the ‘Population, Concept and Context’ (PCC) mnemonic was used (JBI, 2015; Peters et al., 2020) (Table 1). Due to the variation in spellings and terminology internationally, truncation and Boolean operators were used to allow for the different spellings of key terms to be searched. This ensured that the PCC framework incorporated all key, related areas.

Table 1: PCC framework

	Boolean Search Terms
Population	• adults • mechanical* ventilat* • endotracheal tube • ETT • trach* • intubated
Concept	• instilled saline • sodium chloride • 0.9% saline • saline installation • sodium chloride • isotonic sodium chloride, • isotonic saline

	• normal saline • tracheal toilet • pulmonary lavage • lavage • pulmonary toilet • tracheal washout • NSI • alveolar lavage
Context	• Intensive care • critical care • ICU • ITU

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2.5.2 Study selection / eligibility criteria

To identify literature that would address the aims of the review, inclusion and exclusion criteria were initially developed (Table 2). Due to the iterative nature of a scoping review, the eligibility criteria were revised throughout the literature search process to include participants aged >16 years as familiarity with the literature and evidence developed (Peters et al., 2020). To preserve a degree of assurance around methodological rigour and the trustworthiness of findings, only peer reviewed articles were included in the review (Gusenbauer & Haddaway, 2020). Due to financial, time and logistical constraints only articles in English and available as full text were included. Literature dated before 2013 was excluded from the review to ensure current evidence was synthesised and reflected current healthcare strategies and patient management on critical care.

To ensure a methodical and reproducible method of searching the literature, databases were initially searched for key words included in the title and abstract prior to the application of the eligibility parameters. To identify articles poorly or inaccurately indexed, the reference lists of relevant systematic reviews and all articles meeting the inclusion/exclusion criteria identified during the database search were hand searched by two reviewers independently to identify any other relevant primary research. The abstracts of articles identified from the initial database search were then screened for appropriateness by two independent reviewers blinded to each other's judgement and subsequently included/excluded from the study (Stoll et al., 2019). Eligibility disagreements were resolved by a third independent person.

Table 2: Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Study design	Primary observational and experimental studies	Abstracts only Guidelines Secondary research including systematic reviews, meta-analysis and evidenced based practice reviews
Study participants	Adults >16 Any healthcare practitioner on ICU performing ETS in MV patients in ICU	Paediatric aged <16 Non-human studies
Type of intervention	Normal saline instillation during suctioning in MV patients	Use of any other product for instillation during suction in MV patients
Publication	Full-text retrievable In English Peer reviewed	Non-English Conference abstracts or unable to retrieve full text from database
Date range	2013 – 2023	Articles earlier than 2013

2.5.3 Data extraction and Analysis.

A standardised data extraction template recommended by the Joanna Briggs institute (JBI) was initially utilised to minimise bias (Peters et al., 2020). Two reviewers collaboratively revised this data extraction tool to meet the needs of the scoping review which was then piloted on a small sample of extracted literature. Subsequent refinements were made to the categories and format to ensure all necessary data was captured appropriately before a consensus was achieved between reviewers on the final format of the data extraction tool.

To align with the aim and objectives of the scoping review the following data, where available, were extracted: Author and study demographics; study design; aim; sampling technique/sample size; population; eligibility criteria; control/intervention; outcome measures and results.

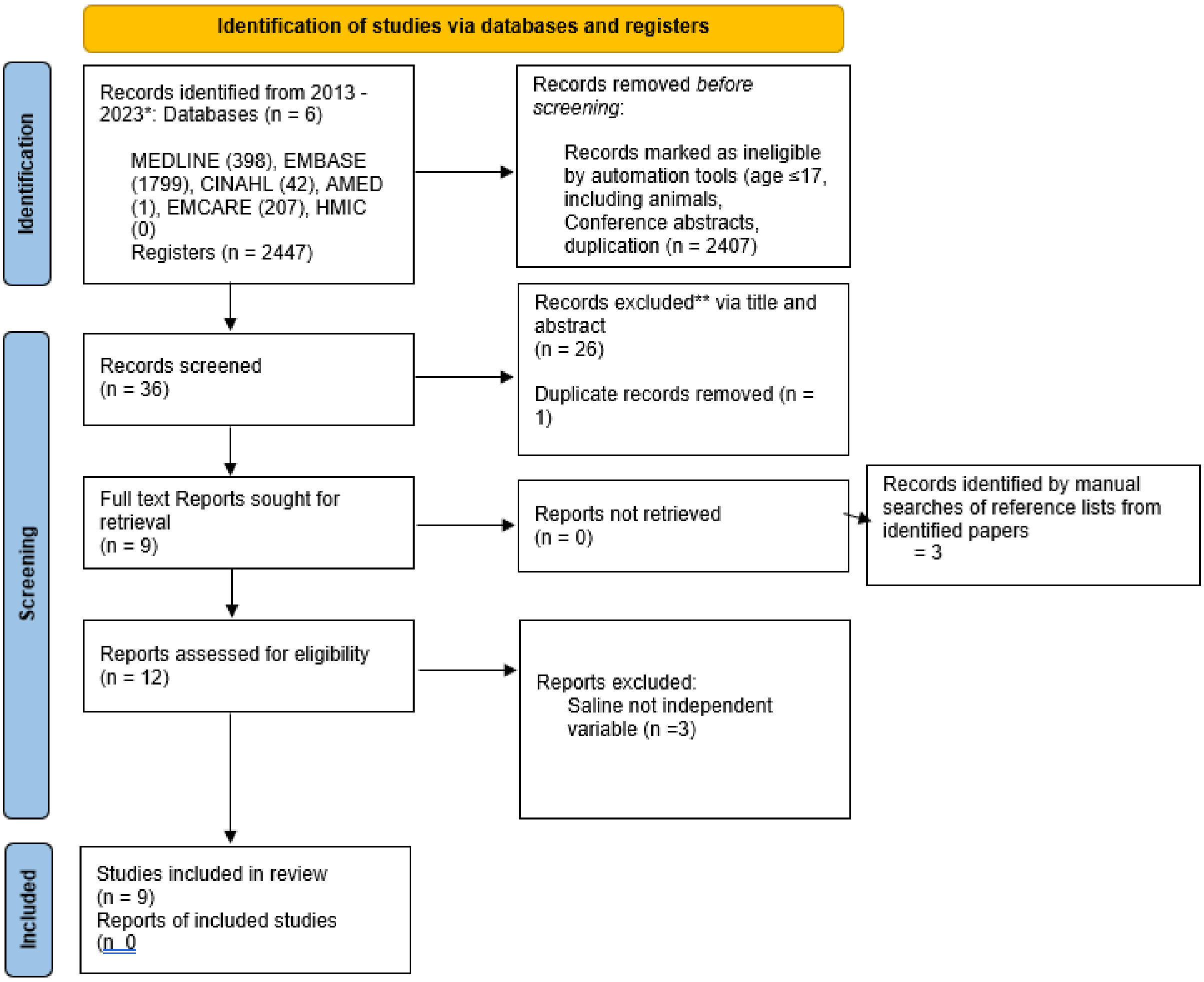
To reduce the risk of error and bias, two reviewers independently evaluated the study outcomes and extracted data from included studies using the data extraction form. The extracted data was summarised using descriptive statistics including frequency counts of populations, location of studies, study design, sampling technique, eligibility criteria, and outcome measures (%) and continuous variables and means (SD) or medians (Inter Quartile Range [IQR]) used to report study sample sizes. These descriptive statistics are displayed in tabular, graph and narrative format. As part of ongoing refinement in the data extraction process studies were clustered into observational and interventional studies to facilitate more meaningful data synthesis.

2.6 Risk of Bias Assessment

In keeping with the PRISMA-SCR recommendations, no meta-analyses were performed and studies were not assessed for risk of bias (Tricco et al., 2018).

2.7 Results

The database searches resulted in retrieving a total of 2447 papers. Discussions with field experts from the Association of Chartered Physiotherapists in Respiratory Care, Chartered Society of Physiotherapy and literature did not yield further articles. A PRISMA flow diagram was used to demonstrate the screening process from the articles retrieved as part of the scoping review (Figure 3). Removal of duplicates, conference abstracts, systematic reviews and meta-analysis, animal and non-English studies, resulted in 36 papers to be screened. Of these 36 papers, 27 were excluded via title and abstract screening. The full text for nine articles were obtained and three further articles were identified by a manual search of the reference lists from the identified papers. Twelve articles were subsequently screened for eligibility based on full text, resulting in three articles being excluded. Nine articles met fully the inclusion criteria and were included in this scoping review.



Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Figure 3. PRISMA Flow diagram (Page et al. 2021)

2.7.2 Publication dates and geographical location of included studies

Within the confines of the search eligibility criteria, publication dates ranged from 2014 (Adib et al., 2014; Deheki et al., 2014; Kalra et al., 2014; Schmollgruber et al., 2014) to 2017 (Ghaleb et al., 2017; Tan et al., 2017; van der Lee et al., 2017). Studies originated from most continents: four (44%) Asia, two (22%) Australasia, one (11%) Canada, one (11%) South

Africa and one (11%) Eurasia (Figure 4). All studies (n=9) were conducted in ICU settings due to the nature of the population and intervention.

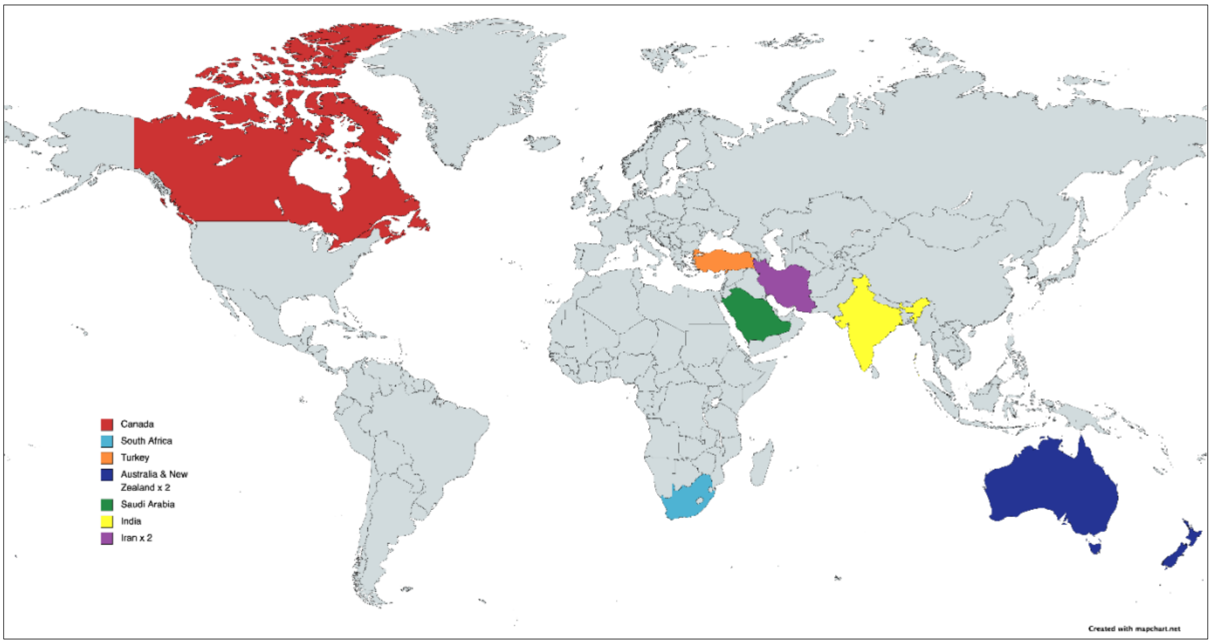


Figure 4. Global map highlighting countries of research origin.

2.7.3 Study Characteristics

An overview of study characteristics including demographics, design, sampling technique were summarised and displayed in Tables 3 and 4.

2.7.4 Study design

Of the nine studies included in the scoping review, four (44%) were cross-sectional surveys of practice and considered observational studies (Ayhan et al., 2015; Leddy & Wilkinson, 2015; Tan et al., 2017; van der Lee et al., 2017) and five (56%) were interventional clinical trials (Adib et al., 2014; Deheki et al., 2014; Ghaleb et al., 2017; Kalra et al., 2014; Schmollgruber et al., 2014) (Figure 5). Ayhan et al. (2015) although a systematic review, had an embedded evaluation of practice and therefore this part of the study is included in data synthesis. All interventional studies adopted an RCT methodology of which three (60%) used a cross-over design (Adib et al., 2014; Deheki et al., 2014; Ghaleb et al., 2017).

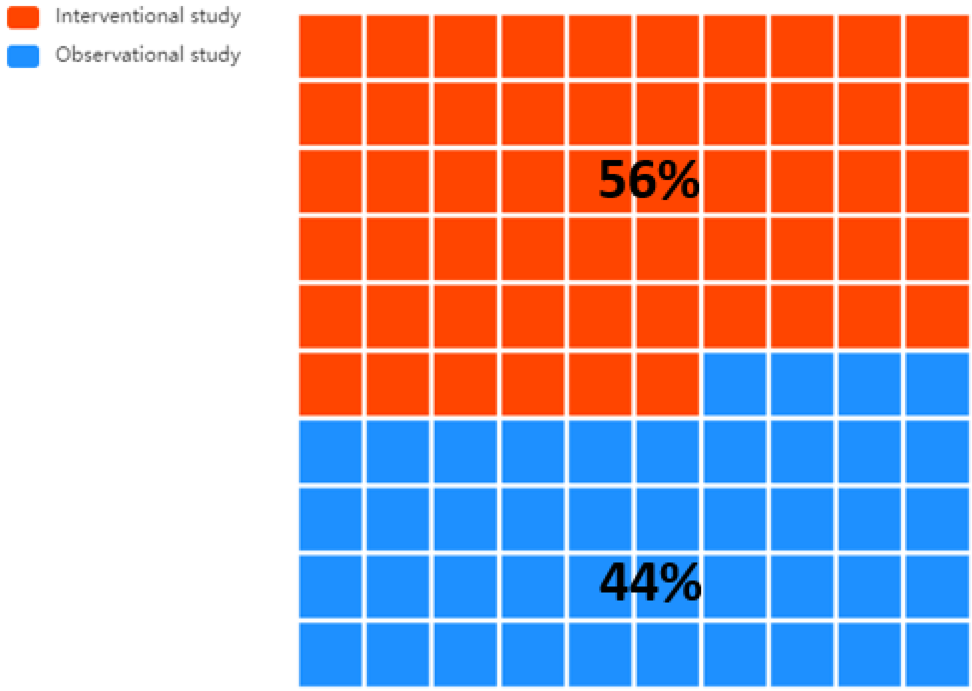


Figure 5. Waffle chart of the methodology used within included studies

To facilitate synthesis and discussion of the literature, interventional clinical trials (n=5) will be first synthesised and then observational studies of current practice (n=4).

2.8 Interventional clinical trials (Table 3)

All five studies aimed to assess the impact of NSI during ETS on cardio-respiratory parameters. Only Deheki et al. (2014) reviewed the effect of NSI on secretion yield, as well as comparing the effect of instilled N-acetylcysteine (NAC) and NSI.

2.8.2 Sampling technique and sample size

Of the five interventional studies, three (60%) utilised convenience sampling (Schmollgruber et al., 2014; Deheki et al., 2014; Ghaleb et al., 2017), one (20%) gradual sampling (Adib et al., 2014) and one (20%) total enumerative sampling (Kalra *et al.,* 2014). Sample sizes ranged from n=25 (Ghaleb et al., 2017) to n=150 (Kalra et al., 2014) with a median sample size of n=65 (IQR 54 – 74). In total 368 participants were included in all studies.

2.8.3 Population and exclusion criteria

All participants in the five interventional studies were MV. There was a wide range of exclusion criteria reported in the studies and displayed in Table 3. Four studies included Cardio-Vascular (CV) stability as part of their eligibility criteria, although no reason was provided (Kalra et al., 2014; Adib et al., 2014; Deheki et al., 2014; Ghaleb et al., 2017). However, the definition of CV stability varied between studies, with two studies excluding participants based on the requirement of vasoactive medication (Deheki et al., 2014; Ghaleb et al., 2017), one study requiring a systolic blood pressure (SBP) >90mmHg (Adib et al., 2014) and one study excluding participants with a reduced cardiac output (Kalra et al., 2014). Schmollgruber et al., (2014) specifically investigated the effects of NSI during ETS in patients undergoing cardiac surgery whilst in the other four studies the ICU speciality/reason for ICU admission was not recorded.

One common exclusion criterion stated in three of the papers was the requirement for frequent ETS (Kalra et al., 2014; Adib et al., 2014; Deheki et al., 2014). However, authors did not explicitly report the rationale for this exclusion criterion.

2.8.4 Control/intervention

All five studies reviewed the effects of NSI compared to no NSI during ETS. The volume of saline instilled before ETS ranged from 2 - 5mls (Table 3). Kalra et al. (2014) investigated different volumes of NSI (2ml vs 5ml) and Deheki et al. (2014) investigated the effects of NAC instillation compared to NSI.

All studies implemented their own standardised protocol for ETS with noticeable differences between protocols, in particular relating to technique (open vs closed suction), use of bag valve mask and suction pressure (Table 3). ETS pressures were documented in three studies (Kalra et al., 2014; Deheki et al., 2014; Ghaleb et al., 2017), ranging from 80mmHg – 200mmHg. Two studies adopted an open suction technique (Schmollgruber et al., 2014; Ghaleb et al., 2017) and three utilised closed-circuit ETS (Kalra et al., 2014; Deheki et al., 2014; Adib et al., 2014). Pre-oxygenation varied in both methodology and duration, with three studies reporting pre-oxygenating for 1 minute at FiO_2 1.0 (Kalra et al., 2014; Schmollgruber et al., 2014; Deheki et al., 2014), one study pre-oxygenating for 2 minutes (Adib et al., 2014) whilst Ghaleb et al. (2017) pre-oxygenated by bagging on FiO_2 1.0 for 1 minute. Only Schmollgruber et al. (2014) delivered a post ETS oxygenation bolus. Duration of ETS was up to 15 seconds however minimum duration of ETS was not documented in any of the studies.

2.8.5 Outcome measures (Table 3)

All studies collected cardiorespiratory outcome measures including SpO_2, heart rate (HR) and blood pressure (BP), except Kalra et al. (2014) who only recorded SpO_2 and HR (Table 3). ABGs were collected in two studies (Schmollgruber et al., 2014; Ghaleb et al., 2017). Adib et al. (2014) looked more in depth at ventilatory parameters including mean and peak airway pressures, end tidal carbon dioxide ($ETCo_2$) and percentage oxygen saturation haemoglobin. Only one study included secretion yield as an outcome measure (Deheki et al., 2014).

Outcomes were collected at varying time intervals ranging from pre ETS to 60 minutes post ETS. The frequency of data capture post ETS ranged from 2 to 5 time points with outcomes at 2 and 5 minutes the most commonly collected.

2.8.6 Interventional study findings

Studies did not demonstrate significant differences in cardio-respiratory parameters with and without NSI, regardless of NSI volume (Kalra et al., 2014; Schmollgruber et al., 2014). Kalra et al. (2014) reported no significant effect of NSI during ETS on SpO_2 & HR irrespective of NSI volume (2 or 5 mL) compared to ETS with no NSI ($p < 0.001$). Schmollgruber et al. (2014) reported no significant difference in SpO_2 between NSI and non-NSI, but 30 minutes post ETS 63.6% of patients in the NSI group did not return to baseline SpO_2 vs 37.5% of patients in the non-NSI group ($\chi2$ p=0.035; Fisher's exact p=0.048). Schmollgruber et al. (2014) also reported a significant drop in arterial blood pH with use of NSI but no significant difference in arterial oxygen saturation, HR, BP or bicarbonate.

Abib et al. (2014) reported a significant increase in diastolic BP, mean arterial pressure and HR immediately post ETS with and without NSI but a significantly greater increase in the NSI group. All CV parameters returned to near baseline within 5 mins in both groups. No significant difference in respiratory rate (RR), peak inspiratory pressure (PIP), mean airway pressure and SpO_2 were observed between groups post ETS. A significant increase in $ETCO_2$ in NSI group at 45 secs post ETS was reported but no significant difference 3 mins post ETS.

Deheki et al. (2014) reported statistically significant changes in HR, BP and RR, all increasing at 2 and 5 mins post ETS in all groups ($p<0.05$). SpO_2 reduced in all 3 groups at the same time points ($p=0.001$) with the greatest change in cardiorespiratory outcome measures in the NSI group at 2 minutes post ETS. They also reported that the use of instilled NAC during ETS yielded the greatest volume of secretions ($p=0.004$).

Table 3. interventional Clinical Trials demographics

Author / date / country	Study design	Aim	Sampling technique / sample size	Population	Exclusion criteria	Control /Intervention	Outcome measures	Results
Kalra *et al* 2014 India	Double blinded RCT Randomised using 'simple randomisation method'	To find effect of sterile isotonic NSI during ETS on SpO_2 and HR	Total enumerative sampling technique N=150	Inclusion criteria - Adults (> 18 years) - Admitted to selected ICUs - MV - Haemodynamically stable i.e. normal Cardiac output Demographics - 44.6% 51 – 71 years of age - 4.7% > 80 years old - 67.3% male - 82.6% MV for 0 – 100hours	Risk of bleeding e.g leukemia, hemophilia, coagulation disorders. Tracheobronchial anomaly Pulmonary diseases like ARDS, COPD, tuberculosis, pulmonary edema ↓cardiac output e.g. IHD, MI Requirement for frequent ETS PEEP > 10 cmH2O	**Control** - ETS no saline **Intervention groups** Group 1 - 2ml isotonic saline during ETS Group 2 - 5ml isotonic NSI during ETS During the intervention groups 2 puffs of bag-valve mask device to 'mix' NSI & secretions ETS protocol: - Pre-oxygenated (FiO_2 1.0) 1min prior to ETS - ETS (maximum 3) for max of 10–15s - Size 14 catheter - suction pressure 100 – 200 mmHg.	Following physiological parameters recorded pre, immediately post, 2 mins and 5 mins post ETS. -SpO_2 - HR	No significant effect of instillation of different volumes of sterile NSI (2 or 5 mL) on SpO_2 & HR (reduced or improved) as compared to ETS in absence of NSI use ($p < 0.001$).
Schmollgruber *et al* 2014	A prospective, randomised and comparative design	To determine the effect of NSI on cardiorespiratory parameters in intubated	Convenience sampling technique N=65	Inclusion criteria - Adults >18 - Intubated & MV	Not documented	Control - No NSI during ETS Intervention - 5mls of NSI during ETS	Following physiological parameters obtained 5 minutes pre ETS and at 1-, 5-, 10-, 30- and 60-minute intervals, post ETS. - SpO_2	**SpO_2** 30 minutes post ETS: 63.6% of patients in the NSI group failed to

South Africa	Simple random sampling	cardiothoracic patients		- With A-line, ECG and SpO_2 monitoring Pt undergoing cardiac surgery including: - CABG - Valve annuloplasty, repair or replacement - Heart or lung transplant, - Thoracotomies - Thoracic aneurysm repairs Demographics - 55.39% underwent CABG - 20.00% mitral valve repair - 15.38% AVR		ETS protocol: - Preoxygenated (FiO_2 1.0) 1 min prior to ETS. - ETS max 8 secs - Size 14Fr catheter - ETS performed 3 x - open technique. - Pre-oxygenated (FiO_2 1.0) for 1 minute post ETS	- HR - BP ABG 5 minutes pre ETS & 60 minutes post ETS	return to baseline SpO_2 v. 37.5% of patients in the non-NSI group ($\chi 2$ p=0.035; Fisher's exact p=0.048). ABG **pH** - Significant drop in pH with use of NSI during ETT **paO2** - Trend towards reduction in Po2 in both groups post Rx but greater drop in pAo2 in NSI group (no significant) **HCO3** - No significant difference in HCO3 **Arterial oxygen saturation / HR / BP** - No statistical difference between groups
Adib *et al* 2014 Northern Iran	Randomised cross over trial	To determine the effects of suctioning methods with and without NSI on hemodynamic and respiratory condition of patients.	Gradual sampling N = 74	Inclusion criteria - Pts MV >48 hours but < 1 week - CV stability (Systolic BP >90mmHg) - Size 7 – 8 ETT Demographics - 70% sedated - 66% male - Aged 18-78 - 82.4% on SIMV	Hx of heart diseases, HTN, COPD, cardiac and respiratory drug use. Use of NMBA MV adjusted in the study period. - Suction frequency > 2 hourly	**Control** - ETS without saline **Intervention** - 5ml NSI prior to ETS ETS protocol - Preoxygenated (FiO2 1.0) 2 min pre ETS. - ETS max 10 secs 120-minute washout between interventions	Outcome measures recorded at baseline, immediately post, 2 & 5 mins post ETS Outcomes - Systolic & diastolic BP - Mean arterial pressure - HR - RR - Mean airway pressure - Peak airway pressure % O2 saturated haemoglobin and ETCo2 at	- Significant ↑ in DBP, MAP and HR immediately post ETS in both groups but all CV parameters returned to near baseline within 5 mins - Statistically significant greater ↑ in HR immediately post ETS in NSI compared to non-NSI - No significant difference in RR, PIP, mean airway pressure, SpO_2 between groups post ETS

							15, 30 & 45 secs & then 1, 2, 3, 4 & 5 minutes post ETS	- Significant ↑ in ETCo2 in NSI group @ 45 secs but no significant difference 3 mins post ETS
Deheki *et al* 2014 Iran	Randomised cross over trial 'permutation random allocation'	Comparing the effect of using normal saline and N-acetyl cysteine with not using them in endotracheal tube suction on physiological parameters and the amount of secretion in intubated patients under MV hospitalized in ICUs.	Convivence sampling N=54	Inclusion criteria - Age > 15 years old - MV via ETT - Normal ICP - CV stability – no inotropes - No COPD - No history of drug addiction Demographics - 57.6% male - Mean age 57.35	Exclusion criteria - Extubated prior to end of trial - Use of inotropes - Bronchoscopy completed during the study - Sepsis - Requires suction intervals of < 2 hours	**Control** - no saline/nac ETS **Intervention** Saline - 3mls instillation down ETT prior to suction N-Acetylcysteine - 2ml inserted down ETT prior to suction. All patients received all 3 interventions. ETS protocol - Preoxygenated (FiO_2 1.0) 1 min pre ETS. - ETS 10 seconds - Suction pressure 80 – 120 mmHg Each ETS modality was completed 3 times. 2 hours washout period between interventions	Following physiological parameters collects pre ETS and 2 & 5 mins post suction - SpO_2 - HR - BP - RR Volume of secretions	**SpO_2/HR/BP/RR** - Statistically significant reduction in SpO_2 in all 3 methods at 2 and 5 mins post suction (p0.001) - Statistically significant increase in HR/BP/RR at 2 and 5 mins post suction in all 3 interventions (p0.05) - Greatest change in SpO_2, HR, BP and RR in the NSI group ($p<0.05$) - Biggest change in SpO_2/HR/BP RR was 2 mins post suction in all interventions **Secretions** - Largest secretion yield was in the N-Acetylcysteine group P=0.004
Ghaleb *et al* 2017	Randomised cross-over experimental	To compare the effect of endotracheal suction with and without	N = 25 Convenience sample	Inclusion criteria - Adults 20 -60yrs	Exclusion criteria - Head injury	**Control** - ETS without saline **Intervention** - ETS with 5mls NSI	Pt demographics, medical hx	**HR** - Statistically significant differences between mean HR were observed between groups in favour of non-NSI p= 0.024

Saudi Arabia	'random sampling'	instillation of normal saline on oxygen saturation, blood pressure, heart rate and arterial blood gases in adult mechanically ventilated patient		- intubated with ETT and supported with MV - CV stable – no vasoactive medication - A-line in-situ Demographics - Mean age 44.64 +- (15.8) - 52% between 50 – 60 years of age - 56% females - 48% respiratory pathology of which 1/3 were aspiration pneumonia - 16% RTC - 12% GI and 12% neuro disorders - 48% were post-op - 68% had an ICU LOS of 1 – 5 days - 60% emergency intubation	- Vasoactive medication titration	ETS technique repeated x2 ETS protocol - Preoxygenated (FiO_2 1.0) 1 min pre ETS using MHI but only 3 bpm - ETS <10 secs - Suction pressure set @ 150mmHg - Open suction - Post ETS MHI for 1 min 2–4-hour washout between interventions	SpO_2, HR, BP measure pre and 1, 2, 3, 4, 5 minutes post ETS ABG pre, 1, 2 and 5 mins post ETS Auscultation post suction $Pa/fi0_2$ ratio	- Within saline group statistical difference between baseline, 1, 2 and 5 mins p= 0.015, 0.026, 0.038 - With saline HR returned to baseline within 5 mins post suction. Without saline HR did not return to baseline values **Blood pressure** - No statistically difference in diastolic BP between groups - Did not do statistical analysis on systolic BP **SpO_2** - No statistically significant difference within or between groups within 5 mins **pH** - No statistical difference between 2 suction techniques **paCO2** - Statistically significant difference within 5 minutes with NSI and suction p=0.021 - Statistically significant difference at 1, 2 mins in NSI p = 0.012, p=0.004 - No statical difference between groups - Without saline pCo_2 returned close to baseline after 2 mins. With NSI returned after 5 mins **PaO2** - Statistically significant difference within 5 minutes with NSI and suction p=0.015

								- Statistically significant difference (increase) at 1, 2 mins in NSI p = 0.012, p=0.020 - No statistical difference between groups - Greater increase in PaO_2 pre and post 5 minutes suction in the NSI group **$Pa/fi0_2$ ratio** - Within NSI statistically significant difference within time points p=0.021 in particular at baseline, 1,2 and 5 minutes p=0.029, p=0.015, p=0.002. - Mean $Pa/Fi0_2$ ratio increased in both groups at 1 and 2 minutes - Unable to interpret due to poor reporting

RTC: randomised controlled trial; NSI: normal saline instillation; ETS: endotracheal suction; SpO_2: peripheral oxygen saturation; HR: heart rate; ICU: intensive care unit; MV: mechanically ventilated; ARDS: Acute respiratory distress syndrome; COPD: Chronic Obstructive Pulmonary Disease; IHD: Ischemic heart disease; MI: Myocardial Infarction; CABG: Coronary artery bypass graft; AVR: Aortic Valve Replacement; BP: Blood pressure; ABG: arterial blood gas; $Pa0_2$: partial pressure of Oxygen; $paCo_2$: partial pressure of carbon dioxide; HCo3: Bicarbonate; CV: cardiovascular; RR: respiratory rate; ETT: endotracheal tube; ICP: intercranial pressure; SIMV: Synchronised Intermittent Mandatory Ventilation; RTC: Road traffic collision; LOS: Length of stay; MHI: Manual hyper-inflation; FiO_2: Fraction of inspired oxygen

2.9 Observational studies / questionnaires of practice (Table 4)

Four studies aimed to review current practice of a range of healthcare professionals including nursing, physiotherapy and registered respiratory therapists and their perceptions, practice and use of NSI in ETS (Ayhan et al., 2015; Leddy & Wilkinson, 2015; Tan et al., 2017; van der Lee et al., 2017).

2.9.2 Sampling technique and sample size.

Three studies adopted a purposeful sampling technique (Leddy & Wilkinson, 2015; Tan et al., 2017; van der Lee et al., 2017) and one used voluntary participation strategy (Ayhan et al., 2015). Sample sizes ranged between 65 (Ayhan et al., 2015) and 170 (Leddy & Wilkinson, 2015) with a median sample size of n=94 (IQR 73 – 127). In total 451 participants were included in the observational studies.

2.9.3 Population and exclusion criteria

All observational studies evaluated the opinions and clinical practice in the use of NSI of healthcare professionals working within ICUs in different global healthcare settings (Table 4b) (Ayhan et al., 2015; Leddy & Wilkinson, 2015; Tan et al., 2017; van der Lee et al., 2017) (Table 4). Leddy & Wilkinson (2015) examined the ETS practices of registered nurses and registered respiratory therapists. Ayhan et al. (2015) looked at ICU nurses in isolation and Tan et al. (2017) and van der Lee et al. (2017) explored the ETS practices of physiotherapists. The setting for Ahyan et al. (2015), Tan et al. (2017) and van der Lee et al. (2017) studies was adult critical care units. The characteristics of the critical care unit in the Leddy & Wilkinson (2015) study is unclear.

Leddy & Wilkinson. (2015) did not define a minimum level of clinical experience to participate in the survey, whilst two studies stated a minimum of three months (Ayhan et al., 2015) and five years of ICU experience of which 12 months was as a senior physiotherapist on ICU in the last five years (van der Lee et al., 2017). Tan et al, (2017) did not quantify the clinical experience required to participate in the study but stated the 'most experienced physiotherapists' were identified by the department manager.

2.9.4 Data Collection tools

All studies (n=4) utilised questionnaires for data capture. Tan et al. (2017) and van der Lee et al. (2017) used online questionnaires with 5-point Likert scales, multiple choice and open-ended questions. The format for the questionnaires distributed by Ahyan et al. (2015) and Leddy & Wilkinson (2015) are unclear. To reduce reporting error, Leddy & Wilkinson (2015) adopted a peer review process when developing their questionnaire.

2.9.5 Outcome measures

Questionnaire domains of all studies (n=4) included participant and ICU demographic data, NSI use and reasons for use and practice related to ETS (Table 4).

2.9.6 Observational study findings

The reported use of NSI as part of ETS varied widely between studies with Tan et al. (2017) and van der Lee et al. (2017) reporting between 42.8% to 51.5% never or rarely used NSI compared to 87.7% use of NSI prior to ETS in the Ayhan et al. (2015) study. All studies report secretion viscosity and difficulty in clearing secretions as reasons for NSI use (Ayhan *et al.,* 2015; Leddy & Wilkinson*,* 2015; Tan *et al.,* 2017; van der Lee *et al.,* 2017). One to 5mls of saline during ETS was reported (Ayhan et al., 2015; Leddy & Wilkinson, 2015). Reasons for non NSI use included lack of evidence (Tan et al., 2017) or risk of harm and ineffectiveness (Ayhan et al., 2015). Practice of ETS and NSI varied between RN and RRTs in terms of pre-oxygenation, use of NSI and awareness of ETS protocols (Leddy & Wilkinson*.,* 2015)

Table 4 - Observational study / questionnaires of practice demographics

Author / date / country	Study design	Aim	Sampling technique / sample size	Population	Exclusion criteria	Data collection method	Outcome measures	Results
Ayhan et al. 2015 Turkey	Descriptive study	To evaluate NSI use for adult patients by ICU nurses and assess the views of nurses on this topic.	Voluntary participation ICUs in Turkey from 01/02/13 to 25/02/13 N = 65 nurse participants	ICU nurses with > 3 months ICU experience	None stated	Questionnaire 11 questions - 5 related to defining characteristics of the nurses - 6 related to the use of NSI before ETS.	Demographics ETS and NSI practice	Demographics - Female 100% - Median age 27 (IRQ 22 – 38) - 87.7% BSc degree - Average ICU experience 3 years 87.7% used NSI before ETS Of those who used NSI; - 100% used to liquify secretions to make easier to clear - 77.1% used NSI based on secretion characteristics - 1 - 4mls saline used - 26.3% used nebulisers - 18% used mucolytic or nebulised medication - 15% changed patient position 42.1% of nurses who use NSI do so despite their belief it might be harmful, with 91.6% thinking it ↑ lung infection risk & 34.8% thinking it ↓ SpO_2 8 nurses never use NSI - 50% (n=4) because they believe NSI is of no use - 50% (n=4) believe NSI is harmful
Leddy et al. 2015	Questionnaire of current practice	To examine the suctioning practices of registered nurses	Convenience sample N = 170 participants	Registered nurses and registered respiratory therapists working within 6 ICUs in Ontario	Not documented	24 question survey titled "Suctioning an Artificial Airway in the ICU" developed by authors and	4 questionnaire topics Demographics - level of education	No significant difference between RN & RRTs demographically RRTs had a significantly higher awareness of unit VAP rates and

Canada		(RNs) and registered respiratory therapists (RRTs) with special attention devoted to the use of NSI.	- 83 RN - 87 RRTs			further reviewed by independent clinicians. Questions were based on peer reviewed scientific literature	- duration of years on ITU - year of qualification - shift pattern Normal (intubated) patient care practices within the ICU - humidification technique - awareness of VAP rates - routine pre-oxygenation - awareness of protocols for mouth care - checking of ETT cuff pressures - suctioning frequency Practices relating to NSI before suctioning - use of NSI - preparation of NSI - NSI practices Influences on individual practice.	protocols for daily checking of ETT cuff pressure and mouth care. RRT significantly more likely to pre-oxygenate patients prior to suctioning No significant difference awareness of presence of a suctioning protocol, experience with suctioning MV patients or suction type routine. Poor awareness of presence of an NSI suction protocol (47% RN & 40% RRT) RN significantly more likely to instil NSI during ETS. No significant difference in NSI preparation or volume of NSI used; - 1 mL to 2 mL (RRT 50.0%; RN 41%) - 3 mL to 5 mL (RRT 46.2%; RN 51.8%); No significant difference between timing of ETS post NSI - Immediately post NSI (RRT 79.2%; RN 67.1%). - up to 1 min post NSI (RRT 16.9%; RN 30.5%) - 1 - 2 min post NSI (RRT 3.9%; RN 2.4%). No significant difference in reasons for use of NSI. Most frequently reported use to loosen secretions or stimulate cough. RRTs reported NSI to thin secretions not reported by NS

								Evidence based practice recorded as the greatest influence on ETS & NSI use in RN & RRT
Lee et al. 2017 Australia	Cross sectional online survey	To identify the degree of variability in physiotherapy practice for intubated adult patients with CAP To explore ICU physiotherapist perceptions of current practice for this cohort and factors that influence physiotherapy treatment mode, duration, and frequency	Nationally distributed survey Survey disseminated through direct contact with physiotherapy manager or via professional networks of the research team N=104 physiotherapists from 88 Australian hospitals	Australian ICUs Physiotherapists with >5 years clinical experience and minimum 12 months experience as a senior physiotherapist working in adult ICU in the last 5 years	8 ICU senior Physiotherapists involved in the piloting process	42 item questionnaire over 3 domains Data collection over 2 x 3-week periods - 22/10 - 12/11/2014 - 22/04 - 13/05/2015 Reminder email sent to participants after 2/52 Categorical scales were used for survey items, which measured demographic and service data Likert scales were used for items, which asked therapists to rate their preferences, beliefs, and clinical reasoning regarding their management of the patient.	Participant demographics ICU and physiotherapy service delivery Physiotherapy management and clinical reasoning for Intubation and MV patients with CAP	72% survey response rate (n = 75). Highest qualification of respondents was BSc degree 50% (n = 24/48), PG dip 2% (n = 1/48), MSc degree 24% (n = 17/48), PhD 10% (n = 5/48), and postdoctoral degree 2% (n = 1/48) 51.5% (n=33/64) rarely or never used NSI. 13% (n = 8/64) used NSI always or frequently 62% (n=37) would use NSI if secretions were very thick or tenacious 20% (n=12) would use NSI when secretions are difficult to suction 10% (n=6) when other techniques for clearing secretions were unsuccessful
Tan et al. 2017 Australia and New Zealand	Electronic survey Cross-sectional observational study	To report the current suctioning practices of experienced physiotherapists working with adult patients who are intubated and MV in an ICU in	Purposeful sampling – utilisation of modified dillman approach to optimise participation Nationally distributed survey to	Hospitals with capacity to intubate and ventilate adult patients for >24hours. Survey responder - 'most experienced physiotherapists' as identified by the physiotherapy department manager.	ICU accommodated primarily neonatal or paediatric case mix No ICU which intubate and ventilate patients for >24 hours	Electronic Survey with 4 sections comprising of 44 questions. 5 point Likert scale 0 – 5 ranging from 'all patients' to 'none of the patients' for the majority of questions Small proportion of questions were in the	Sections 1 & 2 relating to characteristics of ICU and physiotherapists completing the survey Section 3 - Factors that shaped suctioning practices Section 4	Characteristics of ICUs - 59.8% of ICUs had between 1-10 ventilator capable beds and 4.5% of ICU had >30 ventilator capable beds - 51.8% of ICU provided day time physio only - 32.1% provided day time physio and oncall overnight - 0.9% provided 24 hour physio

		Australia or New Zealand.	hospitals via Australian and New Zealand ICU for outcome resource database and the National Health Performance Authority 136 hospitals meeting the eligibility criteria. – 4 excluded due to shared staffing cohort 112/132 (84.8%) participation rate (surveys completed)			format of multiple choice or open ended questions	- Questions relating to Open Sterile Suction vs Closed Sterile Suction - Hyperoxygenation - Hyperinflation - Saline lavage Whether subglottic suctioning was available	Physio characteristics - 75% of physio responders had >5 years experience with cardiopulmonary caseload - 76.8% had BSc and entry level of diploma - 13.4% had a post-graduate physio degree - 3.6% had PhD - 6.3% further post-graduate qualification - 83.9% had worked on 2 or more ICUs Saline lavage - Saline lavage was infrequently used on 'all' or 'most' of the patients (3/112, 2.5%). - Saline lavage reported as never used in 48 (42.8%) responses. - Most frequently reported reasons for not performing saline lavage 'lack of evidence' 13/31 (41.9%) - 64 (57%) responders utilised saline for a proportion of their pt cohort - For staff that reported using saline lavage and provided a documented reason (n=59), 100% reported using it when treating 'thick tenacious secretions that were difficult to clear'

NSI: Normal Saline instillation; ICU: Intensive Care Unit; ETS: endotracheal suction; ETT: Endotracheal tube; SpO_2: peripheral oxygen saturation; RN: registered nurses; VAP: ventilator acquired pneumonia; CAP: Community acquired pneumonia; MV: MV RRT: Registered Respiratory Therapists.

2.10 Discussion

This scoping review of primary interventional and observational studies between 2013 – 2023 looking at NSI use as part ETS identified no primary or observational research completed within the last 5 years, raising questions about the relevance of study findings in modern, post-pandemic healthcare, and demonstrates the need of up-to-date research regarding NSI use during ETS. The identified studies spanned four continents; however, none were European based, limiting the generalisability of clinical findings reported based on differences in medical management, clinical autonomy and potential variance in clinicians underlying knowledge and skills and variations in patient demographics and social determinants of health.

All interventional studies adopted a RCT design demonstrating methodological rigour. Data collection in the observational studies was done via a questionnaire and primarily focused on investigating the reason for NSI practice. Although questionnaires are an efficient and cost-effective way to access a large cohort of participants, it does not allow for a full understanding of phenomena due to the nature of their design and is subject to responder bias (Phillips et al., 2016). None of the included studies utilised focus groups or consensus methodologies to develop criteria around the use of NSI.

Interventional studies primarily focused on the effects and safety of NSI on cardiorespiratory parameters but did not focus their aims on sputum characteristics i.e. yield, and/or viscosity, with only Deheki et al. (2014) including volume of secretions as part of their outcome measures. The aims of the observational studies were to assess current practice and reasons for NSI use as part of ETS and highlighted secretion viscosity and difficultly in clearing secretion as the primary reasons for NSI use. There was a clear disparity between the aims of the interventional studies and the reasons for NSI use highlighting a gap within the literature around interventional studies addressing the efficacy of NSI on secretion clearance.

All interventional studies had relatively small sample sizes which would have resulted in low statistical power, with no power calculations reported. The convenience sampling method adopted by most studies introduces potential sampling bias and raises questions about the external validity of findings. The extensive eligibility criteria and limited ICU specialities included in the interventional studies potentially excludes a cohort of patients with a high secretion burden such as patients with VAP, where the use of NSI would have potential benefit, as rationalised within the observational studies, and reduces the external validity of the finding in clinical practice.

The observational studies sought opinions and daily clinical practice related to NSI during ETS however opinions and practice of critical care physicians was omitted. This is significant given the variance within the scope of practice of different professional groups internationally, where sometimes clinical care is medical consultant prescribed resulting in lack of autonomy in some healthcare settings.

All interventional studies used a ETS protocol. However, there was significant methodological heterogeneity including the volume of NSI, ETS technique e.g. open or closed suction techniques, and surrounding ETS practice e.g. MHI pre/post ETS, and ETS pressures. These are all potentially significant confounding variables when extrapolating the results for interpretation into wider practice e.g., the disconnection of patients from MV to perform open ETS has potential to influence respiratory function through the loss of positive end expiratory pressure and de-recruitment.

All interventional studies recommended against the routine use of NSI during ETS, stating detrimental effects on cardiorespiratory outcome measures. However, the statistically significant changes on cardiorespiratory parameters reported in these studies could be seen as not clinically significant. The results of the observational studies highlight the ongoing polarised opinion in the use of NSI during ETS among critical care clinicians. This is despite the American Association for Respiratory Care (AARC) clinical practice guidelines stating routine use of NSI should be avoided (Blakeman et al., 2022).

It is acknowledged that this scoping review has limitations. By excluding non-English language articles, a potential publication, language and reviewer bias is introduced (Neimann Rasmussen & Montgomery, 2018). However, with the cost and time constraints associated with the translation of non-English work it was not feasible to undertake translation of non-English papers within the scope of this project. There is a risk that primary literature has been inadvertently missed despite the structure and broad eligibility criteria but the use of two independent reviewers in this process minimised the risk or error and improved the rigour of the search (Stoll et al., 2019).

2.11 Conclusion

This scoping review highlighted the limited up-to-date research investigating the effects of NSI during ETS. Methodological heterogeneity in the existing literature makes drawing firm conclusions surrounding NSI practice, informing evidenced based practice guidelines and clinical recommendations challenging. The gap in primary research objectively looking at the efficacy of NSI during ETS on secretion clearance i.e., secretion yield, highlights a future research opportunity.

Based on the finding of this scoping review it is evident that a robust RCT is required to determine the efficacy of NSI on secretion clearance, particularly within physiotherapy clinical practice. However, given the absence of robust evidence to guide an RCT, a feasibility study would be warranted to ascertain acceptability and deliverability of the intervention before proceeding to a definitive trial.

3.0 CHAPTER 3 – Methods

This chapter presents the aims and objectives of the feasibility study. It will outline the methodological approach used and provide justification why the chosen research design is appropriate. It will outline methods and procedures implemented during the study and introduce data collection tools and outcome measures used to answer the research questions. Processes for undertaking analysis of the data will also be described. To ensure transparency and quality of the reporting, the study is reported according to the CONSORT 2010 statement: extension to randomised pilot and feasibility trials (Eldridge et al., 2016).

3.1. Aim and objectives

3.1.1 Research Aim

In this feasibility trial, the aim was to explore patients' acceptability of NSI use during chest physiotherapy and examine the trial design and proposed outcomes measures. Additionally, it is to provide data to demonstrate the feasibility of delivering a definitive RCT examining the efficacy of NSI during chest physiotherapy on secretion yield in patients mechanically ventilated on ICU with a VAP.

3.1.2 Research Objectives

Primary objectives were:

1. To assess how many eligible patients consented to participate in the study.
2. To assess the retention rates of patients recruited to the study.
3. To determine the feasibility of delivering the intervention on ICU to patients MV with a VAP.
4. To assess completion rates of case report forms (CRF) and outcomes measures (missing data).

Secondary objectives were:

1. To assess the feasibility of sputum related outcome measures as methods to measure efficacy of interventions within a definitive trial.
2. To pilot a new method for quantifying sputum yield.
3. To determine the safety of delivering the intervention to patients MV with a VAP.

3.2 Study Design

3.2.1 Research paradigm

Prior to commencing any new study, the philosophy and design of the intended research needs to be considered (Creswell, 2014), as Denzin and Lincoln (2005) state every researcher approaches the world with a set of ideas, a framework (ontology) that specifies a set of questions (epistemology), that he/she examines in a specific way (methodology/analysis). By examining the nature of the research question, the methods required to answer it can be determined.

Quantitative research aligns with a realist ontology and is born from a positivist philosophy. Positivism is guided by the principles of objectivity and deductive logic and arises from the ontological view that there is a single truth or reality out there (Bruce et al., 2018). The goal of the researcher is to find 'the truth', through the collection and analysis of numerical data to test a specific theory or hypothesis (Park et al., 2020). This allows contextual influences to be removed and guides the methods for gathering and analysing data to ensure objective truths and generalisable results are produced (Park et al., 2020). The scoping review highlighted a lack of robust evidence around the use of NSI during chest physiotherapy despite its common use, and consequently provided an opportunity to hypothesise its influence on secretion yield. An experimental design using quantitative methods was therefore appropriate for this study.

3.2.2 Study design.

Interventions within a healthcare setting command robust evaluation, with the consensus amongst most health researchers that this is best achieved with a RCT (Wallace et al., 2022). RCTs are considered the gold standard for evaluating efficacy and safety of interventions and informing healthcare strategies by providing the highest level of evidence (Burns et al., 2011; Wallace et al., 2022; Zabor et al., 2020). However, complex interventions comprising of a high number and variability of outcomes, and a degree of flexibility of the intervention, like that in this study, pose additional methodological and logistical challenges (Djurisic et al., 2017).

The UK MRC guidance on designing and evaluating complex interventions recommend rigorous feasibility work as an integral process towards highlighting challenges and problems that might arise in an RCT of a complex intervention (Skivington et al., 2021). Feasibility testing allows components of a proposed trial to be evaluated and can provide valuable insights into potential problems that might develop in the ensuing definitive trails such as treatment acceptability and data collection processes (Arain et al., 2010). This allows refinement of the subsequent larger trial and ensures research is conducted safely, ethically and produces high quality, cost effective, reliable evidence that is generalisable in a real-world context (Lancaster, 2015; Leon et al., 2011). This is paramount in ICU, where the complex nature of patient care and competing clinical trials can be detrimental to the success of research (Delaney et al., 2008).

The UK MRC guidance also recommends strong and early engagement with patients, practitioners and policy makers when developing complex interventions (Skivinghton et al., 2021). Subsequently, to help develop the intervention in this feasibility study, existing literature on the use of NSI during pulmonary lavage was reviewed, along with endotracheal suctioning guidelines and recommendations from national physiotherapy groups including the ACPRC and Chartered Society of Physiotherapy around the use NSI. This process helped develop and align the intervention with recognised and accepted guidelines utilised within an ICU setting, which has been shown to improve the acceptability and future adoption of interventions in a real-world clinical setting (O'Cathain et al., 2019). Additionally key stakeholders including the research and development team, ICU multi-disciplinary team (medical practitioners, physiotherapists, nursing staff) and ICU specific patient and public involvement (PPI) groups with lived experience of critical illness were engaged throughout all stages of the research process. This iterative process helped refine the intervention and overcome practical barriers associated with its delivery.

Given the identified paucity of research in this area and complex nature of the NSI intervention, a single centre, feasibility, crossover RCT was conducted to determine the merits and viability of the proposed study to answer the question 'can this study be done?' (Bowen et al., 2009)

3.2.3 Cross over trial

To address the studies aims and objectives, a crossover design was used (Figure 6). In crossover trials, participants become both arms of the study, allowing the effect of an intervention to be measured on the same individual and as such participants serve as their own control (Sedgwick, 2014). By doing so, the researcher can minimise the risk of confounding variables and utilise smaller sample sizes (Sibbald & Roberts, 1998). However, Sedwick (2014) highlights the risk for aliasing, in that the effect of the previous intervention may have an effect on the next intervention, therefore reducing the reliability of the results and either over-estimate or under-estimate the treatment effect size. To minimise the risk of aliasing, a washout period between interventions was implemented with one intervention delivered in the morning and one in the afternoon with no ETS performed 1 hour prior unless clinically indicated. A one-hour washout period aligns with methodology used in other clinical trials examining the use of NSI during pulmonary lavage (Ji et al., 2002). It was also felt to be realistic, clinically safe and pragmatic given the likely high secretion burden and suction requirements in patients with a VAP.

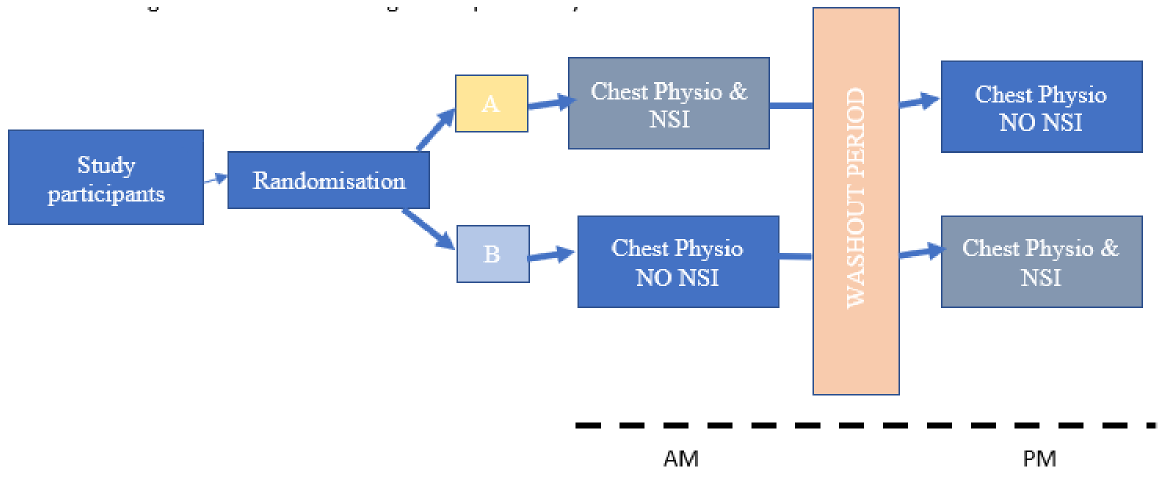


Figure 6 – Crossover design example for day 1 of trial intervention.

3.4 Study Participants

Patients MV on ICU for >48 hours meeting the inclusion/exclusion criteria were eligible for participation (Table 5). The eligibility criteria were created alongside medical practitioners to minimise potential risk of harm in a vulnerable patient group who are acutely unwell and may lack capacity. Patients deemed to have a potential VAP as assessed on the Clinical Pulmonary Infection Score (CPIS) were discussed with the treating ICU consultant to confirm the VAP diagnosis and appropriateness for enrolment in the trial. Substantial variability exists in VAP diagnosis, but CPIS is considered the 'gold standard' diagnostic criteria (Shan et al., 2011). For consistency of data analysis, a committee with two senior intensivists experienced in VAP diagnosis were constituted. If there was disagreement, a third clinician arbitrated the diagnosis of VAP. Criteria for VAP diagnosis used clinical, radiological, and microbiological signs (Table 6)

Table 5: Participant inclusion and exclusion criteria

Inclusion Criteria	Exclusion criteria
• Aged >18 to 85 years old • Sedated and receiving invasive MV via endotracheal tube or tracheostomy >48 hours • Recruited within 48 hours of diagnosis of a VAP • Diagnosis of VAP using the CPIS and medical practitioner confirmation of VAP. • Anticipated to remain on invasive MV for at least 24 hours	• Diagnosis of COVID 19 • Unstable ventilation – SpO_2 of <90% on FiO_2 >.8, PEEP >12 • Chest wall trauma / surgery that impedes physiotherapy treatment techniques that can increase expiratory flow • Treatment withdrawal expected within 24 hours • Unstable cardiovascular or neurological function or injury preventing positioning for physiotherapy pressure • Undrained pneumothorax or bronchopleural fistula • Patients who aspirated during intubation or subsequently whilst intubated • Patient diagnosed with acute respiratory distress syndrome or acute pulmonary oedema • The treating clinician believes that participation in the trial would not be in the best interests of the patient • Patients with a Spinal cord injury • Patients transferred from another hospital

Table 6. Clinical diagnostic criteria for presence of VAP

VAP clinical diagnostic criteria
• Fever or hypothermia (tympanic temperature >37.8°C or hypothermia core temperature <35°C), • Abnormal total white-cell count (>10,000 /mm^3, or leukopenia with a white-cell count <4500 /mm^3) • Deterioration of oxygenation / PaO_2/FiO_2 ratio • Increase in tracheal secretions or change is colour or viscosity. • Chest X-ray (new or progressive infiltrate characteristic of pneumonia or a new consolidation) • C-reactive protein (CRP) measurements.

3.5 Study setting

The study was undertaken at a University Hospital located in the West Midlands area of United Kingdom. The hospital is a single centre, with a 100 bed ICU providing level 2 and 3 care to critically ill adult patients. As a regional major-trauma centre and specialist oncology, liver and cardiothoracic transplant service provider, the hospital's ICU admits approximately 3500 patients annually. It provides elective and emergency care to patients locally, regionally and nationally from medical, surgical, trauma, burns, liver, cardiac and neurosurgical specialities.

3.6 Patient screening

Between June 2023 and January 2024, every weekday morning, the treating physiotherapists screened all patients MV for >48 hours against the inclusion/exclusion criteria to identify eligible patients. Screening data, including reasons for non-enrolment, was recorded onto the trial screening log which was kept in accordance with national research guidelines (MRC, 2007). This was to ensure transparency of the recruitment process, to allow monitoring of recruitment rates and to help justify if the eligibility criteria needed revising (Lewis et al., 2020).

3.7 Consent process

All eligible patients were approached Monday to Friday for participation in the study. Most patients on ICU lack capacity due to an altered level of consciousness as a result of their illness and effects of therapeutic sedation (Bjerregaard Alrø et al., 2024). A personal consultee was therefore approached in a face-to-face meeting or telephone conversation or an independent registered medical practitioner if no personal consultee was available. Personal consultees were the designated next of kin (NOK) in the medical notes. The study was verbally explained by a study team member with Good Clinical Practice (GCP) training and a Consultee Information Sheet (CIS) provided (Appendix 1). All patient/NOK information was co-designed with critical care PPI groups with lived experience of critical illness. Personal consultees were given up to 24 hours to process the information and to decide if they wanted their NOK to participate in the study. If declaration for their NOK to participate was given, a consultee declaration form was signed (Appendix 2).

In accordance with the codes of ethical research, if a patient regained capacity after the initial consent of the personal consultee or registered medical practitioner, they were provided with a Participant Information Sheet (PIS) and consent to continue was sought. It was recognised that this cohort are vulnerable due to the psychological, cognitive and physical impact of critical illness (Newman et al., 2022), therefore giving the patient time to process participant information was paramount. If they declined ongoing participation, data already collected was included in analysis. If the patient died before regaining capacity or failed to regain capacity by hospital discharge, the consultee declaration stood.

3.8 Intervention

3.8.1 Allocation

All patients recruited to the study received 2 sessions of daily chest physiotherapy, one in the morning and one in the afternoon. The intervention lasted for 3 days or until the patient was extubated, whichever came sooner. To minimise the impact of any "time of day" effect, recruited patients were randomised to receive either treatment regime A or B on day 1 of the study (Table 7 & 8). Regime A received chest physiotherapy with NSI during the morning session, and chest physiotherapy without NSI in the afternoon session on day 1. Regime B received chest physiotherapy without NSI in the morning session but chest physiotherapy with NSI in the afternoon. Interventions then alternated between chest physiotherapy treatment with and without NSI.

Table 7 – **Treatment regime A**

Day post recruitment & randomisation	**Am treatment**	**Pm treatment**
Day 1	Chest physiotherapy **with** NSI	Chest physiotherapy **without** NSI
Day 2	Chest physiotherapy **without** NSI	Chest physiotherapy **with** NSI
Day 3	Chest physiotherapy **with** NSI	Chest physiotherapy **without** NSI

Table 8 – **Treatment regime B**

Day post recruitment & randomisation	**Am treatment**	**Pm treatment**
Day 1	Chest physiotherapy **without** NSI	Chest physiotherapy **with** NSI
Day 2	Chest physiotherapy **with** NSI	Chest physiotherapy **without** NSI
Day 3	Chest physiotherapy **without NSI**	Chest physiotherapy **with** NSI

3.8.2 Normal Saline instillation

During chest physiotherapy sessions with NSI, 3mls of 0.9% sodium chloride solution was directly instilled into the patient's lungs via the ETT port using a 5ml syringe for each cycle of 'chest physiotherapy' and closed ETS. Given the absence of national guidelines regarding NSI use during chest physiotherapy, 3mls was chosen in line with data published from a survey of physiotherapy practice by Reeve et al. (2007) which reported 1 – 5mls was most commonly used by physiotherapists. Three millimetres was used in previous clinical trials which demonstrated no adverse events, including rates of atelectasis and ETT occlusion (Caruso et al., 2009; Pattanshetty & Gaude, 2010).

In cases of unilateral VAP or secretion retention, NSI was targeted to lavage the affected lung through patient positioning i.e. For a right lobe VAP, NSI was performed with the patient in right side lying, using gravity and airway anatomy to encourage saline to enter the right lung. The patient was then positioned so the affected lung was uppermost (i.e. right lung) before receiving chest physiotherapy and ETS.

3.8.3 Endotracheal suctioning

To ensure a standardised approach to ETS, the AARC Clinical Practice guidelines for artificial airway suctioning recommendations were used (Blakeman et al., 2022) (Appendix 4). On cessation of the physiotherapy interventions, the suction catheter was flushed with 1ml of 0.9% saline to remove any residual secretions in the suction catheter. This was collected in the sample pot and accounted for when performing sputum analysis (Table 11).

3.8.4 Chest Physiotherapy

The following chest physiotherapy techniques were used during each treatment session.

3.8.4.1 Chest vibrations

Chest wall vibrations (CWV) (McCarren & Alison, 2006) defined as the manual application of a fine oscillatory movement combined with compression to the patient's chest wall will be applied prior to suctioning.   During CWV, physiotherapists compress the patient's chest wall rapidly at the beginning of expiration, with oscillatory pressure continued until expiration is complete. This technique is believed to imitate a huff or cough by increasing expiratory flow and propelling secretions into the larger airways for removal by suction or cough.

Treatment efficacy may be impacted by clinician's experience and CWV technique (amplitude, duration and frequency of vibrations) (Shannon et al., 2010). To minimise variability between and within treatment sessions, the same physiotherapist with >6 months ICU experience delivered the morning and afternoon chest physiotherapy session.

In the case of a unilateral VAP or unilateral secretion retention, patients will be positioned in side lying with the affected lung up before CWV applied. Hands will be positioned anteriorly and laterally on the chest wall to deliver CWV.

In patients with a weak and ineffective cough, this may have been supplemented with an assisted cough during ETS. The use of additional physiotherapy adjuncts i.e., manual and ventilator hyperinflation, to aid secretion clearance was left to the discretion of the treating physiotherapist.   Sedation levels, presence of a cough and use of additional chest physiotherapy adjuncts was recorded on the CRF.

3.8.5 Escalation of treatment in the non-saline arm

NSI use during designated 'no NSI' treatment sessions was at the discretion of the treating physiotherapist. Escalation to the use of NSI was recorded in the CRF.

Standard care in the form of nursing, pharmacological therapy, bronchodilators, antibiotic therapy, as advised by the treating consultant continued as normal throughout the study. Patient management including changes to ventilatory setting also remained at the discretion of the treating consultant.

Confounders recorded on the CRF form are displayed in Table 9.

Table 9. Confounding variables

Confounding variables
• Use of 0.9% sodium chloride and 3 % hypertonic saline nebulisers • Use of mucolytics • Frequency of nursing staff suction over the course of the day • Sedation level on the Richmond agitation scale and presence of a cough reflex on suction • Time since last suction • Type of humidification circuit i.e. HME, Fisher Paykel

3.9 Patient Risks

The risk of harm to trial participants was considered low as ETS and chest physiotherapy are common interventions on ICU. To minimise the risk of transient, short-term hypoxemia reported in the literature, all patients were pre-oxygenated with FiO_2 1.0 for 2-mins before ETS. Hyperoxygenation results in higher levels of arterial oxygen saturation and pressure of arterial oxygen with no adverse effects (Demir & Dramali, 2005).

3.10 Outcome measures

3.10.1 Primary outcome measures

The primary outcome measures were feasibility measures and focused on the ability to recruit and retain eligible participants, deliver the trial intervention and collect outcome data. Thresholds to proceed to a definitive trial are displayed in Table 10.

Table 10. Primary Feasibility outcome measure.
1. Ability to recruit and retain patients to the trial • Patient recruitment - > 75% of eligible patients recruited to the study • Patient Retention – > 75% retention of recruited patients to the study
2. Protocol fidelity • > 75% of patients receive the 2x daily chest physiotherapy sessions • <15% of missing data

Recruitment targets were set at 75% of eligible patients in line with a review by Walters et al. (2017) that demonstrated the median recruitment rate across 141 RCTs was 70% and 75% when analysing single centre studies. To ensure reliability and validity of results, retention rates were set at 75% in acknowledgement that >25% attrition has been shown to increase risk of bias (Gillies et al., 2021).

3.10.2 Secondary outcomes

Secondary outcomes included the objective measurement of secretion yield through calculation of adjusted wet sputum weight and sputum pellet weight after each treatment session (Table 11). Physiological response to interventions with and without NSI was recorded by the treating physiotherapists using the ICU monitor and ventilator located in the patient's bedspace. Physiological measurements were taken at a single time point, immediately before, and at 2- and 10-minutes post intervention. Adverse and safety events were also collected using pre-defined definitions. Baseline demographics and hospital outcomes were collected from electronic patient records.

Table 11. Secondary outcome measures.

Outcome	Definition / method
Adjusted wet sputum weight	Measured using OHAUS Explorerª Precision Balance calibrated digital scales. 25ml Pennine sputum traps were weighed pre and post treatment. To calculate the weight of instilled saline, 10ml syringes containing 9mls of saline and 2ml syringes containing 1ml of saline (flush post treatment) were weighed pre and post treatment. The difference in the syringe weights post treatment represented the instilled saline weight. The difference in sputum

	trap weight minus the saline weight was reported as the adjusted wet sputum weight.
Sputum pellet weight – based on McElvaney et al. (2019) protocol	McElvaney et al. (2019) protocol • Sputum samples were centrifuged at 442g for 10 minutes at 4 degrees before removing the supernatant. (McElvaney et al., 2019) Adopted protocol (Appendix 3) • Sputum samples were centrifuged at 4500g for 10 mins at 4 degrees before removing the supernatant using a pipet. The resultant sputum pellet was weighed on OHAUS Explorerª Precision Balance calibrated digital scales by deducting the weight of the sputum trap pre-treatment from the weight of the sputum trap post removal of the supernatant
Physiological and ventilator markers	- Lung compliance (mls/cmH_2O) - Tidal Volumes (mls) - Peripheral oxygen saturations (SpO_2) - Heart rate (beats per minute) - Systolic and diastolic blood pressure (mmHg)
Safety outcomes	• Incidence of Endotracheal tube plugging off • Significant hypoxemia defined as a drop in SpO_2 < 90% associated with NSI during or up to 30 minutes post treatment requiring an increase in FiO_2 • Ventilator or circuit dysfunction with respiratory deterioration.
Baseline demographics	• Age (years) • Gender • Body Mass Index (BMI) • Acute Physiology and Chronic Health Evaluation (APACHE) II 2 (Knaus *et al.,* 1985) – illness severity score ranging from 0 -71 with increasing score associated with higher risk of hospital mortality • Charlson Co-Morbidity Index (Charlson *et al.,* 1987) - predicts 10-year survival in patients with multiple co-morbidities • Sequential Organ Failure assessment – used to determine extent of individual organ failure or rate of failure (Vincent et al., 1996). Score ranges from 0 (best) – 27 (worst)

3.11 Sample size

As a feasibility study, the National Center for Complementary and Integrative Health (2017) recommend sample size should be set on practical considerations. Given the available time and resources, it was felt a sample size of 30 patients was realistic to recruit over the 6-month study period. This figure aligns with Lancaster et al. (2004) recommendation that a sample size of 30 is sufficient to estimate parameters such as standard deviation for a sample size calculation. For the primary objective of estimating the dropout rate, assuming a rate of approximately 75% retention, a sample size of n=30 would yield a confidence interval width of ±15 percentage points (i.e. 60-90%) which was deemed reasonable (NIHR 2021).

3.12 Sampling technique

Patients were selected using a convenience sampling approach. Specifically, all consecutive patients on ICU Monday to Friday who were MV for >48 hours with a VAP and who meet the eligibility criteria were approached for consent. Convenience sampling is cheap, efficient and simple to implement (Bornstein et al., 2013) and meant patients could be approached and recruited as they became available (Jager et al., 2017). However, the generalisability of results derived from this approach are limited to the sample studied and may lead to under-representation of certain sociodemographic subgroups (Bornstein et al., 2013). The future definitive trail may explore whether probability sampling techniques could be employed to reduce selection bias, but given the available resources for this study, convenience sampling was adopted.

3.13 Randomisation

The randomisation sequence for the intervention was produced prior to commencing the study by an independent statistician using “R” software. Block randomisation was used to prevent excessively long runs of consecutive patients being assigned to the same arm. This approach is beneficial where recruitment targets may not be met, as it ensures sample sizes in the two arms will be similar regardless of the total number of patients recruited. This is paramount for statistical analysis with small sample sizes as, for a given sample size, having unequal numbers of patients in each study arm generally leads to a reduction in statistical power, relative to having equal numbers (Efird, 2011).

A limitation of block randomisations is that if the block size is known, then it can be possible for researchers to predict the allocation of the next patient based on the previous allocations. To negate this, a variable block size was used, with the size of each successive block being randomly selected from the list: 2, 4, 6, 8.

The independent statistician sent the randomisation sequence to an individual independent of the research team. They placed the regime assignments into sealed, opaque envelopes numbered one to 30, which were then stored in a locked draw. After recruiting a patient and obtaining consent, an individual not responsible for collecting outcome measures opened the envelope with the patients' study number to reveal the treatment allocation (A or B). The date and time the envelope was opened was recorded.

3.14 Blinding

Given the intervention, it wasn't feasible to blind the treating physiotherapists to the treatment allocation. However, to minimize detection bias, the outcome assessor for sputum pellet weight was blinded to the treatment session from which samples were obtained. This involved centrifuging and processing all sputum samples regardless of the treatment administered. Furthermore, the researcher responsible for statistical analysis was not involved in data collection pertaining to treatment sessions i.e., physiological parameters.

3.15 Data Analysis

As the primary intention of the study was demonstrating the feasibility of a trial, its goal was descriptive, not inferential. Descriptive statistics were therefore used for primary feasibility outcomes of recruitment, retention, and protocol fidelity, as well as safety outcomes and patients' baseline characteristics. An adapted CONSORT diagram for pilot and feasibility studies was used to illustrate patient flow (Eldridge et al., 2016). Inferential statistics were used for all other quantitative data related to secondary outcomes and then summarised for the cohort as a whole. Continuous variables were assessed for normality graphically, and presented using the appropriate measures of central tendency. Specifically, variables that were approximately normally distributed were reported as "mean ± standard deviation", with "median (interquartile range; IQR)" used otherwise (Krithikadatta, 2014).. Categorical variables were reported as frequencies and proportions.

Session-specific factors were then compared between the two treatment arms. For continuous and ordinal variables, comparisons were performed using Mann-Whitney U tests, with nominal variables assessed using Fisher's exact tests or Chi^2 tests for factors with two, or more than two categories, respectively (Pallant, 2020). Physiological outcomes were measured at three time points, each of which was compared separately between the two treatment arms. Sputum weights were quantified using two different approaches; the consistency of these was assessed using Spearman's rank correlation coefficients (rho) (Pallant, 2020).

All analyses were performed using IBM SPSS 24 (IBM Corp. Armonk, NY), with $p<0.05$ classified as statistically significant throughout. However, it is acknowledged achieving statistical significance was not the primary goal of this feasibility trial. Consequently, the study was underpowered to detect potentially clinically meaningful differences in the secondary outcomes being analysed; hence, these comparisons will have an inflated false-negative rate, and need to be interpreted in light of this (Suresh & Chandrashekara, 2012).

3.15 Ethical Considerations

The research met the criteria for "intrusive research" and thus the outlined patient consent process has been informed by the guidance of the Medical Research Council for non-CTIMP, nonemergency, research in England (http://www.hradecisiontools.org.uk/consent/index.html), which is informed by the Mental Capacity Act 2005.

The study gained approval from the University of Birmingham Research Governance (RRK7898) team in addition to ethical endorsement from the Essex Research Ethics Committee (IRAS ID: 318205) (Appendix 5) and Health Research Authority (HRA) (Appendix 6). The study was locally approved by the Trusts Research and Development department. It was conducted in accordance to the ethical principles derived from the Declaration of Helsinki and followed the principles of GCP and by doing so the potential risks to participants were minimised and informed consent was obtained (Beauchamp & Childress, 2001; MRC, 2007; Worldmedical-association, 2013); International Committee Harmonisation, 2016).

Data collected for individual participants on the CRF were anonymised through a unique participant study number allocated at the time of randomisation. Data from the CRF was entered onto a secure password protected database held on a Trust computer with access restricted to authorised personnel. Due care was taken to ensure data safety and integrity, and compliance with the Data Protection Act 2018. Study documentation and data will be archived after completion for at least 10 years as per the sponsor’s regulations.

4.0 CHAPTER 4: Results

This chapter presents the results of the feasibility study in tabular and graphical format with statistical analysis undertaken for comparing outcomes between treatment arms where appropriate. Results are reported as per the CONSORT 2010 checklist for reporting pilot or feasibility studies (Eldridge et al., 2016)

4.1 Primary Outcomes

4.1.1 Recruitment and Retention

Between June 2023 and January 2024, 37 patients met the initial inclusion criteria and underwent screening. Of these, 32 were deemed eligible and were approached for enrolment. Two patients' (6%) NOK declined patient participation in the study with reasons displayed in **Figure 7**. Consultee declaration was provided for the remaining 30 (94%), who were enrolled.

All 30 patients commenced the study and received at least one physiotherapy session. Two patients (7%) were subsequently withdrawn by the NOK during the study intervention period after undergoing one and three physiotherapy sessions, respectively; no reason for withdrawal was provided. Of the remaining 28 patients, one was transferred to another ICU post intervention, five died in ICU and three died in hospital, meaning consultee declaration remained valid. Of the remaining 19 patients, 10 did not regain capacity at the point of hospital discharge, meaning consultee declaration remained valid. Of the remaining 9 patients, all 9 (100%) provided consent for ongoing participation. Consequently, the primary outcomes of recruitment and retention were achieved, with 94% (30/32) of eligible patients recruited, and 93% (28/30) completing the study intervention..

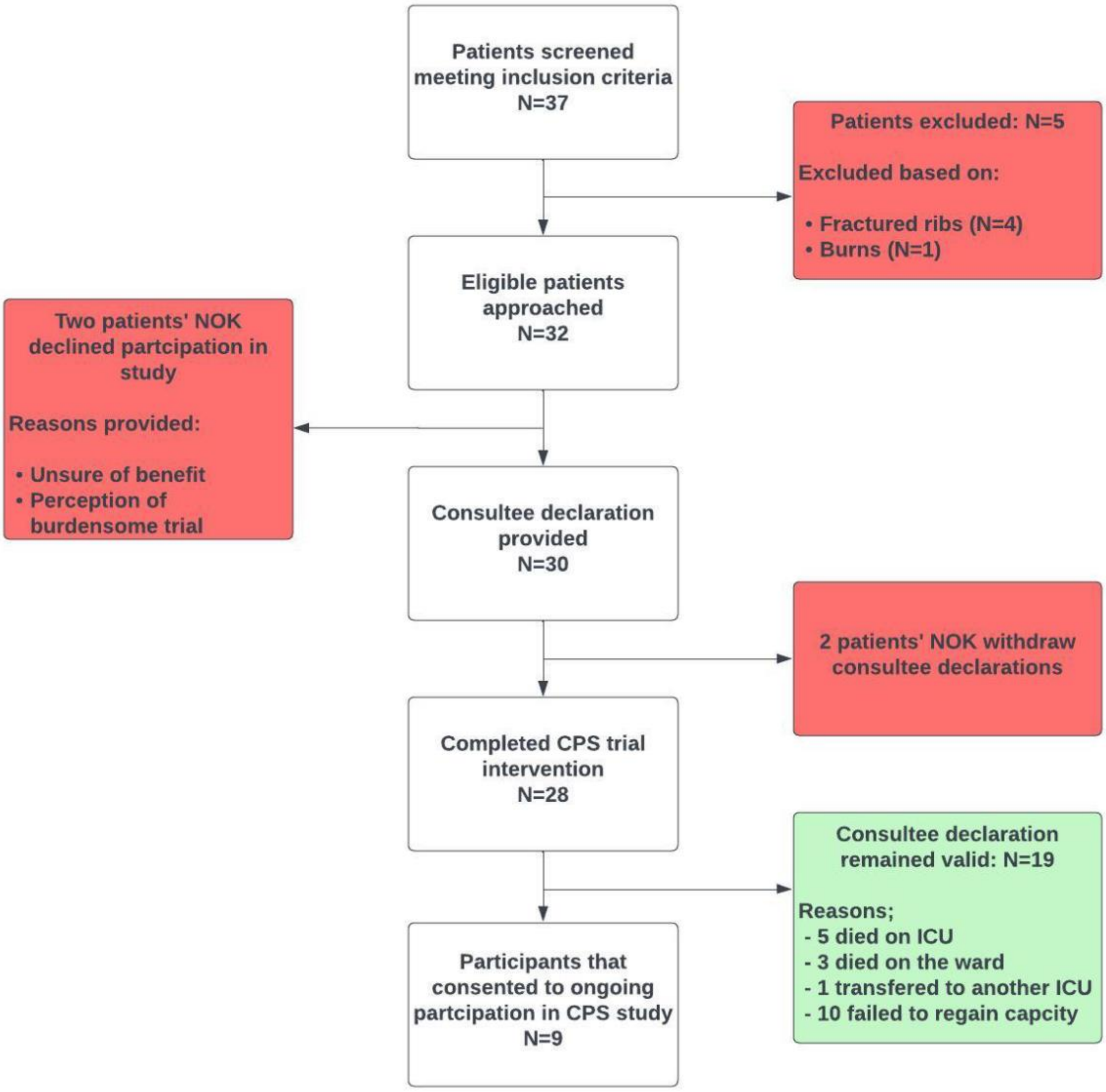


Figure 7. Recruitment and retention

4.2 Cohort Characteristics

Of the 30 patients enrolled in the study, 53% (n=16) were male with a median age of 57 (49–61) years and median Body Mass Index (BMI) of 26.4kg/m^2 (IQR: 23.4 – 30.9). Most patients were of white ethnicity (n=22; 73%) and admitted to ICU for a primary neurological condition (n=17; 57%). The median SOFA score on ICU admission was 8 (IQR: 6 – 8) and the mean APACHE II score was 15.2±6.4 representing an estimated hospital mortality of 24%. The mean CPIS at the point of VAP diagnosis was 7.6±0.6 ***(Table 12).***

Table 12. Patient demographics

Patient Demographics	n =30
Age (Years)	57 (49 – 61)
Gender (% Male)	16 (53%)
Ethnicity *White* *Asian* *Black*	 22 (73%) 7 (23%) 1 (3%)
BMI (kg/m^2)	26.4 (23.4 – 30.9)
Charlson Co-morbidity Index	2 (1 – 3)
Primary Admission diagnosis *Neurological* *Surgery/sepsis* *Respiratory* *Trauma/Burns*	 17 (57%) 6 (20%) 4 (13%) 3 (10%)
SOFA score on admission	8 (6 – 8)
APACHE II	15.2 ± 6.4
CPIS	7.6 ± 0.6

Data are reported as "N (%)", "median (interquartile range)" or "mean ± standard deviation", as appropriate. BMI: Body Mass Index, SOFA: Sequential Organ Failure Assessment – score ranges from 0 (best) – 24 (worst), CPIS: Clinical Pulmonary Infection Score APACHE II: Acute Physiology and Chronic Health Evaluation II. -score range 0 - 71

4.3 Protocol fidelity

Intervention

Twenty-one (70%) patients completed the study intervention receiving six physiotherapy sessions. The remaining nine (30%) patients did not complete the intervention, with the number of missed sessions ranging from one to five per patient, resulting in 27 missed sessions. Patient liberation from MV was the most common reason for failing to meet ongoing inclusion criteria (six patients; 17 sessions), followed by consultee declaration being withdrawn (two patients; eight sessions) and decision to move to end-of-life care (one patient; two sessions). In addition, clinicians deviated from the study protocol for four sessions (3% of completed sessions) in two patients, using NSI in the non-saline session ***(Figure 8)***. Specifically, for one of these patients, protocol deviations occurred in all three planned non-saline sessions, due to secretion viscosity in two instances and mucus plugging in the remainder. The other patient had a deviation to use NSI in their first session, due to secretion viscosity, but was treated as per the protocol for the remaining sessions.

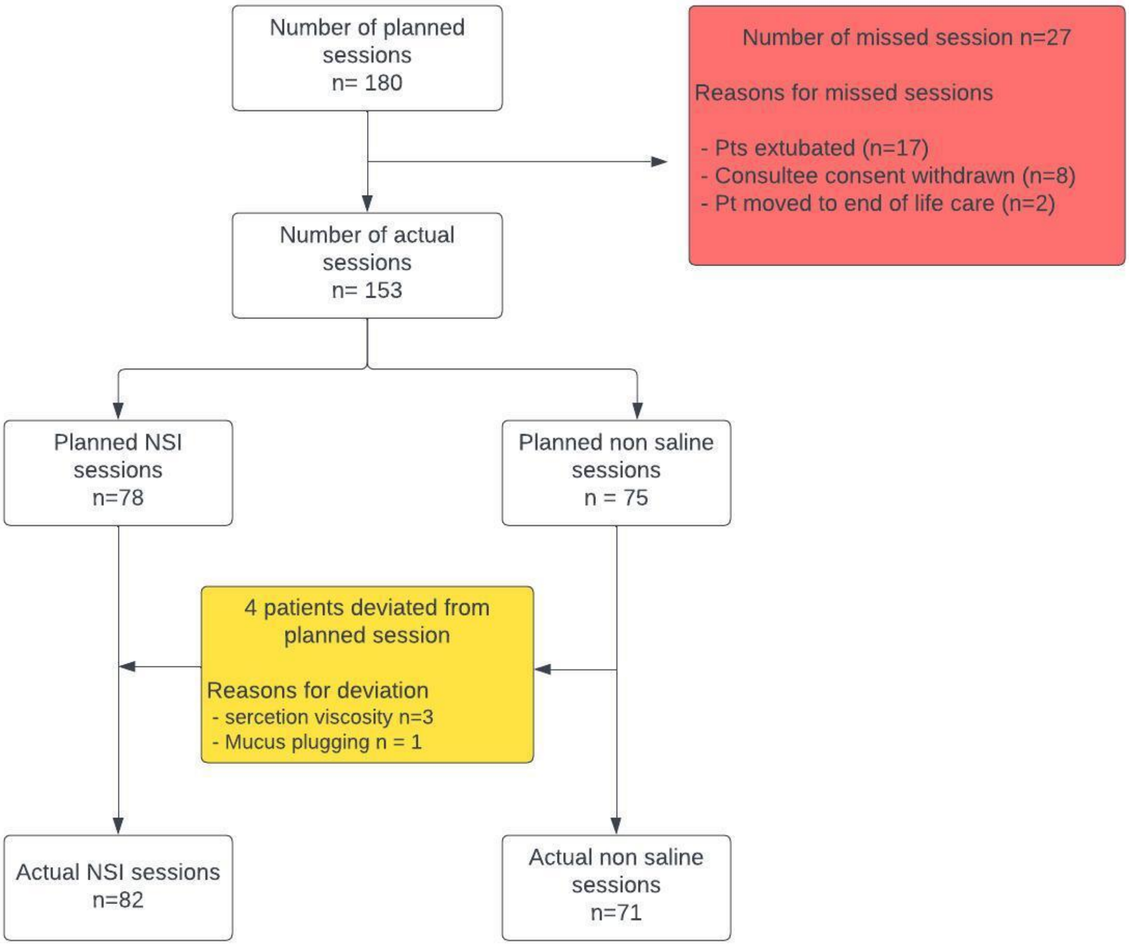


Figure 8. Treatment interventions

4.3.1 Missing data

For the patients enrolled in the study (n=30), data completeness was 100% for all variables collected across the physiotherapy sessions that were performed. Static lung compliance was only recorded in 26 (17%) sessions due to the requirement for the patient to be on mandated modes of ventilation, however this was 100% complete for all relevant sessions.

4.4 Treatment session characteristics

A total of 82 sessions were completed with NSI and 71 sessions without saline, of which 43 (52%) and 35 (49%) sessions were completed during the morning session respectively ***(Table 13)***. No statistically significant differences in the airway, mode of ventilation, sedation practice, medical management, consciousness levels, time from last suction or rates of safety events were observed between saline and non-saline treatment sessions. There was a significant difference in type of humidification used (*p*=0.031); however, this reflected one patient on a heated and humidified circuit who deviated from the study protocol interventions and received NSI in all six sessions. The duration of chest physiotherapy treatment was significantly longer in the NSI group, with a median of 15 minutes (IQR: 10 – 20) vs. 12 minutes (IQR: 10 – 15) (*p*=0.011), with patients receiving a significant greater number of suctions in NSI sessions (*p*=0.002). Additional physiotherapy adjuncts outside of the study protocol were used in 38 sessions, 22 (27%) times in the NSI intervention and 16 (23%) in the non-saline, although not statistically different between arms. The distribution of the reasons for treatment cessation did not differ significantly between arms (*p*=0.148), with "no evidence of retained secretion" being the most common.

Table 13. Treatment session characteristics

Treatment intervention	**NSI**	**Non saline**	***p* value**
Total treatment sessions	n=82	n=71	-
N (%) of AM sessions	43 (52%)	35 (49%)	0.872
Airway			
ETT	62 (76%)	56 (79%)	0.702
Tracheostomy	20 (24%)	15 (21%)	
Mode of ventilation			
Spontaneous	70 (85%)	57 (80%)	0.518
mandatory	12 (15%)	14 (20%)	
Receiving sedation	39 (48%)	36 (51%)	0.747
RASS at time of Ax			
-5	7 (9%)	7 (10%)	
-4	19 (23%)	17 (24%)	
-3	19 (23%)	14 (20%)	
-2	11 (13%)	15 (21%)	
-1	10 (12%)	10 (14%)	0.558*
0	12 (15%)	7 (10%)	
+1	4 (5%)	1 (1%)	
Mucolytics prescribed	30 (37%)	28 (39%)	0.741
0.9% saline nebs prescribed	5 (6%)	5 (7%)	1.000
Cough stimulated (Y)	80 (98%)	68 (96%)	0.664
Type of humidification			
HME filter	76 (93%)	71 (100%)	**0.031**
Heated and humidified circuit	6 (7%)	0 (0%)	
Time since last suction (mins)	115 (70 – 170)	95 (71 – 139)	0.323
Number of suctions completed in session			
1 – 2	25 (30%)	36 (51%)	
3 – 4	32 (39%)	32 (45%)	**0.002***
5 – 6	20 (24%)	1 (1%)	
>6	5 (6%)	2 (3%)	
Sessions were adjuncts used outside of study protocol			

VHI	15 (18%)	11 (15%)	0.673
MHI	6 (7%)	2 (3%)	0.286
Assisted cough	1 (1%)	3 (4%)	0.338
Duration of chest physiotherapy (mins)	15 (10 - 20)	12 (10 - 15)	**0.011**
Reason for treatment cessation			
No evidence of retained secretions	81 (99%)	66 (93%)	
Ineffective treatments	0	3 (4%)	
Patient agitation	0	1 (1%)	0.148
Wheeze	0	1 (1%)	
Unable to pass suction catheter	1 (1%)	0	
Safety events	0 (0%)	1 (1%)	0.464

*Data are reported as "N (%)" with p-values from Chi^2/Fisher's exact test, or as "median (interquartile range)" with p-values from Mann-Whitney U tests, unless stated otherwise; bold p-values are significant at p<0.05. * p-Value from a Mann-Whitney U test, as the factor is ordinal. ETT: Endotracheal Tube, RASS: Richmond Agitation & Sedation Scale, VHI: Ventilator Hyper-inflation, MHI: Manual Hyper-inflation*

4.5 Secondary outcomes

4.5.1 Sputum outcomes

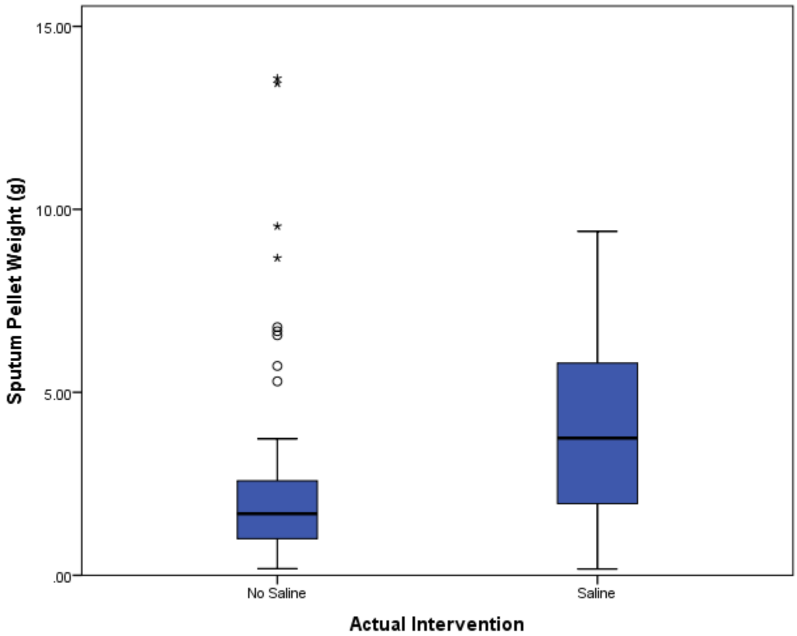
The mean weight of saline instilled during NSI sessions was 5.75g±2.59. There was no significant difference in the proportion of samples with a visible loss of the sputum sample (p=0.131) between arms ***(Table 14).***

Table 14. Sputum outcomes

Treatment intervention	NSI	Non saline	P value
Total treatment sessions	n=82	n=71	
Saline weight used including 1ml flush'(g)	6.80 ± 2.57	1.05 ± 0.09	n/a
Saline weight instilled (g)	5.75 ± 2.59	0	n/a
Sessions with visible loss of sputum sample	13 (16%)	5 (7%)	0.131
*Estimated volume loss (mls)**	2 (1 – 3)	2 (2-3)	0.416
Adjusted Wet Sputum Weight (g)	-0.40 (-2.15 – 1.11)	0.97 (0.22 – 2.11)	**<0.001**
Sputum Pellet Weight (g)	3.75 (1.96 – 5.80)	1.68 (0.99 – 2.60)	**<0.001**

*Data are reported as "N (%)", with p-values from Fisher's exact tests, or as either "median (interquartile range)" or "mean ± standard deviation", with p-values from Mann-Whitney U tests; bold p-values are significant at p<0.05. *In sessions with visible loss of sample. 'g': grams*

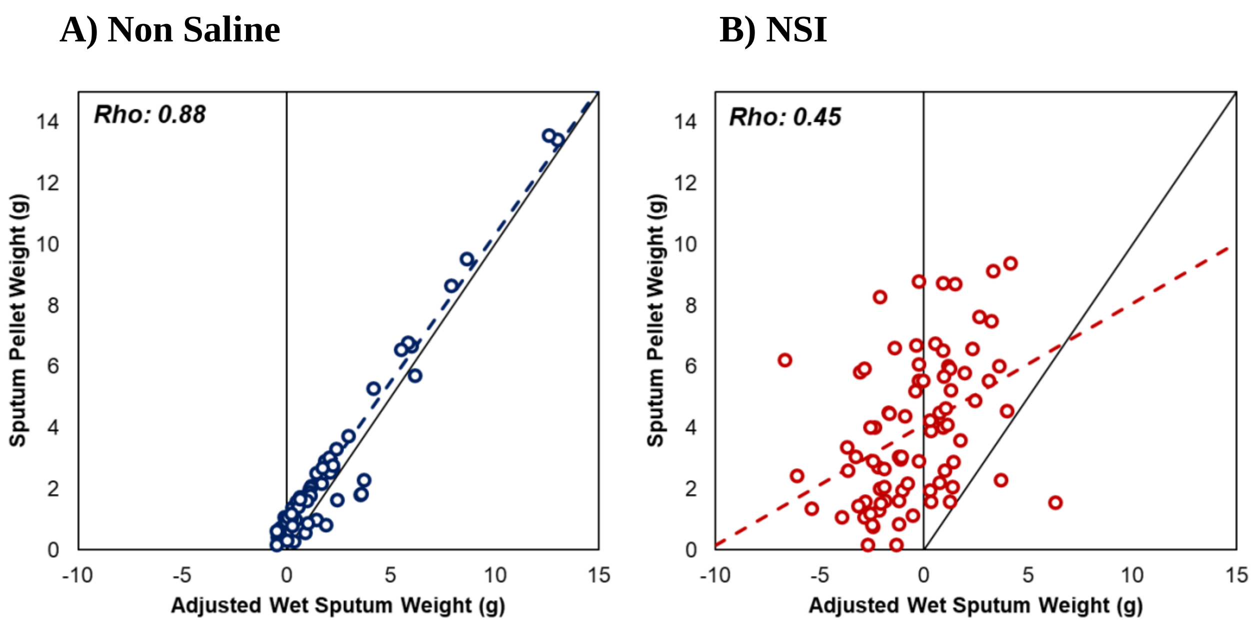
The quantity of sputum cleared was quantified using two different approaches. The adjusted wet sputum weight was found to be significantly higher in interventions without saline (median: 0.97g vs -0.40g; *p*<0.001) compared to interventions where saline was used. However, the negative median value in the NSI interventions indicated that not all instilled saline was retrieved during the treatment session. Consequently, this measure was unlikely to be reliable quantification of sputum clearance where saline was used. The alternative measure of sputum pellet weight was found to be significantly higher in the NSI intervention arm (median: 3.75g vs 1.68g; $p<0.001$) compared to the non-saline arm ***(Figure 9).***



Points represent outliers, as defined by the Tukey's Fences rule

Figure 9. Box plot of sputum pellet weight for no saline and saline interventions

In an attempt to explain the discrepancies between the two measures of sputum clearance, the correlation between these was assessed within each study arm (***Figure 10***). This identified a strong correlation between the sputum pellet weight and adjusted wet sputum weight in the non-saline intervention arm (rho: 0.88), with both approaches giving similar values. However, a weaker correlation was observed for the NSI intervention arm (rho: 0.45), with the adjusted wet sputum weight consistently giving lower values than the sputum pellet weight.



Points represent pairs of sputum measurements from individual treatment sessions. The solid line is plotted at y=x; hence, points on this line are where both assessment methods returned identical sputum weights. The broken line is from a linear regression model; separate models were produced for the no saline and saline arms. Rho: Spearman's rank correlation coefficient.

Figure 10 – Comparison between sputum weight assessment methods

Table 15 – Sputum outcomes based on time of treatment

	Am Sessions (N=79)	PM Sessions (N=74)	p-Value
Treatment			0.872
SI	43 (54%)	39 (53%)	
Non-SI	36 (46%)	35 (47%)	
Adjusted Wet Sputum Weight (g)	0.32 (-1.07, 1.22)	0.64 (-0.56, 1.84)	0.399
Sputum Pellet Weight (g)	2.73 (1.58, 5.69)	2.05 (1.09, 4.12)	0.066

Analyses are performed based on whether the session occurred in the morning or afternoon. Data are reported as "N (%)", and "median (interquartile range)" with p-values from Mann-Whitney U tests. Abbreviations: NSI: normal saline instillation.

To evaluate whether there was a time-of-day effect on sputum yield, analysis was undertaken comparing the median adjusted wet sputum weight and sputum pellet weight in morning and afternoon sessions, regardless of whether sessions included NSI. No significant difference in sputum yield were observed between morning and afternoon sessions (Table 15).

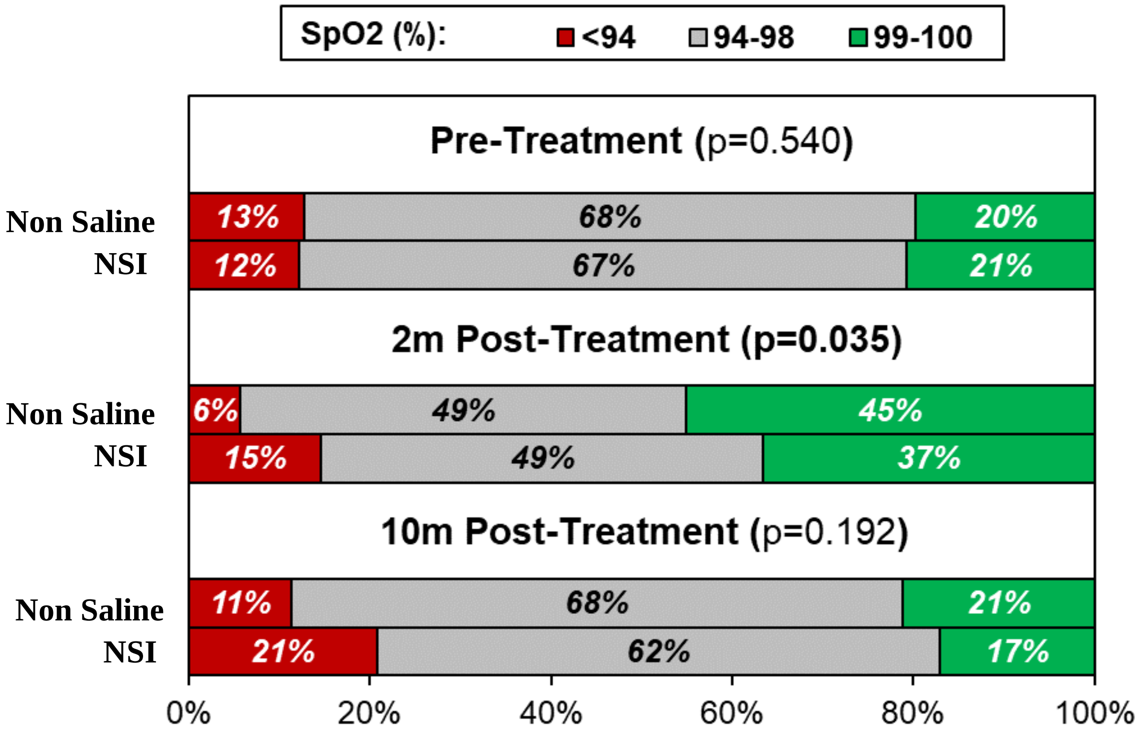
4.5.2 Physiological Outcomes

None of the physiological outcomes were found to differ significantly between the two arms when assessed prior to treatment (***Table 15***). Assessments made post-treatment, both at 2 and 10 mins, were also similar in the two arms for HR, BP, V_t and Compliance. However, a significant difference was detected in SpO_2 assessed 2 mins post-intervention, with lower SpO2 observed in the NSI arm (median: 97% vs. 98%, p=0.035). Specifically, 15% of patients in the NSI arm had an SpO_2 of <94%, compared to 6% in the non-saline arm ***(Figure 11)***. However, 10 mins post-intervention, SpO_2 was similar in the NSI and non-saline arms (median: 96% vs. 96%, p=0.192).

Table 16. Physiological outcomes

	NSI (n=82)	**Non saline (n=71)**	**P value**
Heart rate (bpm)			
Pre Rx	95 (75 - 105)	90 (73 -104)	0.754
2 mins Post Rx	94 (73 - 105)	92 (76 - 106)	0.924
10 mins Post Rx	94 (74 - 104)	91 (76 - 103)	0.914
Systolic Blood Pressure (mmHg)			
Pre Rx	129 (110 - 142)	131 (117 - 149)	0.193
2 mins Post Rx	131 (117 - 145)	133 (120 - 147)	0.309
10 mins Post Rx	128 (114 - 144)	131 (118 - 149)	0.498
Diastolic Blood Pressure (mmHg)			
Pre Rx	63 (57 - 71)	63 (57 - 72)	0.621
2 mins Post Rx	64 (59 - 74)	65 (59 - 71)	0.546
10 mins Post Rx	63 (57 - 74)	63 (69 - 70)	0.865
SpO_2			
Pre Rx	97 (95 - 98)	96 (95 - 98)	0.540
2 mins Post Rx	97 (95 - 99)	98 (96 - 100)	**0.035**
10 mins Post Rx	96 (94 - 98)	96 (95 - 98)	0.192
Tidal Volumes (mls)			
Pre Rx	475 (430 - 540)	476 (406 - 560)	0.746
2 mins Post Rx	493 (444 - 601)	523 (450 - 592)	0.517
10 mins Post Rx	504 (428 - 575)	501 (443 - 607)	0.685
Compliance (mls/cm/H_2O)*	N = 12	N= 14	
Pre Rx	48 (41 - 53)	45 (37 – 49)	0.425
2 mins Post Rx	46 (42 - 54)	48 (40 - 52)	0.570
10 mins Post Rx	45 (42 - 54)	46 (38 - 54)	0.661

*Data are reported as "median (interquartile range)" with p-values from Mann-Whitney U tests comparing across the two arms; bold p-values are significant at p<0.05. *Compliance could only be assessed for patients* *on mandatory modes of ventilation; mmhg: millimetres of mercury, SpO2; saturation of peripheral oxygen, mls; millimeter, bpm: beat per minute.*



Since SpO_2 levels had a limited range of values, and followed a skewed distribution, data were visualized as the proportions of sessions within three intervals of SpO_2, to better visualize the differences between arms. p-Values are from Mann-Whitney U tests on the ungrouped SpO2 data, and bold p-values are significant at $p<0.05$.

Figure 11 – SpO_2 levels by treatment arm

4.6 Harms

A single safety event occurred, namely an instance of sputum plugging, in the non-saline group, resulting in an increase in oxygen requirements (Table 13).

5.0 CHAPTER 5. Discussion

This study assessed important methodological criteria to establish the feasibility of a definitive RCT, targeting an ICU population with known thick tenacious secretions where NSI use during chest physiotherapy is common. This chapter presents reflections on the acceptability of the proposed study in relation to the primary outcomes of patient recruitment and retention. It also presents a discussion of the feasibility of delivering the intervention and collecting proposed outcome data as well as the safety of NSI during chest physiotherapy. Secondary outcomes looking at the impact of NSI on secretion yield will also be reviewed with a focus on the protocol for obtaining sputum pellet weight, along with strengths and limitations of the study.

5.1 Primary feasibility outcome measures

5.1.1 Recruitment

Recruitment to the feasibility study achieved the pre-determined targets, with >75% of eligible patients consenting to participate. Although relatives have been shown to have a positive attitude towards research in ICU due to the perceived benefit of participation in a clinical trial (Mahafzah et al., 2020), strategies to optimise recruitment were implemented in the design and delivery of the study. This included embedding critical care specific PPI in the development of the protocol and consent processes. Utilising patient groups with lived experience of conditions has been shown to improve patient information, ensure patient-centred care, and provide insight into acceptability of interventions, resulting in improved recruitment and retention (Crocker et al., 2018). PPI within the study highlighted the challenges associated with NOK declaration given the narrow recruitment window and subsequently substitute decision making processes in the form of medical practitioner declaration was agreed with the REC. This method is commonly used to retrieve consent for ICU research and considered to improve enrolment to clinical trials in acute healthcare (Barrett et al., 2012). This decision proved prudent with 33% (n=10) of patients recruited via medical practitioner consent.

Additional challenges to recruitment included the availability of trained personnel to take consent (Pattison et al., 2017). To increase the department's recruitment capabilities, physiotherapists routinely working on ICU completed GCP and informed consent training prior to the study's commencement. This strategy aimed to share the burden of screening and consenting patients among the research team (Paddock et al., 2021). Physiotherapists were also incentivised to recruit patients to the trial with non-monetary rewards and recognition, such as certificates. Studies have demonstrated such incentives can effectively motivate staff in an ICU setting to recruit patients and mitigate recruitment fatigue (Chaudhari et al., 2020).

Despite achieving recruitment targets, there were observed challenges, providing valuable lessons and insight for the future definitive trial. The recruitment period extended beyond the initially planned six months, with a one-month extension requested from and granted by REC. Although strategies to mitigate predicted recruitment challenges were implemented, staffing constraints associated with the current physiotherapy weekend working model on ICU meant physiotherapy staff, familiar with the research protocol, were not always available, impacting on patient screening. Therefore, recruitment was primarily biased to the earlier part of the week. Additionally, processing sputum samples posed an increased burden, particularly during weekends, periods of annual leave, and when multiple patients were enrolled in the trial. These challenges stemmed from logistical and training barriers imposed by the laboratory team. If proceeding to a definitive trial, upskilling of the research team to alleviate these aspects of the protocol would be warranted.

Since the study was conducted in a large teaching hospital, competing clinical trials also presented challenges to recruitment with co-enrolment not always feasible. Clinical uncertainty and equipoise regarding comparative merits of trials in relation to patient and financial gains meant it was agreed with the R&D team and ICU trial portfolio manager to divide the pool of patients on ICU, reducing the number of potentially eligible patients by 50%. Despite this it was deemed feasible to deliver the study within the current trial portfolio. However, this is an important consideration when moving to a larger trial as extensions to clinical trials have significant financial implications (Bentley et al., 2019).

5.1.2 Retention

Retention throughout the trial was deemed successful, exceeding the >75% outlined to proceed to definitive trial. Two (7%) patients' NOK withdrew consultee declaration but did not provide a reason for withdrawal. In accordance with ethical codes of conduct, participant's NOK are not required to provide reasons for withdrawal (MRC 2007). However, it is acknowledged the families of critically ill patients can be overwhelmed by the prognostic uncertainty regarding their loved one's condition, and decisions around participation in research can be burdensome (Paddock et al., 2021).

The failure to retain patients to clinical trials and collect outcome data can lead to biased results (Chaudhari et al., 2020). The observed 7% attrition rate in this study is consistent with the average loss reported in 132 published clinical trials in a review by Hewitt et al. (2005). Schulz and Grimes (2002) argue that loss to follow-up of 5% or lower is typically of little concern, while a loss of 20% or greater warrants careful scrutiny due to the potential for bias; however losses between 5% and 20% may still be a source of bias (Fergusson et al., 2002). The risk of bias was minimised further as the protocol stipulated data collected prior to withdrawal was available for analysis. Consequently, the attrition rate was deemed acceptable to proceed to a definitive trial.

Of the 30 patients that were consented to participate in the trial, 28% died whilst in hospital, therefore consultee declaration remained valid. This mortality rate exceeds the 13% for patients who develop VAP reported in Melsen et al. (2013) meta-analysis. However, this disparity can be attributed to the high illness severity and the prominent admission diagnosis of severe traumatic brain injury, which is associated with a 30-50% mortality rate (Arnold-Day & Semple, 2020). Loss of follow up due to death can result in missing data and incomplete follow up, compromising internal validity of studies (Marino et al., 2021). However, the protocol design and short duration of data collection during patient's ICU admission meant mortality was not deemed to significantly influence our study results.

Several patients discharged from ICU did not regain capacity prior to hospital discharge so were unable to provide informed consent for ongoing participation in the study. Consequently, the consultee declaration obtained on ICU remained valid. Neuro-cognitive impairment is a recognised sequalae of critical illness, occurring in between 30-80% of patients, with a higher incidence of PTSD and severe cognitive deficit observed in patients admitted with traumatic brain injuries (Myers et al., 2016). Notably, neuro-trauma patients accounted for 67% of patients recruited to the trial, which is reflected in the high levels of consultee declaration participation in the study.

Nine patients regained capacity, with all providing informed consent for ongoing participation in the trial. Lengthy, burdensome trials that require multiple follow-up appointments that interfere with daily life have been associated with higher attrition rates (Chaudhari et al., 2020). However, the study design did not necessitate additional data collection or appointments beyond hospital discharge which would likely have contributed to the acceptability of the study and high retention rates.

5.1.3 Protocol fidelity / missing data

There was good protocol fidelity with all (100%) eligible patients receiving two sessions of chest physiotherapy daily and no missing outcome data. Achieving >80% fidelity has been suggested by Borrelli et al. (2005) as a threshold to demonstrate a high level of fidelity. Protocol fidelity is important as it reflects the extent to which the protocol was accurately implemented. This enables researchers to ascertain the feasibility of delivering a study protocol and ensuring the trial results are reflective of the intervention and methodology rather than confounding variables that could be introduced through deviation from the protocol (Borrelli, 2011).

There was some deviation from the study protocol with NSI used during non-saline treatment sessions, resulting in an imbalance between groups. Significant imbalance between groups risks reducing statistical power, which is largely dependent on the sample size of the smaller group, making it less likely to detect a difference between groups and resulting in a type II error (Pallant, 2020). Clinicians' pre-conceived opinions regarding the benefits of NSI to clear thick, tenacious secretions may introduce selection bias if deviating from the study protocol i.e., using NSI in the non-NSI treatment arm, in patients thought to have difficult secretions to clear. This could result in underestimating the level of secretion clearance in the non-saline group. Given the clinical equipoise around the benefits of NSI on secretion clearance, emphasising NSI should not be used in the designated non-saline interventions at site initiation training could improve protocol adherence. However, scoping work in the form of a national survey looking at the acceptability of this amongst physiotherapists may be warranted before proceeding to a full trial.

5.2 Secondary outcomes

As a feasibility study, the study was not powered to specifically examine the efficacy of NSI on secondary outcomes (Arain et al., 2010). However, it allowed feasibility testing on proposed outcomes, essential for defining the primary outcome measure in the definitive study. Feasibility of sputum related outcomes and emerging trends within the findings are discussed.

5.2.1 Physiological parameters

No significant difference in HR, Systolic BP, Diastolic PB, V_t and pulmonary compliance was observed between treatment arms at the three specified time points. Previous studies have reported conflicting outcomes related to the CV stability of adult patients, with Wang et al. (2017) systematic review and meta-analysis reporting no difference in HR and BP when saline was used as part of routine pulmonary lavage, compared to Chang et al. (2023) who found a significantly higher HR associated with NSI five minutes post suction. This inconsistency in findings is likely to have contributed to the differing clinicians' attitudes towards NSI and use of NSI in clinical practice reported in the scoping review (Chapter 2).

A significant reduction in SpO_2 was observed 2 minutes post ETS with NSI in this feasibility study with more patients saturating <94%. Evidence exploring the impact of NSI on SpO_2 is contradictory, with some suggesting NSI is detrimental to SpO_2 short-term (Ackerman & Mick, 1998; Akgül & Akyolcu, 2002; Kinloch, 1999; Schmollgruber et al., 2014), whilst others suggest it has no significant impact (Adib et al., 2014; Ayhan et al., 2015; Kalra et al., 2014).

This may reflect the heterogeneity in the ETS protocols adopted across studies, with variable suctioning approaches (i.e. open vs closed) and pre-oxygenation periods as identified in the scoping review. The disconnection of the ventilator to perform open ETS is associated with a loss of Positive End Expiratory pressure, alveolar de-recruitment, reduced lung volumes and reduced oxygenation (Maggiore et al., 2003), which may account for the short-term decrease in SpO_2 observed in some studies. However, despite adopting a closed ETS technique and a 2-minute pre-oxygenation period, a significant reduction in SpO_2 2 minutes post ETS was observed in this feasibility study.

An alternative explanation is that the decrease in SpO_2 could be attributed to saline retention in the lungs in the NSI arm, leading to atelectasis and compromised gas exchange. Various factors may have contributed to saline retention, including poor cough efforts, inability to generate enough PEF to create an expiatory flow bias, or due to the distribution of saline within the bronchial tree making clearance challenging. Klockare et al. (2006) using gamma camera imaging to assess distribution of instilled saline, demonstrated a greater proportion of instilled saline was likely to end up in the right posterior lobe due to the anatomical differences in the left and right main bronchus. In contrast to previous research, this study sought to target NSI through patient positioning to help gravity direct the saline towards the lung with evidence of secretion retention. Additionally, physiotherapy adjuncts were utilised to improve patient cough effectiveness and PEF. However, without imaging, the effectiveness of these measures is uncertain. The clinical significance of retaining relatively small volumes of saline and experiencing transient, small drops in SpO_2 are debatable, given the likely rapid absorption of residual saline into the pulmonary epithelium. The return of SpO_2 to baseline measurements 10 minutes post ETS further supports this assertion, however low SpO_2 should form part of physiotherapists clinical reasoning if considering NSI use.

Due to the reported negative association between NSI during ETS and oxygenation in some clinical trials, ETS guidelines currently advise against the routine use of NSI (AARC, 2022). However, the statistically significant reductions in SpO_2 associated with NSI maybe perceived as clinically insignificant due to the minimal absolute differences (98% vs 97%), which typically have little impact on the patient's overall clinical status, with similar changes also observed with other routine ICU care e.g. repositioning or mobilisation (Hodgson et al., 2018)

A recent systematic review and meta-analysis by Chang et al. (2023) reported NSI was associated with reduced incidence of VAP and improved airway secretion clearance. Our scoping review highlighted the primary reason for NSI use among physiotherapists and healthcare professionals on ICU, is to aid secretion clearance. It could, therefore, be argued that the potential benefits of NSI outweigh the short-term reduction in SpO2, especially in populations with a high secretion burden, like patients with VAP, thus providing justification for the definitive RCT looking at NSI use and secretion yield.

5.2.2 Adjusted wet Sputum weight

The use of wet sputum weight has been reported in the lihterature to assess the benefit of NSI on airway secretion clearance, with studies suggesting NSI during ETS increases secretion yield (Giakoumidakis et al., 2011; Gray et al., 1990). However, a limitation of these studies is they do not account for the weight of instilled saline when weighing the sputum samples, meaning the increased weight could be attributed to the aspirated saline. It is therefore difficult to place a causal relationship between NSI and increased secretion yield, and the value of this research is uncertain.

To mitigate this known limitation, in this study adjusted wet sputum weight was calculated by deducting the weight of instilled saline from the overall sputum trap weight. However, this method of sputum analysis yielded a median sputum weight that was negative in the NSI arm. The negative values reported in some cases indicates this method of analysis tends to underestimate the weight of the sputum yielded during the treatment session and implies not all instilled saline was retrieved during ETS. This theory gains credence from the observation that the adjusted wet sputum weight was significantly lower in the saline group compared to the no saline group, where larger quantities of saline were instilled and potentially more saline lost, resulting in a greater underestimation of sputum weight in the NSI arm. Adjusted wet sputum weight wet is ultimately unlikely to reliably quantify sputum weight, particularly where saline is used. As a result, its utility in the definitive trial is not validated.

5.2.3 Sputum pellet weight

A significantly higher sputum pellet weight was reported in NSI sessions. It has been hypothesised the increased secretion yields associated with NSI use may be attributed to the stimulation of a stronger cough reflex or the loosening of secretions from bronchial walls. However, a study by Hanley et al. (1978) using NSI labelled with technetium 99m suggested NSI did not affect secretions beyond the mainstem bronchi. This raises questions about the validity of some of these proposed mechanisms and highlights further studies using imaging to confirm the passage of saline and its impact on secretions are required.

Sputum pellet weight exhibited a fairly strong correlation with the adjusted wet sputum weight in the non-saline group, but a much weaker correlation in the saline group. Additionally, sputum pellet weight was consistently higher than the adjusted wet sputum weight in the saline group. This observation potentially suggests some instilled saline was mixed in with the sputum when estimating the pellet weight and the method for removing saline from the sample was ineffective. This theory is strengthened by the fact that the sputum pellet weight is significantly higher in the saline group, as more saline used potentially means more saline mixed in with/left in the sputum sample, and a larger overestimation of the sputum pellet weight.

Despite conducting an extensive literature search and consulting with experts in the clinical and respiratory laboratory fields, to my knowledge, this study marks the first attempt to separate 0.9% saline from sputum samples obtained from ETS. Subsequently, no published and validated protocol for processing samples to obtain sputum pellet weight exists. Initially, McElvaney et al. (2019) protocol for processing bronchoalveolar lavage samples, involving low speed centrifugation of samples containing large volumes of 0.9% saline and sputum to preserve cellular integrity, was adopted. However, after preliminary work this was deemed ineffective. Studies by Demers and Saklad (1973) and Hanley et al. (1978) suggest sputum and 0.9% saline are immiscible even when vigorously shaken and therefore should be amenable to separation. As cellular analysis was not required as part of this feasibility study, consultation with consultant microbiologists in respiratory laboratories led to a decision to increase centrifugal speed. Higher rotational centrifugal speed has been linked with better separation (Wu et al., 2015), aiming to create a distinct sputum pellet and supernatant layer. Results have been photographically documented and displayed in Appendix 4, revealing some degree of separation. However, it cannot reliably be confirmed that all saline was removed from samples before weighing which could have skewed results.

The use of valid outcome measures in research is paramount to ensure useful and trustworthy conclusions about the efficacy of interventions are drawn, which is required to bring change in policy or practice (Coster, 2013). As the method that underestimates sputum weight found that there is less sputum in the saline group, and the one that overestimates sputum found that there is more sputum in the saline group, it is difficult to draw reliable conclusions on the benefits of NSI on secretion yield. The lack of a validated technique for processing sputum samples is a major limitation of the analysis and an area requiring further work.

5.3 Implications for practice

It is acknowledged that the use of NSI during chest physiotherapy for mechanically ventilated patients with VAP is only a single variable in a complex clinical picture. Chest physiotherapy treatments are based on clinical reasoning in response to varying clinical presentations and clinician experience. As a result, testing specific components of chest physiotherapy in isolation, such as NSI, continues to pose challenges to researchers. The impact of the intervention investigated in this study on days mechanically ventilated, ICU and hospital length of stay is difficult to ascertain due to the highly complex, multifactorial nature of critical illness and these hypotheses should be tested in future research. However, the findings of this feasibility study could act as a starting point for informing physiotherapists and the wider MDT around NSI practice where there is currently limited research and no clinical guidelines.

6.0 CHAPTER 6: Conclusion

MV remains an integral therapeutic intervention for the management of acutely unwell patients in ICU. Despite the recognised benefits of MV on patient outcomes, its adverse effects on secretion clearance are well documented, and shown to result in retained pulmonary secretions, impaired gas exchange and the development of secondary complications such as VAP. This sequalae of morbidity associated with MV is detrimental to patient and hospital outcomes and imposes a financial burden on NHS organisations.

Chest physiotherapy for patients on MV is considered standard care, aiming to facilitate secretion clearance and treat respiratory failure. Physiotherapists employ multimodal interventions to optimise removal of pulmonary secretions, with NSI being reported as one adjunct. However, the use of NSI in clinical practice remains controversial, with concerns around cardiovascular stability and hypoxemia reported in the literature. Its routine use as part of ETS in MV patients is therefore not advocated in published guidelines.

While the literature shows support of NSI amongst the multidisciplinary team when secretions are thick, tenacious and difficult to clear, the scoping review highlighted a dearth of recent, European-based research focusing on the effect of NSI on secretion yield in MV adults, with no publication on this topic within the field of physiotherapy. In the limited historic studies analysing the effects of NSI on secretion yield, significant methodological weakness poses serious concerns about the validity of findings. Further research looking at the effect of NSI on secretion yield was therefore warranted, severing as impetus for this project as it could be argued the potential benefits of NSI, such as reduced VAP rates and increase secretion yield, outweigh potential risks.

To my knowledge, this was the first feasibility study to look at the effect of NSI on secretion yield during chest physiotherapy in an adult population known to have an increased secretion burden. In light of the scarce evidence, the primary objectives were to evaluate the feasibility and acceptability of conducting a trial on ICU to address the research question ‘does NSI during chest physiotherapy improve secretion yield?’. The feasibility study findings indicate that the delivery of an RCT would be both safe and feasible, as evidenced by successful recruitment, retention and adherence to the protocol.

In accordance with some other published research, a short-term reduction in SpO_2 was observed with NSI but this was transient and does not represent a contraindication to continue with a future trial. However, it provides justification for the eligibility criteria which includes low starting SpO_2 and high FiO2 requirements as an exclusion criteria. No adverse events were associated with NSI, demonstrating the safety of the intervention.

Methodological challenges and limitations pertaining to the proposed primary outcome measure, namely sputum pellet weight, were highlighted during trial delivery and data analysis. These insights shed light on why sputum pellet weight may not have been used as an outcome in previous published work. Data analysis also re-enforced the known limitations and poor utility of wet sputum weight as a measure to quantity sputum yield. Consequently, an informed decision can be made to exclude this outcome from the definitive trial.

This feasibility study has therefore been a valuable and enlightening process, providing critical insights that will shape a future trial. There is a clear need for more robust and relevant clinical trials looking at NSI during chest physiotherapy, focusing on outcomes that are clinically pertinent and related to the reason for NSI use i.e. to aid secretion clearance, in cohorts with a high secretion burden. Validation of a method for processing sputum samples to obtain a sputum pellet and mitigating the limitations identified in previous clinical trials is therefore a research priority. While current clinical guidelines do not advocate the routine use of NSI during ETS, its judicious application in specific clinical scenarios when secretions are thick and tenacious may still be warranted.

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Appendix

Appendix 1 – Consultee Information Sheet

Efficacy of instilled saline in conjunction with chest Physiotherapy on Secretion clearance in adults diagnosed with a Ventilator Acquired Pneumonia: a feasibility trial

Information for Consultee
IRAS ID: 318205, Version 2.0, Date 13.12.22

Introduction

We feel your Spouse/relative/Next of Kin (NOK)/patient is unable to decide for himself/herself whether to participate in this research.

To help decide if he/she should join the study, we'd like to ask your opinion whether or not they would want to be involved. We'd ask you to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence.

If you decide your Spouse/relative /Next of Kin (NOK)/patient would have no objection to taking part we will ask you to read and sign the consultee declaration on the last page of this information leaflet. We'll then give you a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or you think your relative/friend should be withdrawn.

If you decide that your Spouse/relative /Next of Kin (NOK)/patient would not wish to take part it will not affect the standard of care they receive in any way.

If you are unsure about taking the role of consultee you may seek independent advice.

We will understand if you do not want to take on this responsibility.

The following information is the same as would have been provided to your Spouse/relative /Next of Kin (NOK)/patient.

Chest **P**hysiotherapy and instilled **S**aline – The CPS study

Information Sheet for Consultee
IRAS ID: 318205

Efficacy of instilled saline in conjunction with chest Physiotherapy on Secretion clearance in adults diagnosed with a Ventilator Acquired Pneumonia: a feasibility trial

Your spouse/relative/Next of Kin (NOK)/partner/patient is eligible to take part in a research study as they are a patient in Intensive Care Unit (ICU). Unfortunately, your spouse/relative/NOK/partner is not well enough to be able to decide for themselves whether or not to take part. Therefore, we need you to read this Information sheet carefully and give your opinion as to whether or not, you think your spouse/relative/NOK/partner would wish to take part, if they had the capacity to make the decision for themselves.

When your spouse/relative/NOK/partner has regained consciousness and has the ability to understand the purpose of this study, a member of the research team will explain the study to them and seek their permission to continue in the research. Your spouse/relative/NOK/partner's decision to continue in the study or withdraw will override the declaration you provided on their behalf.

What is the purpose of the study?

When patients are critically ill and admitted onto ICU, one of the common forms of treatment is to place them on a breathing machine (ventilator). This involves placing a tube down into their lungs and attaching it to a ventilator to help their breathing and ensure enough oxygen gets into their blood. Whilst placing them on a ventilator is an important part of their treatment, some patients will develop a lung infection known as a ventilator acquired pneumonia (VAP). Patients who develop a VAP will produce a lot of secretions (sputum) which can often be thick and difficult to clear. This can make breathing more difficult and cause patients to spend longer on the ventilator and longer on critical care and in hospital. There are a number of reasons why it can be difficult to clear these secretions. The breathing tube makes it more difficult and the effects of sedation can make patients drowsy and not able to cough. A lack of natural moisture in the airways can also make secretions sticky and thick.

To help clear secretions, chest physiotherapy is regularly provided to patients whilst they remain on the ventilator. Chest physiotherapy involves positioning the patient and shaking their chest to help loosen secretions before a suction tube is used to remove them. This will improve the patient's ability to breathe.
As part of chest physiotherapy, a small amount of Saline will often be put down the breathing tube whilst the patient is on the ventilator. Saline is water that contains salt and is used during many medical investigations of the lungs whilst patients are ventilated on ICU. During chest physiotherapy saline is used to help loosen secretions by mixing it with the thick secretions and stimulating a cough. A recent survey showed 96% of physiotherapists would use saline if secretions are thought to be thick. However, we do not know for certain if the use of saline really helps.

The purpose of the study is to investigate whether using saline during physiotherapy increases the amount of secretions cleared compared to when it is not. We also want to know if the use of saline during chest physiotherapy can improve other important outcomes during a patient's hospital stay; such as how long people remain on the ventilator and how long patients stay on ICU and in hospital. However, before we can answer this question we want to know if it is possible to run this study by understanding if patients are happy to participate in the study

What data will be collected as part of the CPS Study?

We will look at how many people who are approached to take part in the study agree and how many people drop out of the study. We will also record whether patients experience any medical side effects from using saline during chest physiotherapy. We plan to recruit 30 patients from the critical care unit at the Queen Elizabeth Hospital, Birmingham.

Why has my spouse/relative/NOK/partner been invited to take part?

Unfortunately your spouse/relative/NOK/partner/patient has developed pneumonia whilst they were on the ventilator (VAP) and is producing an increased amount of secretions on their chest. Therefore, we are inviting you to sign a declaration for your spouse/relative/NOK/partner/patient to take part in this study based on what you believe their wishes and feeling would be likely to be if they had capacity, to help us find out whether saline during chest physiotherapy is beneficial for patients with a VAP and increased secretions.

Does my spouse/relative/NOK/partner have to take part?

No. It is up to you to decide whether or not your spouse/relative/NOK/partner takes part. If you feel your spouse/relative/NOK/partner would not wish to take part in the study, the standard of care they will receive will not be affected. If you do decide that they can take part, you will be given this Information Sheet to keep and you will be asked to sign a study consent form. **You are still free to withdraw your consent for your spouse/relative/friend/partner to take part, at any time and without giving a reason.**

What will happen to my spouse/relative/NOK/partner if they take part?

Figure 1 on page 5 explains what will happen during the CPS trial. Patients who are enrolled into the study will be put into one of two groups on the first day of the study. This selection is random. This means neither you nor the doctor treating your spouse/relative/ NOK/partner can choose the treatment group, so the study treatments can be compared fairly. Patients have an equal chance of being in either of the groups. This type of study is called a randomised cross over design and it ensures that the treatments are compared fairly.

The treatments for each group are as follows:

If you agree for your spouse/relative/partner/NOK to take part in the study, they will receive 2 sessions of daily chest physiotherapy; one in the morning and one in the afternoon.

If your spouse/relative/partner/NOK is allocated to group 'A' they will receive chest physiotherapy in the morning with saline and then in the afternoon chest physiotherapy without saline. On day 2 your spouse/relative/partner/NOK will receive chest physiotherapy in the morning without saline and chest physiotherapy in the afternoon with saline. Chest physiotherapy will continue to be alternated between these regimes for a maximum of 3 days or until the breathing tube is removed, whichever is sooner (See figure 1 on page 2).

If they are allocated to group ‘B’, they will receive the opposite i.e. day 1 chest physiotherapy in the morning without saline and chest physiotherapy in the afternoon with saline. After the study ends, your spouse/relative/partner/NOK will continue to receive chest physiotherapy as required but no information on the amount of secretions cleared will be collected.

Your spouse/relative/NOK/partner’s medical notes will be reviewed by the doctors and physiotherapists for the CPS study, to find out if the treatment they receive has had any effect. The study team will review your spouse/relative/NOK/partner’s progress on a daily basis whilst they are on ICU.

After your spouse/relative/NOK/partner is discharged from critical care we will follow up their medical status at hospital discharge by accessing their medical notes. After hospital discharge no further information is required from your spouse/relative/NOK/partner.

Figure 1. What happens if I take part in the CPS Study?

BEFORE THE STDUY

Staff review ALL patients on critical care requiring a breathing machine (ventilator) for suitability for the CPS study

⇩

Patients with a lung infection (Ventilator Acquired Pneumonia) who meet the CPS eligibility criteria will be invited to participate

⇩

The patients personal consultee (Usually a spouse / Next of Kin / relative/ partner or a senior ICU doctor) is given an information sheet and discusses the CPS study with the research team. ***The percentage agreeing to participate will be recorded***

⇩

AFTER JOINING THE STUDY

If a declaration is signed to join the CPS study, patients will be allocated to a treatment regime – regime A or B,
Patients have an equal chance of being in each group

A

	Am chest physio	**Pm chest physio**
Day 1	Saline	No saline
Day 2	No saline	saline
Day 3	Saline	No saline

B

	Am chest physio	**Pm chest physio**
Day 1	No Saline	Saline
Day 2	Saline	No saline
Day 3	No saline	Saline

ALL PATIENTS WILL RECEIEVE NORMAL MEDICAL MANAGEMENT:
antibiotics / nebulisers / mucolytic / nursing care

⇩

PATIENT FOLLOW-UP During ICU stay Up to hospital discharge	- Twice Daily sputum samples day 0 – 3 - Daily health data collected from medical notes - Days on the ventilator - ICU and hospital LOS

All patients who regain capacity will be approached to provide their consent to continue in the CPS study.
The dropout rate will be recorded

What will happen to your spouse/relative/NOK/partner's sputum samples?

The sputum samples collected from your spouse/relative/NOK/partner during chest physiotherapy will be anonymised by labelling them with a specific study identification number. This is to protect your spouse/relative/NOK/partners confidentiality. Samples will be taken to the Queen Elizabeth Hospital Birmingham laboratory for weighing. This will happen the same day that they are collected. Once the sputum samples have been weighed they will be disposed of according to appropriate regulations.

What are the possible benefits of taking part?

Taking part in this study will contribute to the development of a larger study that will inform physiotherapy practice and may improve treatment of patients with a ventilator acquired pneumonia (VAP) in the future. This may lead to better patient outcomes including reduced ICU and hospital length of stay and improved survival rates. There is also evidence that research active hospitals also have better patient outcomes.

What are the risks or disadvantages of taking part?

The potential risks involved in taking part are considered to be low. The procedures involved are commonly performed on ICU patients. The intervention is being delivered by qualified physiotherapists with ICU experience. A small number of patients may experience a very brief minimal drop in oxygen levels during the process of putting the saline down the breathing tube. To prevent this, the physiotherapist will give your spouse/relative/NOK/partner additional oxygen before putting the saline down the breathing tube. Current government guidelines and local safety procedures will be adhered to in relation to the ongoing pandemic to minimise any risk of exposure to the virus.

What if something goes wrong?

If you have concerns about any aspect of this study, you should contact the local Principal Investigator (contact details at end of the form). The principal investigator is responsible for overseeing the study at the Queen Elizabeth Hospital. They will answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Patient Advice and Liaison Service (PALS) via email; PALS@uhb.nhs.uk or phone 01213713280

Will there I receive any payment or financial reimbursement for taking part?

No payments or financial reimbursements will be offered for taking part in this study.

How we will use information about your spouse/relative/NOK/partner taking part in this study?

We will need to use information from your spouse/relative/friend/partner medical records during the course the study. This information will include your spouse/relative/NOK/partner, initials, NHS number, name, and contact details. People will use this information to do the research or to check your spouse/relative/NOK/partner records to make sure that the research is being done properly. People who do not need to know who your spouse/relative/NOK/partner are will not be able to see their details. Your spouse/relative/friend/partner data will have a code number instead. We will keep all information about them safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that your spouse/relative/NOK/partner took part in the study.

What are your choices about how your spouse/relative/friend/partner information is used?

You can withdraw your spouse/relative/NOK/partner at anytime, without giving a reason, but we will keep information about your spouse/relative/NOK/partner that we already have. We need to manage their records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold.

Where can you find out more about how your spouse/relative/NOK/partner information is used?

You can find out more about how we use their information:

- At www.hra.uk/information-about-patients/
- By asking one of the research team
- By contacting the data protection Officer at the University of Birmingham on dataprotection@contacts.bham.ac.uk

You can find out more about how we use your spouse/relative/NOK/partner data information by contacting the data protection Officer at the University of Birmingham on dataprotection@contacts.bham.ac.uk

What will happen to the results of the research study?

The results of the study will be written up by the Principal Investigator as part of their University Master's degree which is due to be completed in January 2024. It is also planned that publication of the results will follow shortly after this, through medical journals and appropriate conferences and will be disseminated through the Clinical Research Ambassador Patient and Public Research Group.

Who is organising and funding the study?

The CPS study is being organised by clinicians from the University Hospitals Birmingham (UHB) NHS Foundation Trust (physiotherapists and doctors) and University lecturers from the University of Birmingham. The study is a project towards a Master of Research degree and any costs will be absorbed by the critical care and physiotherapy department at the UHB NHS Foundation trust. The sponsor of the study is the University of Birmingham. The study sponsor is the organisation responsible to ensure the study is carried out to a high standard to safeguard patient rights and safety, and the quality of the research data.

Who has reviewed the study?

This research has been reviewed and given a favourable opinion by an independent group of people, called a Research Ethics Committee (REC), to protect your safety, rights, well-being, and dignity. The Ethics Committee is completely independent from the study team. The study has also been reviewed by the regulatory body, the Health research Authority (HRA) who have approved the study. If you have any questions that remain unanswered or require further information, you may contact the Principle Investigator via the contact details who will answer these for you.

How long can I think about my spouse/relative/NOK/partner joining the study?

You do not need to decide straight away. Take your time to read the information sheet and ask any questions. However the research team need to know whether you think your spouse/relative/NOK/partner would wish to take part in the study within 48 hours of the initial discussion.

Where can I or my spouse/relative/NOK/partner access information and support following ICU discharge?

ICU Steps is a registered charity, run by former intensive care patients and relatives, with the aim to improve the care and support available to patients recovering from critical illness. https://icusteps.org/. The website provides information to support recovery, and links to online and face-to face support groups throughout the UK. You can message via email on the website or leave a voicemail on 03003020121.

There is also support from the Queen Elizabeth hospital's critical care follow up service who will see your spouse/relative/NOK/partner on the ward after discharge from ICU. Your spouse/relative/NOK/partner will also be invited to attend a follow up clinic after hospital discharge were they can discuss their ICU stay and access services to support their recovery.

Thank you for taking the time to read this Information Sheet and considering taking part in the CPS study

Contact Details
Principal Investigator: University Hospitals Birmingham NHS Foundation
Name: Jonathan Weblin
Address: jonathan.weblin@uhb.nhs.uk
Telephone: 07827815182

Chief Investigator: University of Birmingham
Name: Nikolaos Efstathiou
Address: N.Efstathiou@bham.ac.uk
Telephone: 07732813741/01214158587

Chief Investigator: University Hospitals Birmingham NHS Foundation
Name: Dr. Dhruv Parekh
Address: dhruv.parekh@uhb.nhs.uk
Telephone: 07909892230

Complaints/concerns: University Hospitals Birmingham NHS Foundation
Name: Patient Advice and Liaison Service
Address: PALS@uhb.nhs.uk
Telephone: 0121371328

Appendix 2 – Consultee declaration

Consultee Declaration Form

Centre number:
Study Number:
Participant Identification Number for this study:

Title of project: Efficacy of instilled saline in conjunction with chest Physiotherapy on Secretion clearance in adults diagnosed with a Ventilator Acquired Pneumonia: a feasibility trial

Name of Researcher: Jonathan Weblin, Dr Dhruv Parekh, Nikolaos Efstathiou

Please initial all boxes against each statement

1. I confirm that I have received a personal copy of the information sheet for the above study. I have read and understand the information sheet dated …. (version ….**)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that I am giving this declaration based on what I believe would be my spouse/relative/next of kin's/partner's/patient's wishes. In my opinion, they would be willing to participate in this study	
3. I understand that my spouse/relative/next of kin's/partner/patient participation is voluntary and that I am free to withdraw them at any time without giving any reason if I believe they would no longer wish to participate in the study, without their medical care or legal rights being affected.	
4. Should I wish to withdraw my spouse/relative/next of kin/ partner/patient, I agree that any information already obtained from them in this study up to that point may still be used	
5. I understand that relevant sections of my spouse/relative/next of kin's/partner/patient's medical notes and data collected during the study may be looked at by individuals from the University of Birmingham, regulatory authorities or from the UHB NHS Foundation Trust, where it is relevant to their taking part in this research. I give permission for these individuals to have access to my relative/friend/partner/patients records.	
6. I understand data obtained from the research may be used in the publication of this trial but that, as a participant, my spouse/relative/next of kin/partner/patient will not be identified in any way.	
7. I believe my spouse/relative/next of kin/partner/patient would agree to having sputum samples collected, weighed and analysed for this study.	
8. I agree to my spouse/relative/next of kin/partner/patient taking part in the CPS study based on what I believe would be their wishes if they had capacity.	

Name of Participant Date Signature

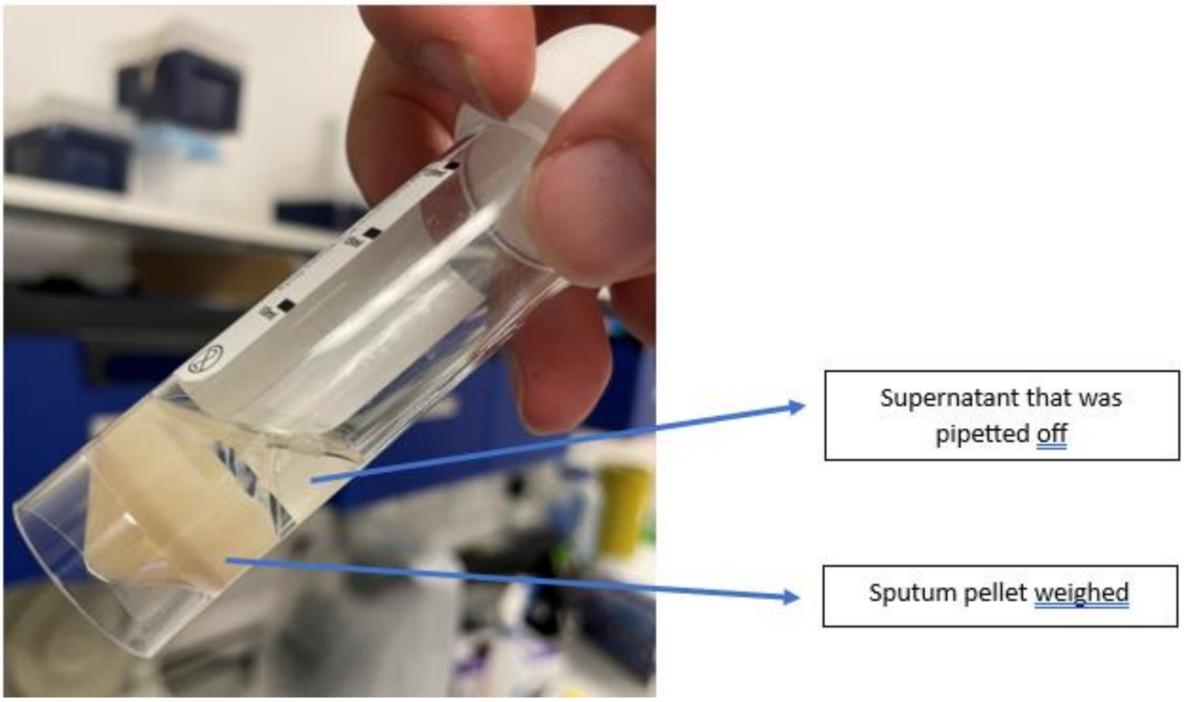
Name of Consultee providing declaration Date Signature

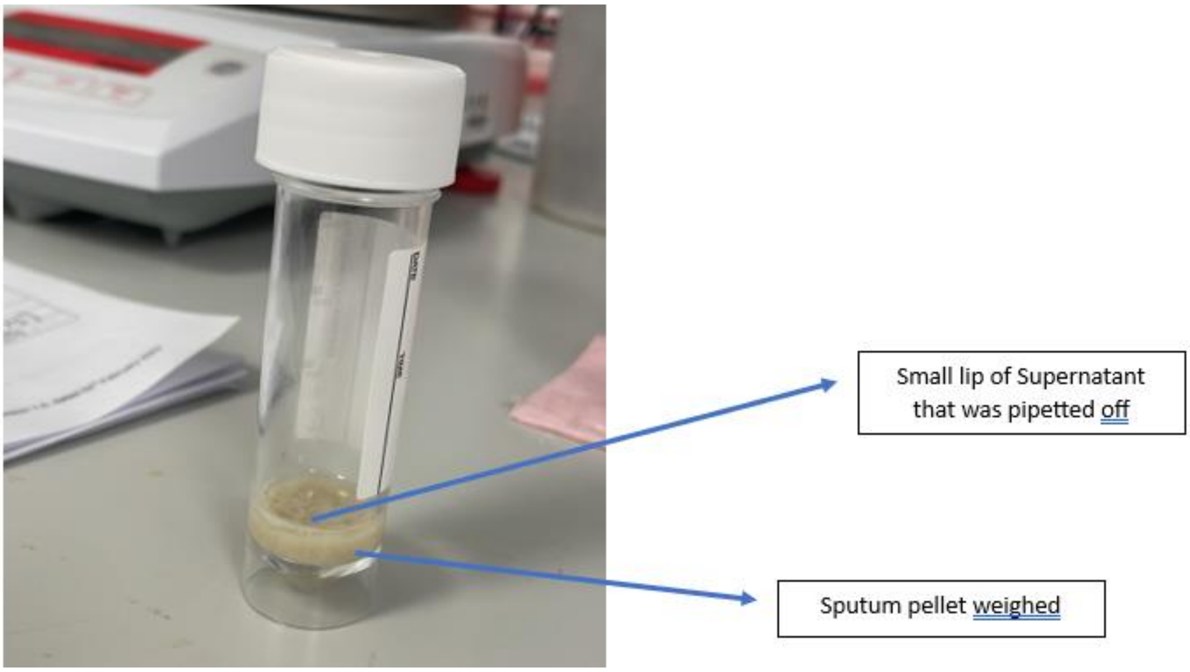
Name of person seeking declaration Date Signature

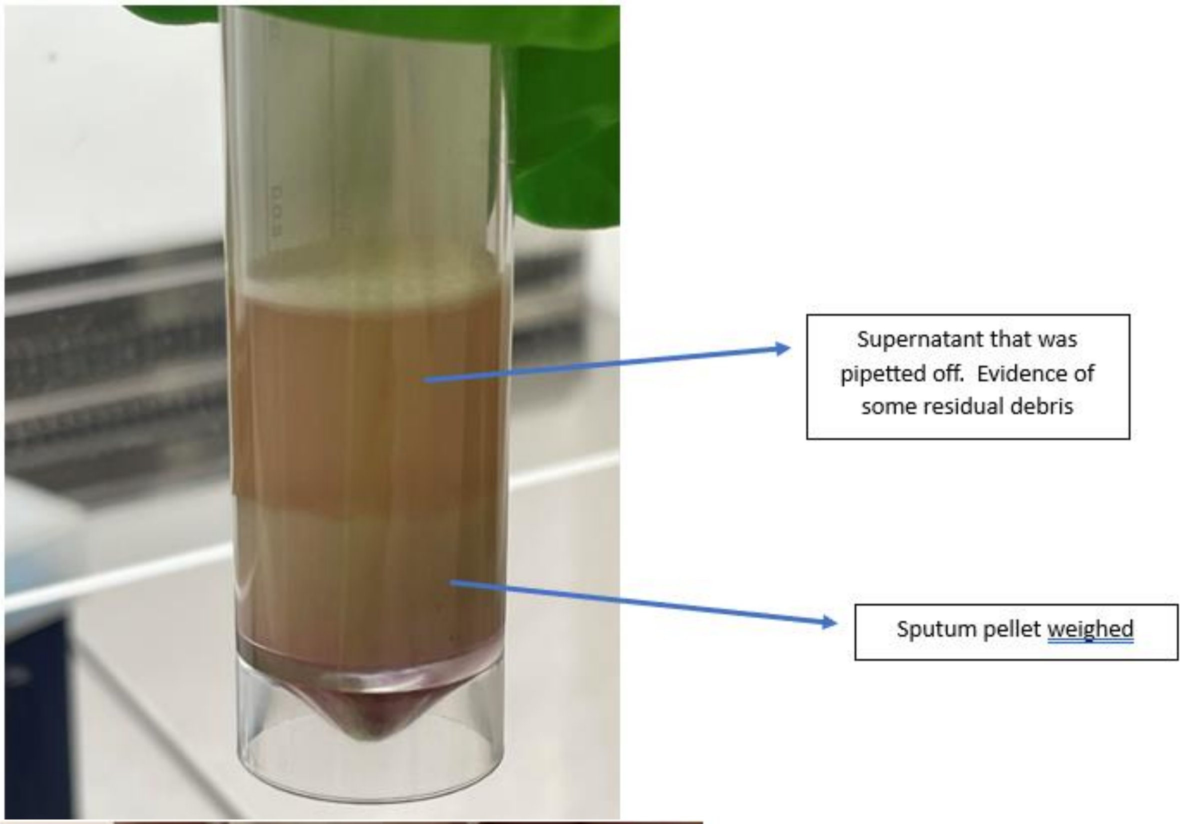
One copy for the consultee One copy to patient notes One copy to research records

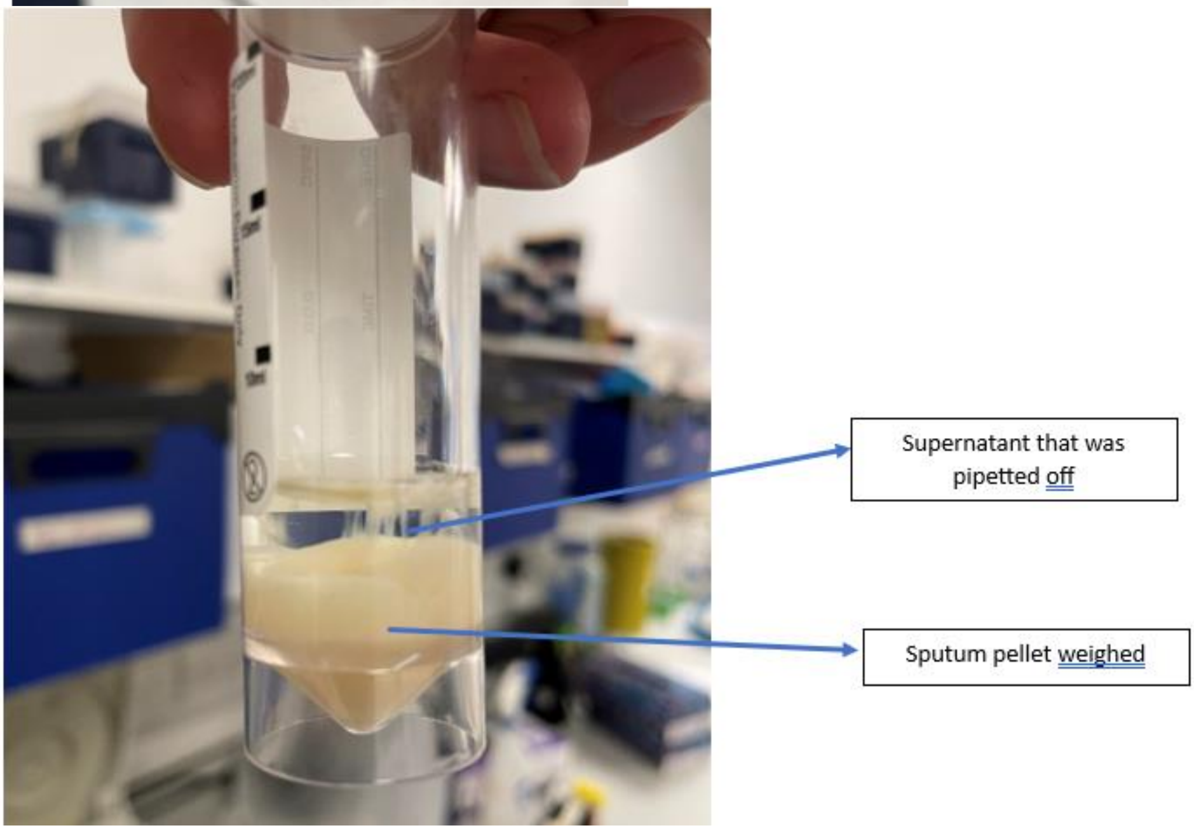
Appendix 3- Sputum processing to obtain sputum pellet weight.

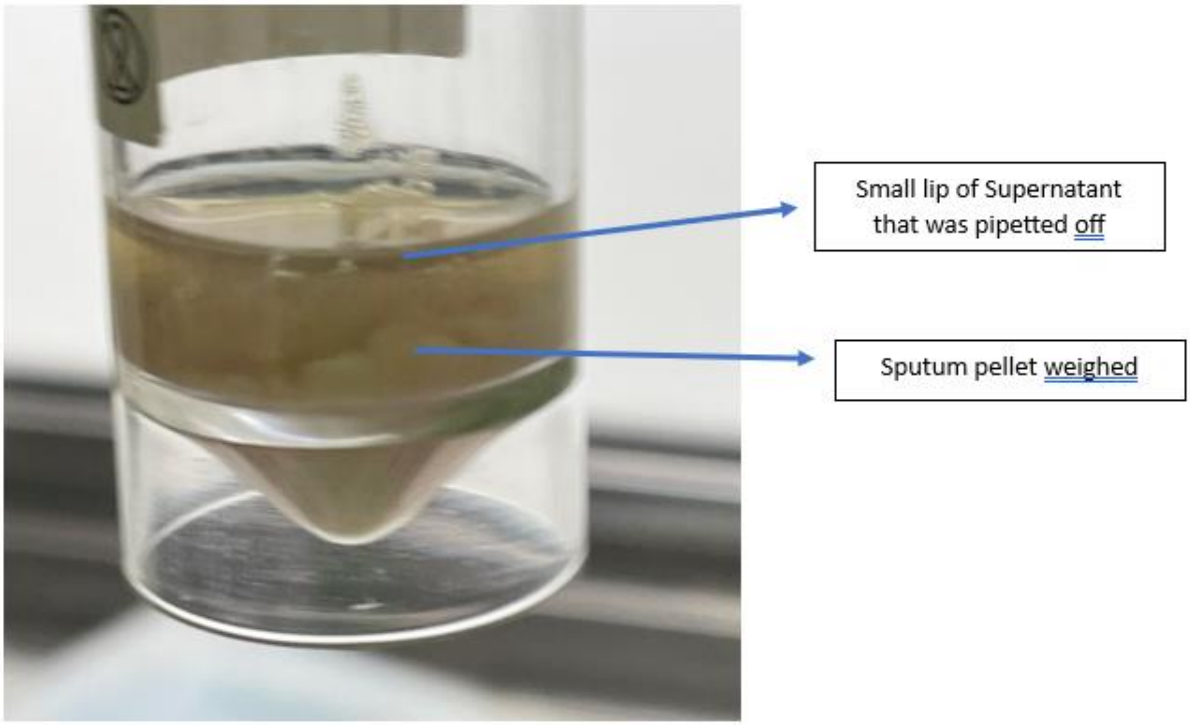
Sputum samples underwent centrifugation at 4500 xg at 4 degrees Celsius for 10 minutes to generate a supernatant and a sputum pellet. Examples of separation achieved through this methodology are shown below.

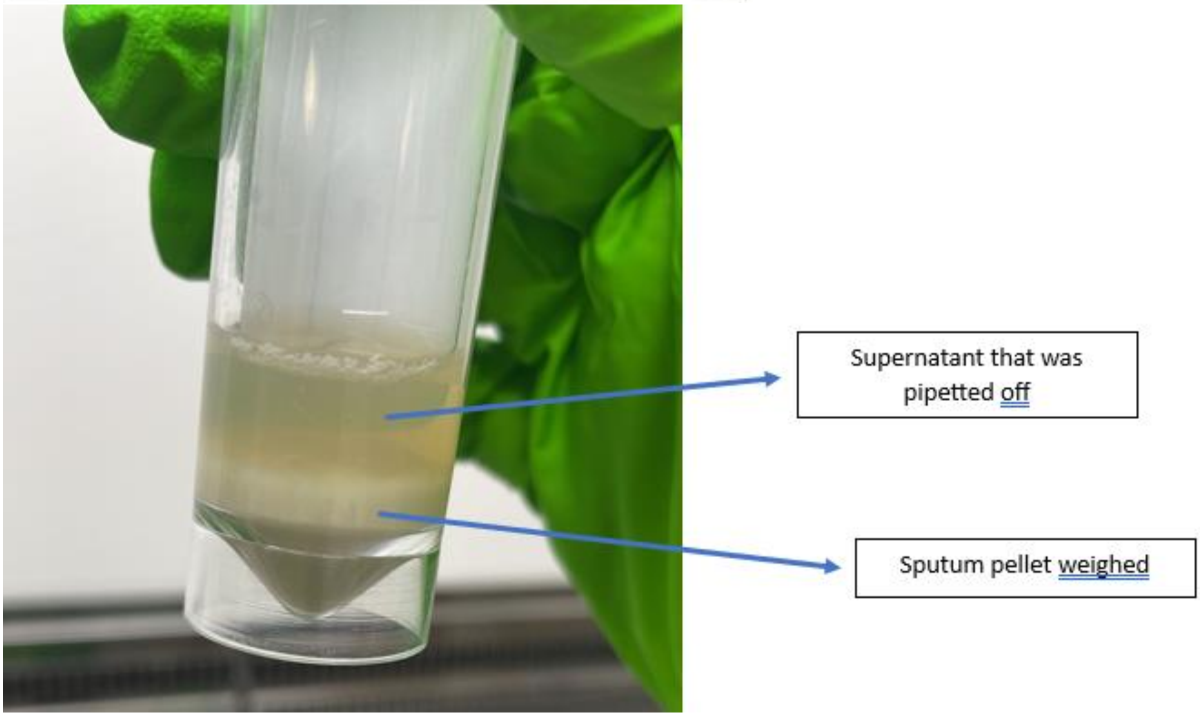

Supernatant that was pipetted off
Sputum pellet weighed


Small lip of Supernatant that was pipetted off
Sputum pellet weighed


Supernatant that was pipetted off. Evidence of some residual debris
Sputum pellet weighed


Supernatant that was pipetted off
Sputum pellet weighed


Small lip of Supernatant that was pipetted off
Sputum pellet weighed


Supernatant that was pipetted off
Sputum pellet weighed

Appendix 4 – Standardised ETS procedure based on AARC recommendations

Table 1. Endotracheal suction procedure
1. Appropriately skilled staff to perform the procedure i.e. qualified physiotherapist 2. Hand hygiene and appropriate personal protective equipment worn 3. Ensure appropriate closed-circuit suction is attached – Unomedical size 12 or 14 4. Attach in-line sterile sputum trap – Pennine 25ml mucus specimen trap 5. Ensure suction pressure set at 200mm Hg 6. Physiotherapists to draw up 3mls sodium chloride solution using a 5ml syringe from a 10ml sodium chloride vile 7. Quantity of saline in syringe to be confirmed by bedside nurse 8. Pre-oxygenation at Fi02 100% for 2 mins 9. Insert suction catheters 0.5cm past the end of the endotracheal tube 10. Instil 3mls of saline via the endotracheal port (patient positioned appropriately for unilateral disease) 11. Following positioning of the patient so upper lung is completed in conjunction with chest physiotherapy 12. Insert suction catheter till cough stimulated (if no cough stimulated physiotherapist will augment a cough using manual techniques such as assisted cough) 13. Suction is applied during catheter withdrawal with procedure lasting no longer than 15 seconds 14. Following last suction, the sputum trap will be removed. A patient label must be adhered to the sputum trap and then placed in an appropriately labelled microbiology specimen carrier bag to be sent to the laboratory with the patient's unique study identification number

Appendix 5: Research Ethics Committee letter of approval

NHS
Health Research Authority

East of England - Essex Research Ethics Committee
Equinox House,
City Link,
Nottingham
NG1 4LA

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

31 January 2023 (re issue 24.02.2023 to update document list)

Mr Jonathan Weblin
2 Hawthorne Road
Birmingham
B30 1EE

Dear Mr Weblin

Study title:	**Efficacy of instilled saline in conjunction with chest Physiotherapy on Secretion clearance in adults diagnosed with a Ventilator Acquired Pneumonia: a feasibility trial**
REC reference:	**22/EE/0284**
IRAS project ID:	**318205**

Thank you for your letter of 31 January 2023, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Appendix 6: Health Research Authority letter of approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mr Jonathan Weblin
2 Hawthorne Road
Birmingham
B30 1EE

Email: approvals@hra.nhs.uk

01 February 2023

Dear Mr Weblin

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Efficacy of instilled saline in conjunction with chest Physiotherapy on Secretion clearance in adults diagnosed with a Ventilator Acquired Pneumonia: a feasibility trial**
IRAS project ID:	**318205**
REC reference:	**22/EE/0284**
Sponsor	**University of Birmingham**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.