The use of Mechanical Insufflation Exsufflation to prevent extubation failure in adult intensive care

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Abstract

Introduction

A failed attempt to remove artificial ventilatory support in intensive care is associated with increased length of stay, impaired quality of life and higher mortality. One cause of this failure, secretion retention, results from poor cough effectiveness. The Mechanical Insufflation-Exsufflation technique simulates cough, to aid secretion clearance which may help with the removal of artificial ventilation.

Aims

The aims of this research were to:

- Summarise the evidence-base regarding Mechanical Insufflation-Exsufflation in intensive care;
- Explore barriers and enablers for Mechanical Insufflation-Exsufflation use as perceived by clinicians working in intensive care; and
- Determine the feasibility of conducting a randomised controlled trial exploring Mechanical Insufflation-Exsufflation to promote successful removal of artificial ventilation.

Methods

A scoping review of primary research studies investigating the use of Mechanical Insufflation-Exsufflation with critically ill invasively ventilated adults was undertaken. Semi-structured online interviews were carried out with clinicians with experience of working in intensive care. Transcripts were analysed using content analysis, assigning quotes to Theoretical Domains Framework.

A single centre feasibility randomised controlled trial compared standard physiotherapy to Mechanical Insufflation-Exsufflation plus standard care. Trial analyses was descriptive based on feasibility outcomes. Electrical Impedance Tomography explored lung recruitment/de-recruitment during Mechanical Insufflation-Exsufflation. Semi-structured online interviews with patient participant and clinicians explored acceptability.

Results

The scoping review (28 studies) demonstrated variation in the methods used to deliver Mechanical Insufflation-Exsufflation as well as the outcomes measured, limiting the ability to make recommendations. A lack of qualitative data was also apparent.

Clinician interviews (n=29) indicated that knowledge and skills can facilitate initiation of Mechanical Insufflation-Exsufflation. Use of the technique varies across specific professional groups. Culture and hierarchy are barriers to MI-E implementation, and skill and knowledge development.

In general, feasibility and acceptability of a definitive trial was demonstrated but clinician interviews highlighted challenges regarding intervention timing and outcomes used. Patients described benefit from Mechanical Insufflation-Exsufflation despite experiencing discomfort.

Conclusion

This research demonstrated complex interplay between sources of knowledge and factors influencing Mechanical Insufflation-Exsufflation initiation. The design of a future definitive trial needs to take account of existing MI-E use, methods of application and outcome measurement.

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My name may well be on the front cover of the thesis, but there are so many people that have supported me over a number of years to (finally) get to the point of submitting this story. Doing a virtual PhD was not what I had planned, but a pandemic popped up and we all know what happened with that!

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Willemke, how we completed a scoping review at the height of the pandemic via online meetings dressed in scrubs and FFP3 masks is beyond me. I've enjoyed every minute of

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This submission is for Han. She didn't really like phlegm and didn't really see the point of writing so many words. However, knowing that so many opportunities have been taken away, I've done it simply because she can't.

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AfC	Agenda for change
AIM	Acceptability of Intervention Measure
APACHE II	Acute Physiology and Chronic Health Evaluation Score
APRV	Airway pressure release ventilation
ASB	Assisted Spontaneous Breathing
BCW	Behaviour change wheel
Bpm	Breaths/beats per minute
CAP	Community Acquired Pneumonia
CDRF	Clinical Doctoral Research Fellowship
CASP	Critical Appraisal Skills Programme
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus disease 2019 (SARS-CoV-2)
Cm H_2O	Centimetres of water
CPAP	Continuous positive airway pressure
CPF	Cough peak flow
CPOT	Critical Care Pain Observation Tool
CRF	Case Report Form
CT	Computed Tomography
CTU	Clinical Trials Unit
CVS	Cardiovascular system
DBP	Diastolic blood pressure
DoS	Director of Studies
EILV	End Inspiratory Lung Volumes
EIT	Electrical Impedance Tomography
ERCC	Expiratory rib cage compressions
ETT	Endotracheal tube
EU	European Union
FIM	Feasibility of Intervention Measure
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HAP	Hospital Acquired Pneumonia
HRA	Health Research Authority
HFNC	High Flow Nasal Cannula
H_2O	Water
IAM	Intervention Appropriate Measure
ICU	Intensive Care Unit
IQR	Interquartile range

Abbreviation	Definition
ID	Identification (number)
IMP	Investigational medicinal product
IMV	Invasive mechanical ventilation
LOS	Length of stay
LUS	Lung Ultrasound Score
L	litres
L/min	Litres per minute
mg/kg	Milligrams per kilogram
MAC	Manual assisted cough
MDT	Multi-disciplinary team
MHI	Manual hyperinflation
MI-E	Mechanical Insufflation-Exsufflation
mL/kg	Millilitres per kilogram
MMAT	Mixed Methods Assessment Tool
mmHg	Millimetres of mercury
MRC	Medical Research Council
MV	Mechanical ventilation
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIV	Non-invasive ventilation
NRS	Numeric rating scale
NRS-O	Numeric rating scale-oral
NRS-V	Numeric rating scale-visually enlarged
O_2	Oxygen
PAG	Patient advisory group
PEEP	Positive end expiratory pressure
PEF	Peak expiratory flow
Phigh	Pressure high
PIF	Peak inspiratory flow
Plow	Pressure low
PMH	Past Medical History
PS	Pressure support
PSV	Pressure support ventilation
QALY	Quality adjusted life years
QOL	Quality of life
RCT	Randomised Controlled Trial
REC	Research ethics committee
ROI	Regions of interest
RR	Respiratory rate
SAE	Serious adverse event
SAG	Study advisory group
SAR	Serious adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Abbreviation	Definition
SBP	Systolic blood pressure
SBT	Spontaneous breathing trial
SD	Standard deviation
SIMV	Synchronised Intermittent Mandatory Ventilation
SOP	Standard operating procedure
SpO_2	Peripheral oxygen saturations
SUSAR	Suspected unexpected serious adverse reaction
TDF	Theoretical domains framework
Te	Expiratory time
TFA	Theoretical framework of acceptability
Ti	Inspiratory time
TMF	Trial master file
TMG	Trial management group
UHBW	University Hospitals Bristol and Weston
UK	United Kingdom
UWE	University of the West of England
VAP	Ventilator Acquired Pneumonia
VHI	Ventilator hyperinflation
WOB	Work of breathing

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Chapter 1

Introduction

1.1 Chapter overview

This thesis explores the application of a technique to aid removal of secretions in invasively ventilated patients in intensive care to promote the success of removing artificial ventilation. This chapter provides the background and rationale to the research presented in this thesis, including the aims and objectives and concludes with a guide to the overall thesis content.

1.2 Background

In the United Kingdom (UK) approximately 250,000 patients are admitted to adult intensive care units (ICU) on an annual basis (NHS Digital, 2022). Many of these patients require help with their breathing (40-50%), from a machine (ventilator) and a tube placed down their throat and into the airway (invasive mechanical ventilation (IMV)) (approximately 40%) (NHS Digital, 2022). Most adults are able to wean (a process of reducing mechanical respiratory support) and are successfully removed from the breathing machine (extubation). However, the medical literature reports that between 2 and 25% of patients fail extubation and are unable to breath by themselves once the tube has been removed and it needs to be put back in (reintubation) (Rothaar and Epstein, 2003; Boles et al., 2007; Thille et al., 2011; Glover and Glossop, 2017; Terzi et al., 2018). Extubation failure is defined as the need for

reintubation and reinstitution of ventilatory support within a pre-defined time period. The defined time period varies across studies from 24-72 hours following extubation (Rothaar and Epstein, 2003), through to any time during the hospital stay (Torrini et al., 2021). Extubation failure is associated with subsequent increased duration of IMV, extended ICU length of stay (LOS) and a raised mortality rate between 2.5 and 10 times that of those who extubate successfully (Rathaar and Epstein, 2003; Thille et al., 2011; Torrini et al., 2021).

Although lifesaving, IMV can cause negative sequalae including muscle weakness, reduced physical function, sleep deprivation, delirium due to sedative drug exposure, and longer term psychological and cognitive consequences such as depression and anxiety (Gosselink et al., 2008; Gobert et al., 2017; Latronico et al., 2017). The negative effects of prolonged IMV in combination with the high cost of an ICU bed (approximately £2000 per day in the UK (NHS Digital, 2022)), means that successful extubation is a clinical priority that warrants further research (Gosselink et al., 2008; Rose, 2017).

1.3 Extubation failure

The pathophysiology of extubation failure is multi-factorial and it is not always possible to identify the specific factors responsible for failure in each individual patient. A recent systematic review and meta-analysis aimed to determine risk factors associated with extubation failure in the critically ill, adult population (Torrini et al., 2021). On reviewing risk factors at the time of extubation, 26 variables were identified relating to age, presence of comorbidities, acute disease severity and physiological characteristics. In relation to

physiological characteristics, secretion management was associated with the most variables; highlighting the importance of evaluating secretion presence prior to extubation. It was concluded that extubation failure was most likely impacted by several variables and extubation checklists should not focus on a single component (Torrini et al., 2021). A key limitation of the published research identified in the systematic review included the lack of a standardised definition of extubation failure.

Multiple studies have highlighted secretion retention, resulting from an inability to cough effectively, as a specific cause of extubation failure (Khamiees et al., 2001; Smina et al., 2003; Thille et al., 2011). An 'unmanageable secretion load' was previously reported in 89% of patients requiring reintubation, compared to 39% of those successfully extubated (Khamiees et al., 2001). An early observational study (Smina et al., 2003) examined extubation outcomes of 95 patients (with no prior neuromuscular disease (NMD) diagnosis) equating to 115 extubation episodes. In total there were 13 unsuccessful extubation attempts. In this observational study the mean peak expiratory flow (PEF) of those patients who had experienced unsuccessful extubation episodes was significantly lower than the mean of those with successful extubation (64.2±6.8L/min v 81.9±2.7L/min respectively, p=0.03). A PEF ≤60L/min was also associated with longer ICU length of stay and higher mortality, and it was recommended that this critical threshold be considered prior to extubation in the clinical setting (Smina et al., 2003).

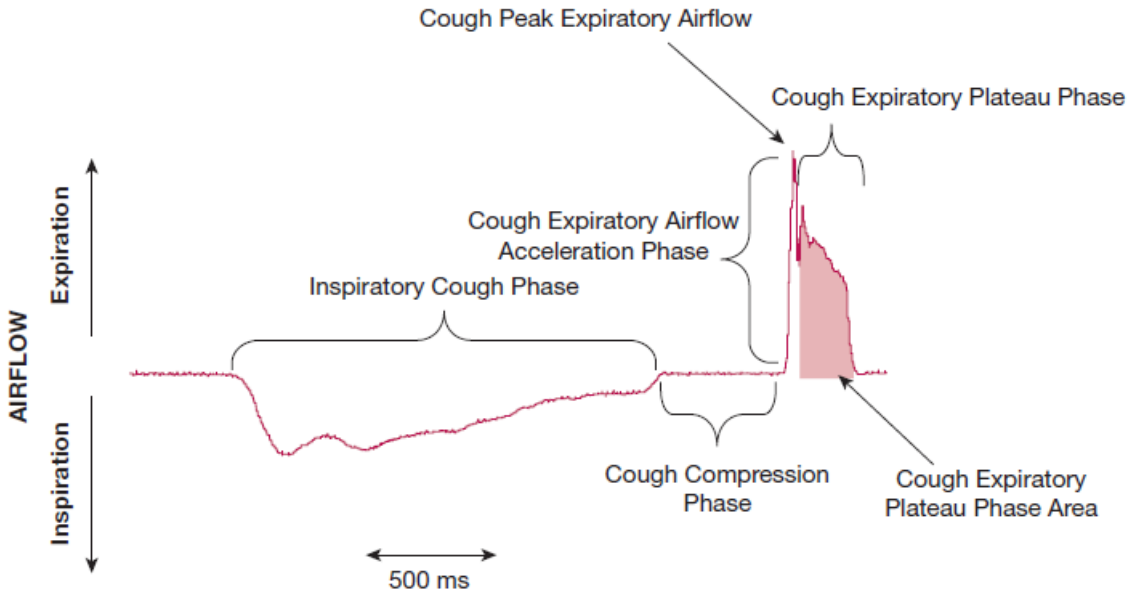
More recently Xiao et al., (2017) completed an observational study, to determine independent risk factors associated with reintubation in an ICU setting. A total of 139

patients who had successfully completed a spontaneous breathing trial (SBT) were recruited. A SBT is carried out with patients on IMV prior to extubation. A total of 22 patients failed extubation and required re-intubation within 72 hours of extubation. Key risk factors associated with the failed extubation episodes included multiple SBT attempts, reduced cough peak flow (CPF) and reduced albumin levels. Specifically, in patients with CPF ≤60, 61-89 and ≥90L/min, reintubation rates were 29.4, 16.7 and 1.9% respectively. To further understand the effects of IMV on cough and subsequent secretion management, it is necessary to consider cough physiology.

1.4 Cough physiology

Cough is an essential defence mechanism, clearing sputum and debris from the airways through high velocity airflow (Lee et al., 2021). The physiological mechanisms of cough have been previously described as a sequence of events made up of three key phases; the inspiratory phase, a compression phase and the expulsion phase (McCool, 2006; Lee et al., 2021) (Figure 1.1).

Figure 1.1 The 3-phase flow pattern of a classical cough (from Lee et al., 2021 with permission)



The 'inspiratory phase' is characterised by an increase in volume, initiated by key muscles of inspiration including the diaphragm and external intercostals. This volume increase can be up to 80-90% of vital capacity. This optimises the length-tension relationship of the expiratory muscles, resulting in the generation of positive intrathoracic pressure (pressure in chest cavity being higher than the pressure outside). Positive intrathoracic pressure is ideally required for the generation of an expiratory flow however it is not essential as an effective cough can still be produced from inhaling smaller volumes (McCool, 2006; Lee et al., 2021). An inspiratory volume of at least 50% of vital capacity has been documented for an effective cough (Brennan et al., 2022).

The 'inspiratory phase' is followed by the 'compression phase'. The glottis closes for approximately 0.2 seconds which helps to maintain lung volumes and subsequently creates

a further increase in subglottic and intrathoracic pressure. Once the glottis rapidly re-opens, the ‘expulsion phase’ begins, generating a high velocity expiratory flow. This expiratory flow peaks in the early phase (peak expiratory flow) followed by a sustained flow (plateau phase). The cough ceases when expiratory flow returns to baseline.

Originally, cough was thought of and described as a single effort (McCool, 2006) but is now understood to compromise multiple efforts (Lee et al., 2021). The term ‘cough reacceleration’ describes a cough effort that is composed of multiple expulsive efforts following a single inspiration (Lee et al., 2021; McGarvey et al., 2021). In this situation, the glottis re-closes resulting in a second compression phase. On subsequent glottis re-opening a second expiratory flow is generated. This second expiratory flow still generates an acceleration in flow from baseline but often to a lesser extent than the initial generated expiratory flow. The repeated generation of sheering forces from the cough reacceleration is thought to further augment airway clearance (Lee et al., 2021).

Cough expiratory airflow can be measured and quantified. CPF refers to the maximum expiratory flow during the compression cough phase, immediately following glottis re-opening. A CPF exceeding 360-840L/min is regarded as normal in healthy adults (Leiner et al., 1963; Lee et al., 2021). However, CPF that meets the critical threshold is not solely sufficient to ensure effective airway clearance. Mucociliary movement and the impact of gravity are also important determinants of airway clearance. Additionally, a third factor is a bias of cephalad airflow, meaning a higher PEF than peak inspiratory flow (PIF). This promotes movement of secretions away from the distal lung regions to a more proximal

location making secretions easier to remove (Kim et al., 1986; Kim et al., 1987; Benjamin et al., 1989; Volpe et al., 2008).

Bench studies exploring the influence of flow bias on sputum movement have illustrated that a PIF/PEF ratio higher that 1.1 (Kim et al., 1987) or an absolute PIF-PEF difference >17L/min (Volpe et al., 2008) causes sputum to be further embedded into the distal lung regions, making clearance more challenging. There are limitations to these bench studies, for example, they lack the impact of 'normal' anatomy, positioning and use simulated mucus. Despite these limitations it is evident that strategies to clear sputum need to optimise an expiratory flow bias.

1.5 Cough physiology during and following IMV

In patients who are invasively ventilated via an endotracheal tube (ETT) (breathing tube via the mouth), cough mechanisms and subsequent airway clearance effectiveness can be impaired. An ETT abducts (opens) the vocal cords, preventing the compression phase of a cough. During IMV, when no spontaneous effort is present, PEF is influenced by inspiratory volume, resistance and elastic recoil of the lungs. As such, values of cough strength will typically be higher than those recorded during expiratory flow manoeuvres as a PEF refers to the maximum expiratory flow after full inspiration through an open glottis, such as in the presence of an artificial airway. However, despite the anatomical change due to the presence of an ETT, patients are still able to simulate a 'cough', through a huffing manoeuvre (Winck et al., 2015; Lee et al., 2021). An ineffective cough during IMV may also be due to respiratory muscle weakness, prolonged inactivity and altered mucociliary

clearance (Branson, 2007; Tronstad et al., 2022). Furthermore, cough effectiveness may be impaired or absent due to the use of sedatives and paralysing agents. Dry inhaled gases also cause mucus to be more viscous and impair the mucociliary transport system specifically through a reduction in cilia beat frequency and synchronisation (Branson, 2007; Fahy and Dickey, 2010; Tronstad et al., 2022). Additionally, during IMV, positive pressure ventilation has been shown to promote an inspiratory flow bias (Ntoumenopoulos et al., 2011). These findings support an earlier lab-based study which illustrated the impact of mechanical ventilation settings on generated flow rates (Volpe et al., 2008).

Following extubation, the impact of IMV on cough strength and effectiveness may still be evident. The sequalae of critical illness on respiratory muscle strength is well documented and this can last for long periods predisposing a patient to an increased risk of extubation failure (Branson, 2007; McGarvey et al., 2021). Once a patient is spontaneously breathing, active abdominal effort further contributes to the generated PEF (Shannon et al., 2010). However, due to weakness the contributions of inspiratory volume and abdominal effort may not be sufficient. Additionally, it is not uncommon for patient levels of consciousness to fluctuate.

The relationship between CPF and extubation outcomes has been previously described. A prospective observational study explored the correlation of CPF and reintubation rates in a cohort of 139 ICU patients (Xiao and Duan, 2017). Low reintubation rates were reported when CPF was ≥90L/min. Re-intubation rates were reported to increase to 16.7% and 29.4% in patients with a CPF of 61-89L/min and ≤60L/min respectively. Xiao and Duan (2017)

concluded that methods to optimize cough strength, in addition to sputum mobilisation strategies, warranted further investigation. This supports the importance of examining the role of airway clearance techniques, such as Mechanical Insufflation-Exsufflation (MI-E), in the ICU setting.

1.6 Airway clearance strategies in ICU

In order to minimise the impact of retained secretions, a number of secretion clearance techniques can be used during IMV and following extubation. These treatment techniques aim to mobilise sputum and/or augment cough. Cough augmentation techniques mimic a cough and strengthen the resultant cough. Additionally, suctioning (the mechanical clearance of pulmonary secretions from a patient using a soft catheter tube orally, nasally or via an artificial airway) can stimulate a cough in order to clear secretions from the larger airways (Tronstad et al., 2022).

In 2008, a combined Taskforce group of the European Respiratory Society and the European Society of Intensive Care Medicine published recommendations on physiotherapy for critically ill patients (Gosselink et al., 2008). A more recent review of cardiorespiratory physiotherapy during IMV describes preventative and interventional treatments (Tronstad et al., 2022), with treatment choice determined through a comprehensive patient assessment. Routine prophylactic care includes the use of humidification, suctioning, optimal positioning and regular re-positioning and mobilisation of patients. Additional physiotherapy treatments include the use of manual ‘hands on’ techniques (percussion,

expiratory vibrations and shakes), hyperinflation breaths and cough augmentation through the use of manual or mechanical assisted coughs. A brief overview of these techniques will now be provided.

1.6.1 Suctioning

Suctioning (via the breathing tube) is a key component of airway management in the ICU and is completed by a range of multi-disciplinary team (MDT) members. Suctioning is considered a safe technique but has associated complications relating to physiological responses. These include short-term changes to heart rate, mean arterial blood pressure and oxygen desaturations (Seymour et al., 2009; Maggiore et al., 2013; Dexter et al., 2019). Longer term consequences have also been documented including airway mucosa damage and hospital acquired infection (Carroll, 2010; Dexter et al., 2019). In 2022, the American Association for Respiratory Care produced a clinical practice guideline for artificial airway suctioning (Blakeman et al., 2022). The guideline included 11 recommendations based upon 84 studies. It was acknowledged that all recommendations in the guideline were based on low level evidence and/or expert opinion and more research on the effectiveness and safety of suctioning via an artificial airway was required.

1.6.2 Manual techniques

'Manual techniques' is an umbrella term for interventions used to facilitate secretion mobilisation and clearance; including percussion, chest wall vibrations and compressions, and manual assisted cough.

Percussion

During percussion, clinicians manually use a cupped hand, to produce clapping of the chest wall, during both inspiration and expiration. Percussion occurs over a lung area that is consolidated with the aim of producing oscillation, which in turn mobilises secretions from peripheral to more central airways (Ciesla et al., 1996; Tronstad et al., 2022). Percussion is commonly used in combination with other strategies such as positioning and hyperinflation techniques (see section 1.6.3). However, there is a lack of evidence regarding effectiveness specifically in the ICU population (Clini and Ambrosino, 2005; Tronstad et al., 2022). Furthermore, the impact of percussion on secretion clearance is unknown (Tronstad et al., 2022).

Chest wall vibrations and compressions

Vibrations are used during the expiratory breath with the aim of enhancing expiratory flow. Clinicians place their hands around the patient's chest wall and rapidly apply an initial compression during expiration, followed by a continued oscillatory pressure (vibration) until the end of the expiration breath (Shannon et al., 2010; Tronstad et al., 2022).

Research supports repeatability of techniques when performed by the same clinician but variation between clinicians with regard to the magnitude of forces and amplitude of oscillations (Van der Schanns et al., 1999; Shannon et al., 2009; Shannon et al., 2010). The timing of vibration application has been considered via a bench study (Shannon et al., 2010). Enhanced expiratory flow rates occurred when vibrations were performed at the start of

expiration or during mid to late inspiration. There was no change to expiratory flow when the vibrations were performed during early to mid-expiration. An increase in peak inspiratory pressure (up to 56cmH_2O) was also recorded when vibrations were applied mid to late inspiration which could have a detrimental impact on a patient in the clinical setting. It was suggested by the authors that the timing of application of chest wall vibrations was important but findings should be extrapolated into the clinical setting with caution (Shannon et al., 2010).

A lack of evidence remains regarding the impact of chest wall vibrations used in isolation on clinical outcomes for patients in an ICU. Studies to date have investigated chest wall vibrations in combination with other techniques without specific exploration of the additional benefits. Ntoumenopoulos et al., (2002) examined the inclusion of 'chest physiotherapy' for the prevention of ventilator acquired pneumonia (VAP) in 60 adult patients on IMV. In this study 'chest physiotherapy' involved the use of positioning, chest wall vibrations and suctioning. Analysis showed that chest physiotherapy was independently associated with a reduction in the occurrence of VAP. However, it is unknown whether results were due to the combination of techniques or whether a single technique could have had the same effect. Furthermore, the study findings are at risk of bias due to the non-randomised design and small sample size.

Expiratory Rib Cage Compressions (ERCC), also termed 'squeezing' is a technique that aims to enhance expiratory flow and stretch the intercostal muscles. ERCC involves the delivery of a manual compression (via hand placement) to the chest wall during expiration, followed

by a rapid release at the onset of inspiration. The compression and rapid release are synchronised with the patients breathing rate (Unoki et al., 2005; Guimaraes et al., 2014). Hand placement description and detail varies across studies but generally involves hand placement on the lower and lateral ribs (Marti et al., 2013; Guimaraes et al., 2014). The compression phase of the technique is proposed to compress airways to enhance airflow velocity and resultant mucus transport (Unoki et al., 2005). However, ERCC has not been associated with enhanced secretion clearance or positive changes in oxygenation or ventilation in animal or human based ICU studies (Unoki et al., 2004; Unoki et al., 2005; Marti et al., 2013). Potential negative sequalae have been reported in animal studies including exacerbation of alveolar and airway collapse and adverse changes in cardiac output (Unoki et al., 2004; Marti et al., 2013).

Manual assisted cough

A manually assisted cough (MAC) is the application of external force (compression) to the thoracic, abdominal or thoraco-abdominal areas around the chest wall during the expulsion phase of cough. MAC aims to generate an expiratory flow bias and augment resultant cough strength (Sivasothy et al., 2001; Spinou, 2018; Spinou, 2020). Traditionally a MAC is used in the NMD and spinal cord injury population due to muscle weakness and has more recently been explored in the ICU setting. Silva et al., (2012) compared MAC application to 'optimised MAC' which included increased positive end expiratory pressure (PEEP) settings and inspiratory time (Ti) in 35 patients on IMV. Results demonstrated increased PEF in the optimised MAC group versus the MAC group (112.3±15.6 v 95.8±18.3L/min, p=0.05).

Additionally, a significant reduction in respiratory system resistance was seen in the optimised MAC group.

1.6.3 Hyperinflation techniques

Hyperinflation techniques can be performed manually using a resuscitation bag (manual hyperinflation, (MHI)) or via the ventilator, (ventilator hyperinflation, (VHI)). Atelectasis refers to deflated or collapsed alveoli and lung units resulting in little or no volume which impacts gas exchange. Hyperinflation techniques aim to re-inflate collapsed areas in order to increase lung volumes (alveolar recruitment), improve oxygenation and ventilation and facilitate secretion clearance through the generation of expiratory flow (Paulus et al., 2010; Paulus et al., 2012; Tronstad et al., 2022). This is achieved through the delivery of a larger than normal tidal volumes (the amount of air that moves in or out of the lungs with each respiratory cycle) at low/slow inspiratory flow rates, followed by an inspiratory hold. When completing MHI, the inspiratory hold is followed by a quick release of the resuscitation bag to generate higher expiratory flow rates and a resultant expiratory flow bias (Paulus et al., 2012).

MHI, also referred to as 'bagging' and 'bag squeezing' is a commonly used adjunct first described in 1968 (Clement and Hubsch, 1968). In order to perform MHI, the patient is required to be disconnected from the ventilator to attach the resuscitation bag. Care is required when treating patients who have increased levels of PEEP as this distends distal alveoli, preventing a loss in volume (de-recruitment). A sudden loss of PEEP, as experienced during ventilator circuit disconnection, may result in de-recruitment, causing a loss in lung

volume and associated oxygen desaturations (Barker and Adams, 2002; Tronstad et al., 2022). The technique has been shown to improve oxygenation through atelectasis resolution and alveolar recruitment, increased compliance (ability of lungs to stretch and expand) and improvements in secretion clearance (Patman et al., 2000; Paratz et al., 2002; Paulus et al., 2010; Paulus et al., 2012). However, a systematic review of MHI showed that these improvements were short-term with minimal or no impact on patient outcomes (Paulus et al., 2012)

VHI is a newer treatment technique in comparison to MHI, first being described in 2002 (Berney and Denehy, 2002). VHI works along the same treatment principles as MHI but uses the ventilator to achieve the hyperinflations. One advantage of this technique over MHI is that it does not require disconnection from the ventilator and provides greater accuracy of treatment parameters with consistency over time (Tronstad et al., 2022). Despite studies demonstrating short term benefits in oxygenation, sputum clearance and compliance, the variation in the treatment parameters that have been investigated makes recommendations for best clinical practice challenging (Lockstone et al., 2023).

A systematic review compared the effects of VHI versus MHI and included four randomised controlled trial (RCTs) (Anderson et al., 2015). Review findings suggested that the two techniques of hyperventilation had similar effects on secretion clearance, dynamic and static compliance and cardiovascular stability. Reported limitations of the included studies included variation in protocols, participants and outcomes measured with additional research recommended.

1.6.4 Mechanical Insufflation-Exsufflation

MI-E is an airway clearance technique delivered using a specific machine that can be used in patients with and without a breathing tube. The use of MI-E aims to strengthen cough through the delivery of alternating positive and negative pressures. Firstly, a positive pressure breath (insufflation) is delivered which aims to give the patient a really big breath in. The machine then quickly switches to a negative pressure breath (exsufflation) that sucks the air back out again. It is this quick switch from positive to negative pressure that is thought to simulate a cough and generate expiratory flow rates sufficient to improve secretion clearance (Homnick, 2007; Toussaint, 2011; Chatwin et al., 2018).

The first commercial device produced to deliver MI-E was available in 1952, called the CoF-Flater (OEM, Morwalk, Connecticut), with pressures delivered via a facemask. Research into this device focused on individuals with polio and expanded into other chronic conditions such as bronchiectasis and asthma. Following these very early descriptions of MI-E use there was a gap in publications, likely due to the advances in IMV and the use of tracheostomies. Over 40 years later, John Bach published work describing use of the CoughAssist In-Exsufflator (JH Emerson/Respironics, Murrysville, Pennsylvania) concurrently with non-invasive ventilation in a NMD population (Bach and Saporito, 1996). This device was able to deliver alternating positive and negative pressures via a facemask or a tracheostomy tube. Traditionally, MI-E has been used in a NMD population and existing research in this population has shown MI-E use to augment peak cough flow and to reduce respiratory exacerbations, infection rates, antibiotic use and hospital admissions (Bach et al., 1996; Bach et al., 2015; Chatwin et al., 2018).

An early bench study (Gomez-Merino et al., 2002) explored pressure, volume and flow relationships across a range of MI-E pressure and time settings. Results demonstrated the importance of the insufflation setting, particularly how insufflation duration impacts resultant expiratory flow rates. That is, a slower breath in (longer Ti) enhances generated expiratory flow. The results showed that pressure settings less than +/-30cmH_2O did not achieve the critical threshold of 2.7L/sec cough flow rates in order to achieve effective airway clearance. These early findings have been supported by subsequent studies (Sancho et al., 2004; Volpe et al., 2018, Marti et al., 2022). Volpe et al., (2018) examined two MI-E manoeuvres with differing insufflation settings; standard MI-E (a fast insufflation) versus optimised MI-E (a slow insufflation) across a range of pressure settings and variable test lung resistance and compliance settings with simulated mucus and a test lung set up. The optimised MI-E manoeuvre (slow insufflation) reduced peak inspiratory flow whilst enhancing both the expiratory flow bias and PEF-PIF difference, therefore resulting in mucus movement away from the lungs, simulating enhanced airway clearance. Furthermore, exploration of the impact of symmetrical and asymmetrical pressure settings showed that asymmetrical pressure settings optimised sputum movement due to a greater PEF-PIF difference when compared to symmetrical pressure settings.

1.7 The role of MI-E in promoting extubation success

A Cochrane review (Rose et al., 2017) of cough augmentation techniques for facilitating weaning (the process of reducing ventilator support) and extubation from IMV identified only three RCTs for inclusion (Niranjan and Bach, 1998; Crowe et al., 2006; Gonçalves et al.,

2012) with only one study including MI-E (Gonçalves et al., 2012). The RCT investigating MI-E included 75 critically ill adults intubated for >48 hours (Gonçalves et al., 2012). MI-E (with standard medical care) was compared to a standard medical therapy only which included supplemental oxygen, non-invasive ventilation, chest physiotherapy and the use of antibiotics. When comparing the MI-E group to the control, lower re-intubation rates (48% v 17%), mechanical ventilation durations (mean (standard deviation (SD)) 17.8 (6) v 11.7 (3.5) days) and ICU LOS post-extubation (9.8 (6.7) v 3.1 (2.5) days (all $p<0.05$)) in the MI-E treatment arm were identified. Despite positive findings, limitations to the Gonçalves et al., (2012) study should be acknowledged. Authors reported no significant difference in baseline characteristics across study groups at baseline, however there was a slightly higher rate of hypoxemic respiratory failure in the control group. This could account for the higher use of non-invasive ventilation (NIV), higher rate of extubation failure and need for re-intubation in the control group. Longer term clinical outcomes such as ICU and hospital mortality were not analysed. Instead authors focused on outcomes within the initial 48hours following extubation. Authors acknowledged that the study took place in a centre that was highly specialised with MI-E, thus limiting generalisability into the wider ICU setting. Due to the limited evidence available, Rose et al (2017) concluded that the role of cough augmentation techniques in promoting extubation success was unclear and additional robust research, including understanding of intervention safety and optimal treatment intensity, was essential.

Non-controlled studies that did not meet the inclusion criteria for the Cochrane review have explored MI-E efficacy in the intubated population, suggesting improved CPF and increased

extubation success (Bach et al., 2010; Bach et al., 2015; Khan et al., 2015; Tan et al., 2017). RCTs published since the Cochrane review have demonstrated the superiority of MI-E (versus no MI-E) on physiological outcomes including the volume of aspirated sputum weight, static lung compliance, airway resistance and work of breathing (Coutinho et al., 2018; Ferreira de Cammillis et al., 2018; Sanchez-Garcia et al., 2018; Martinez-Alejos et al., 2021). Although these publications add to the quantity of evidence examining the use of MI-E in the ICU population, not all studies would have fulfilled the inclusion criteria of the earlier Cochrane Review (Rose et al., 2017). Methodological limitations are present across studies including small sample sizes and lack of blinding thus limiting the ability to strengthen or advance statements on the use of MI-E in this patient group. This supports the need for more specific, high quality studies.

In the absence of comprehensive evidence from clinical trials, bench studies have also examined the use of MI-E and provide a focus on the physiological consequences and simulated clinical outcomes such as sputum movement. A study by Guerin et al., (2011) examined the impact of an artificial airway in a bench setting on pressures and flows generated by an MI-E device. MI-E pressures ranging from +/-30-50cmH_2O were explored with both ETT and tracheostomy tubes. Results demonstrated that the presence of an artificial airway significantly reduced generated PEF, with a narrower tube having a greater reduction in generated PEF. Furthermore, analysis indicated that pressures of +/-40 and +/-50cmH_2O should be used in patients on IMV in order to achieve PEF thresholds to optimise resultant airway clearance. It was concluded that higher pressures may be required in the presence of an artificial airway to overcome the additional resistance to airflow.

Most recently, Marti et al., (2022) examined the impact of MI-E set up on mucus displacement, respiratory flows, respiratory mechanics and haemodynamics of six intubated and ventilated pigs. All MI-E pressure setting combinations resulted in an increased mucus velocity. As with previous studies, results demonstrated the impact of the insufflation breath on resultant inspiratory flow rates. It was recommended that insufflation pressures were therefore limited in order to prevent an inspiratory flow bias and optimise PEF-PIF flow bias. An increase in transpulmonary pressure with insufflation pressures >50cmH_2O was highlighted but was not deemed clinically significant.

Despite the growing evidence base from in vivo and in vitro studies, a survey of UK ICUs illustrated a lack of MI-E uptake with respondents identifying a range of barriers to use in the intubated population (Swingwood et al., 2020). Of the 166 respondents, 99% reported that they had access to an MI-E device and almost all (99%) reported MI-E use in the extubated population; whilst only 53% indicated that it was used with an intubated population. Barriers to MI-E use in the intubated population included the need for additional training and experience with the device; resource and evidence availability and ICU culture (Swingwood et al., 2020). These findings supported those from a Canadian survey (Rose et al., 2016) which indicated moderate adoption of cough augmentation strategies, including MI-E, with similar barriers to use reported. Only 21% of respondents used MI-E during weaning from IMV, with 19% and 27% of respondents reporting MI-E use to prevent initial intubation and reintubation respectively.

Despite this emerging evidence, author conclusions across studies frequently relate back to the need for additional larger scale, randomised research studies of MI-E that investigate clinically important changes and patient focussed outcomes. Furthermore, barriers to device implementation warrant further investigation to support future implementation of evidence.

1.8 Aim and objectives

The overall aim of this programme of research was to investigate the use of MI-E, as an airway clearance technique, to promote extubation success in the critically ill, intubated adult population in the ICU setting and determine the feasibility of carrying out a definitive RCT.

The thesis objectives were:

- To summarise the evidence base regarding the use of MI-E in the ICU setting;
- To explore the barriers and enablers of MI-E use in the intubated population; and
- To investigate the feasibility of conducting a randomised controlled trial exploring MI-E use to promote extubation success

1.9 Researcher position

As the doctoral fellow, it is important to recognise and acknowledge my professional background and experience of using MI-E within an ICU setting.

I qualified as a Physiotherapist in 2005 and had exposure to acute respiratory patient settings very early in my career, having completed an undergraduate placement in an adult ICU and my first rotation as a qualified physiotherapist being within paediatric intensive care. I have always found respiratory physiotherapy fascinating, including the need to consider and think about the physiology of multi-organ failure and subsequent impact on the respiratory system and physiotherapy role. Clinically I have extensive ventilation and airway clearance experience in both adult and paediatric settings. I am recognised for work with MI-E through conference presentations and industry training. I currently have roles within key stakeholder organisations including the Physiotherapy Advisory Board and Education Committee for the Intensive Care Society; and as a member of the Equity, Diversity and Belonging Committee of the Chartered Society of Physiotherapy. I have previously held national roles for the Association of Chartered Physiotherapists in Respiratory Care as Chair, and as the physiotherapy representative on the Education and Training Committee of The British Thoracic Society.

Academically, I completed a postgraduate MSc in Advanced Cardiorespiratory Physiotherapy in 2012. This included a small physiology bench study using MI-E and a test lung. I thoroughly enjoyed the challenge of postgraduate education, particularly the research elements. I subsequently secured small local research grants and regional training fellowships to advance my research skills which underpinned a successful National Institute for Health and Care Research (NIHR) fellowship application that has supported the work reported in this thesis. I have chosen to focus my research on the use of MI-E because I think it has wider potential in the clinical setting.

My beliefs prior to commencing the Doctoral Fellowship were that optimal airway clearance in the critically ill intubated patient, and therefore the role of physiotherapy, was vital. Whilst there had been a focus on early mobilisation and rehabilitation of the critically ill patient over the previous 12 years, most likely linked to the publication of The National Institute for Health and Care Excellence (NICE) Guidance (NICE, 2009), it was my view that airway clearance also had a vital role. I therefore believed that there was a need to strengthen the evidence base and raise awareness of the role of the physiotherapist in benefitting patient outcomes.

1.10 Research Management

An overarching research management process was in place to support the doctoral fellowship. Where relevant, further specific detail is provided in subsequent chapters.

1.10.1 Funding

This fellowship was funded by the NIHR through a Clinical Doctoral Research Fellowship (CDRF) held by the doctoral fellow, Ema Swingwood which commenced in September 2020.

1.10.2 Supervision

Professor Fiona Cramp was the Director of Studies (DoS) for the doctoral fellow during both the development of the research fellowship application and throughout the award, supported by primary academic supervisor, Professor Sarah Voss. Both the DoS and primary

academic supervisor are based at the University of the West of England (UWE Bristol) which was the academic host for the PhD.

The wider supervisory team included Professor Louise Rose, Kings College London; Professor Lyvonne Tume, Edgehill University; Dr Jeremy Bewley, ICU Consultant at University Hospitals Bristol and Weston (UHBW) and Dr George Ntoumenopoulos, Consultant Physiotherapist, St Vincent's Hospital, Australia. All supervisory team members supported the development of the CDRF application and advised the doctoral fellow throughout the research reported in this thesis.

1.10.3 Key Collaborators

The study sponsor was UHBW, supported by UWE Bristol as the academic host and Bristol Trials Unit (clinical trials unit). Throughout the fellowship, an important collaboration was made with Dr Willemke Stilma, a PhD student and ICU nurse based in the Netherlands, via a shared supervisor, Professor Louise Rose. Collaborative work is described in Chapter 2 of the thesis.

1.10.4 Trial Management Group

Membership of the Trial Management Group (TMG) included key stakeholders for the trial including Professor Fiona Cramp; a Bristol Trials Unit representative and a UHBW Research and Development representative as study sponsor. This group met 6 monthly throughout the fellowship to discuss study governance.

1.10.5 Patient Advisory Group

The Patient Advisory Group (PAG) included 8-10 ICU survivors and relatives of ICU patients, supported by clinicians from acute care including the doctoral fellow and ICU research matron. The group was chaired by a Consultant in Emergency Medicine independent to the study. The group met on a quarterly basis (both face to face and online) and contributed to study protocol development and interpretation of results.

1.10.6 Study Advisory Group

Membership of the Study Advisory Group (SAG) included a representative from the PAG; expert multi-disciplinary clinicians from outside of the Trust and Trust multi-disciplinary representatives. This group was chaired independently and externally by an Associate Professor with expertise in cardiorespiratory physiotherapy. This group met on a six-monthly basis during the fellowship to advise on protocol development, results interpretation and dissemination.

1.11 Guide to thesis

This thesis explores the use of MI-E in ICU settings to promote extubation success in an acutely intubated, critically ill adult population. Three distinct studies are reported in the thesis; 1. a scoping review, describing the evidence for MI-E use in an ICU setting (Chapter 2); 2. clinician interviews, examining barriers and enablers to MI-E use in an ICU setting (Chapter 3) and 3. a feasibility intervention study, examining the use of MI-E to promote

extubation success in an acutely intubated, critically ill adult population in an ICU setting (Chapters 4 and 5), with an nested exploratory physiology study (Chapter 6).

Across the subsequent thesis chapters each study is presented, with results considered in relation to previous published work, implications for subsequent studies in the thesis and the wider clinical picture. The final chapter (Chapter 7) provides an overall discussion of all findings, with implications for practice and recommendations for future research.

Chapter 2

A scoping review of Mechanical Insufflation-Exsufflation in invasively ventilated critically ill adults

The scoping review protocol and results have been published in Systematic Reviews and the Respiratory Care journal respectively (Swingwood et al., 2020; Swingwood et al., 2022) (Appendix 1 and 2).

2.1 Introduction

MI-E use in the ICU across the UK remains varied despite a pre-doctoral survey showing that devices were widely available (Swingwood et al., 2020). Responses to the survey indicated that physiotherapists were mainly using MI-E in the extubated rather than intubated population (Swingwood et al., 2020). Furthermore, a lack of supporting evidence and clinical experience were highlighted as potential barriers to MI-E implementation in the intubated ICU population, alongside knowledge of how to use the device in this specific patient group. The survey did not explore how clinicians were using MI-E regarding patient selection, device set up and outcomes and this remains a gap in the evidence base.

A previous Cochrane review (Rose et al., 2017) examined the literature to determine the impact of cough augmentation strategies on extubation success specifically in critically ill patients (adults and paediatrics) with acute respiratory failure. Secondary objectives considered associated patient harm of using cough augmentation strategies and

determining if there were particular patient groups who may and may not benefit from such strategies. Authors of the Cochrane review concluded that there was insufficient evidence for or against the use of cough augmentation to promote extubation success. Due to a sparsity of evidence the authors were neither able to comment on the effect of cough augmentation on other outcomes such as re-intubation rates, ICU LOS, safety of such strategies, nor provide recommendations on specific patient groups who may benefit from such techniques. Further review of the literature was warranted to determine whether any research published after the Cochrane review search end dates (2016) would alter the conclusions and to explore the wider literature relating to MI-E beyond the RCT design.

2.2 Study aim and research questions

To provide an overview of current and emerging evidence on how MI-E is used in invasively ventilated, critically ill adults.

Specific study questions were:

1. What primary clinical diagnoses and/or reasons for mechanical ventilation are an indication to use/not use MI-E during invasive ventilation?
2. What are the clinical indications and contraindications for commencing MI-E in invasively ventilated critically ill adults?
3. What MI-E settings are used for invasively ventilated critically ill adults (such as, interface type, flow, pressure and time settings)?

4. What outcomes are reported in studies of MI-E for invasively ventilated critically ill adults and how are these outcomes measured?
5. What adverse events attributed to MI-E use are reported, and how are these defined/described?
6. What perceived barriers and facilitators to using MI-E for invasively ventilated critically ill adults are described, and how are these defined?

2.3 Methodology

2.3.1 Review approach

With a rapid growth of reviews of the literature, a plethora of terminology has been generated but with a lack of consistent definition (Arksey and O'Malley, 2005; Colquhoun et al., 2014). There are a number of approaches to completing a review of the evidence base (Munn et al., 2018) and as much as there are similarities across approaches there are also some important differences regarding their purpose and potential outputs. It is therefore important to consider which approach is most suited to the specific research aim.

A *systematic review* aims to address a very specific and defined research question (Arksey and O'Malley, 2005). This approach follows a pre-defined and systematic method which ensures results are reliable and meaningful in the context of the research question (Munn et al., 2018). Due to the specificity of the research question, a systematic review may include a relatively small number of studies that are all quality assessed. This may result in some

generated evidence and findings not being included in the final report and detail can be lost in the process if not related to the original research question.

Scoping reviews address broader topics and aim to describe evolving concepts and identify gaps through examining the volume and characteristics of primary research (Arksey and O'Malley, 2005; Levac et al., 2010; Munn et al., 2018). Scoping reviews enable a researcher to examine a range of methodologies (not limited to RCTs) against a broader research question (Arksey and O'Malley, 2005; Levac et al., 2010; Colquhoun et al., 2014; Munn et al., 2018); providing an overview of the evidence. Scoping reviews are frequently an independent piece of work, but can be a precursor for a subsequent systematic review as research questions and inclusion criteria are refined through the process (Munn et al., 2018). There are limitations to scoping reviews that should be acknowledged. They do not routinely include an appraisal of the quality of studies which may result in a high quantity of studies being included. This is an important consideration when planning a scoping review as authors needs to ensure there is sufficient time to review the body of evidence generated (Levac et al., 2010). However, some authors have recommended the inclusion of quality assessment (Colquhoun et al., 2014).

A more traditional approach is the *literature review* which can be used to summarise research on a specific topic (Munn et al., 2018). It has a similar concept to a scoping review but in comparison lacks rigor. A literature review tends not to have a pre-defined protocol making it less reproducible; no peer reviewed search strategy thus limiting reliability of the results; and does not routinely use data extraction forms. As a result, a literature review can

be seen as a subjective review process, often relying on the knowledge base and subject expertise of the reviewer (Munn et al., 2018).

In the current project, use of MI-E in an intubated population remains an emerging practice technique. Rather than determining effectiveness of MI-E as a treatment intervention in intubated adults, the aim of the review was to examine and understand how the device was being used and described within the literature. By gaining an understanding of how MI-E was being investigated and how the relevant research had been conducted, results would inform subsequent phases of the doctoral studies and research studies planned by others. A scoping review enables the inclusion of publications, irrespective of study method which would ensure that the full range of examples of MI-E use in this population were included. This would enable a wider review of citations in comparison to the earlier Cochrane review (Rose et al., 2017). Therefore, a scoping review was selected as the most appropriate approach for the research aim and objectives of this study.

As with systematic reviews, a methodological framework for scoping reviews has been proposed. The initial guidance for the design and completion of a scoping review was published in 2005 (Arksey and O'Malloy., 2005) with the aim of providing detail to the required methods and in turn enhancing the reliability of findings and increasing methodological rigor. Authors described a six-stage process which included 1. Identification of a research question; 2. Searching for relevant studies; 3. Selecting studies; 4. Charting data; 5. Collating, summarising and reporting results and 6. an optional consultation process (stage 6).

Advancements and additional commentary to this initial framework have been published (Levac et al., 2010; Daudt et al., 2013; Colquhoun et al., 2014; Munn et al., 2018) as authors from these research groups believed there was a lack of consensus regarding terminology and inconsistency in the quality for published scoping reviews including a lack of methodological description and detail of data analysis. Levac and colleagues (2010) used their extensive research experience in rehabilitation to bridge the gap and provide further practical recommendations to support the use of the original framework (Arksey and O'Malloy., 2005). More recently a framework for the reporting of scoping reviews has been published, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-extension for Scoping Reviews (Tricco et al., 2018).

2.4 Methods

2.4.1 Study collaborations

This scoping review was completed in collaboration with Willemke Stilma (WS), a PhD student and ICU nurse based in the Netherlands. Throughout this chapter I will describe and specify our roles and provide reflection on the collaboration.

2.4.2 Study design

The methods of the current scoping review followed the guidance originally outlined by Arksey and O'Malley (2005) and advanced by other authors (Levac et al., 2010; Daudt et al., 2013; Colquhoun et al., 2014; Munn et al., 2018). The scoping review methods are

presented below with reference to the relevant frameworks to illustrate how the protocol was developed.

2.4.3 Study identification

Search strategy and study selection

As previously outlined it was important to identify all relevant material to accurately describe the use of MI-E in the acutely intubated population. Limitations to the generated results of the Cochrane Review had been identified; a lack of literature limited the authors' ability to draw conclusions about the use of cough augmentation strategies and subsequent impact on extubation success. Further to this, the focus on patient outcomes did not enable authors to comment on how cough augmentation strategies were being used in the ICU population. A modified version of the Cochrane review search terms was used (see Appendix 3). Search terms were adapted to provide a sole focus on MI-E as the treatment intervention, ensuring inclusion of all relevant wording for MI-E.

Databases MEDLINE, EMBASE, CINAHL, PROSPERO, in addition to The Cochrane Library, ISI Web of Science and the International Clinical Trials Registry Platform were searched between January 1990 to April end 2021. The year 1990 was chosen to coincide with the resurgence of MI-E literature following the release of the CoughAssist In-Exsufflator which could be used via tracheostomy tubes as well as via face masks. A strength of the previous Cochrane Review (Rose et al., 2017) was the breadth of searches completed which was therefore replicated. The International Clinical Trials Registry Platform was included to

highlight relevant ongoing studies or potential unpublished work of completed studies. Research published prior to 1990 was excluded as it was deemed unlikely to be relevant to current ICU practice.

Study inclusion and exclusion criteria are presented in Table 2.1. The review was restricted to an adult population due to the complex differences in ICU clinical management strategies across adult and paediatric cohorts. Patient cohorts within eligible studies needed to include patients who were acutely invasively ventilated via an endotracheal tube or tracheostomy tube, based in a relevant clinical area such as ICU or a high dependency or weaning unit. There were no exclusions based on study design (Colquhoun et al., 2014; Khalil et al., 2016). The Cochrane Review (Rose et al., 2017) had excluded randomised crossover trials because such approaches do not contribute to the determination of intervention efficacy. The current scoping review did not have such focus and so randomised crossover trials were included alongside other study designs such as cohort studies, qualitative approaches, case reports and research letters that presented original research data. Furthermore, there were no exclusions based on the language of publication with the aim of generating a wide review of evidence.

All citations obtained through the search were uploaded into EndNoteX9 (Clarivate, Philadelphia, Pennsylvania); this online system was used throughout the scoping review process to manage citations. All citation duplications were removed prior to commencing the screening process. Study screening of titles and abstracts occurred independently by two reviewers (doctoral fellow and WS). Any uncertainties were taken through to full text

article review. Both reviewers screened all remaining full text articles against the inclusion/exclusion criteria (Levac et al., 2010).

Table 2.1: Scoping review inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Mechanically ventilated adults via tracheostomy or endotracheal tube in a relevant clinical location (intensive care, weaning centres, respiratory high care/dependency areas)	Children (<18 years)
Any primary study design; (includes randomised controlled trials, quasi and non-randomised clinical trials, before and after studies, interrupted time series cohort studies, qualitative designs, mixed methods, cross-sectional design, case reports/series, and research letters which present original data)	
Describes use of MI-E	Editorial pieces; letters to the Editor; Bench and animal studies; review articles
Published from 1990 onwards	

Abbreviations: MI-E, mechanical insufflation-exsufflation

2.4.4 Data extraction

The data extraction form was developed by the doctoral fellow and WS against the scoping review research questions and piloted with five papers. The piloting ensured the same process was being interpreted and used by both reviewers (Levac et al., 2010; Daudt et al., 2013) and provided opportunity for refinement as required (Appendix 4). The final data extraction form recorded information as listed in table 2.2.

Table 2.2: Data extraction form data collection points

Data descriptors	Detail of data collection
Paper descriptors	• Author • Year of publication • Study design • Sample size • Recommendations and study summary
Population descriptors	• Population description (study inclusion criteria) • Study setting • Interface (ETT/TT) • Primary diagnosis/reasons for mechanical ventilation
MI-E descriptors	• Indications for MI-E • Contraindications/precautions against MI-E • Device used to deliver MI-E • MI-E settings (mode, in/exsufflation pressure, in/exsufflation time, pause, flow profile, insufflation repeats, oscillations (amplitude/frequency)) • MI-E applied by • Intervention (treatment regime, frequency/day, total number of interventions, control intervention, observation time) • Primary outcomes/results • Secondary outcomes/results • Adverse events (definition and results)

Abbreviations: ETT, endotracheal tube; MI-E, mechanical insufflation-exsufflation; TT, tracheostomy tube

When reviewing included papers for data extraction, reviewers contacted corresponding authors for clarification of methods and additional data if required. Contact of corresponding authors occurred for all publications that were only available as abstracts in an attempt to gain additional detail and to ascertain if a full manuscript would be published. Any disagreements during the review process were recorded and resolved by discussion. In the case of no consensus, a third reviewer (supervisor - LR) was available for arbitration.

2.4.5 Assessment of methodological quality

The lack of study quality appraisal has been highlighted as a potential limitation of scoping reviews due to the inability to make robust recommendations for future practice or policy in comparison to the outputs from a systematic review (Munn et al., 2018). Traditionally, the quality appraisal process was not viewed as an essential component of analysis (Arksey and O'Malley., 2015; Tricco et al., 2018). However, more recently the inclusion of such a process has been recommended to enhance the rigor of the extracted data (Daudt et al., 2013; Colquhoun et al., 2014).

For the current scoping review an assessment of methodological quality was completed using the Mixed Methods Assessment Tool (MMAT) to provide an overview of the validity of the evidence (Pluye et al., 2009; Pace et al., 2012). The MMAT was initially developed in 2009 (Pluye et al., 2009) and later revised in 2011 to include both an assessment checklist and user tutorial (Pace et al., 2012).

Prior to undertaking the review, the Critical Appraisal Skills Programme (CASP) (www.casp-uk.net) was also considered as an alternative appraisal tool. Checklists such as CASP and MMAT facilitate the systematic appraisal of health research and determine trustworthiness, relevance and value of the studies. The CASP consists of a range of different checklists specific to the type of study with lists available for RCTs, systematic reviews, qualitative studies and cohort studies. Questions are answered either yes or no rather than any

quantification or scoring which makes it challenging to compare and contrast different study types.

In contrast the MMAT is a single appraisal tool that can be applied to all study designs and allows concurrent appraisal of studies against quality criteria. The study designs include 1. Qualitative studies 2. Quantitative randomised controlled 3. Quantitative non-randomised 4. Quantitative observational descriptive and 5. Mixed methods. For studies to be assessed using the MMAT they must be complete, including methods and results, otherwise a complete score will not be recorded and results will be skewed. Each study is judged within its relevant methodological domain to provide a quality score. This measure was appropriate for the current scoping review because it was not known what type of studies the review would identify. The MMAT can be used to assess multiple study approaches meaning a quality assessment could be completed for multiple citations of full publications. Previous studies have shown the MMAT to be an easy to use tool with good content validity (Pluye et al., 2009) and moderate to perfect inter-rater reliability (Pace et al., 2012).

Citations of completed study publications only, were scored by assigning previously recommended quality scores 0 - 100% (0% 'no criteria met' - 100% 'all criteria met') with 20% assigned per methodological criteria of which there were five per study design. Score ratings > 80% were classified as high quality, 80% moderate quality and < 80% low quality (Pace et al., 2012). This process was completed independently by the reviewers (ES and WS) and then compared and discussed to generate consensus on ratings.

Generated quality scores can be used to guide the inclusion and exclusion of studies. In the current scoping review, quality scores were not used in this way because a breadth of information was key to describing the current evidence. Instead, quality scores were used to provide additional commentary on the studies and facilitate description of rigour across studies included in the scoping review.

2.4.6 Data analysis and reporting

Descriptive statistics were used to summarise quantitative data accompanied by a narrative synthesis of findings. The Theoretical Domains Framework (Michie et al., 2005; Cane et al., 2012) was used to interpret qualitative data relating to barriers and facilitators of MI-E use in invasively ventilated critically ill adults.

2.5 Results

There were no amendments made to the protocol during the conduct of the scoping review.

The electronic database search generated 3090 unique citations. Following the removal of duplications and screening of titles and abstracts, 133 full text papers were assessed for eligibility. Once study inclusion and exclusion criteria were applied 34 citations, representing 28 studies remained which included one additional conference abstract highlighted through direct author contact. Direct author contacts also provided access to additional full text papers in place of abstracts that had been identified through the original search. The 28 studies were taken forward for data extraction. The use of a third reviewer (supervisor-LR) was not required for arbitration during the review process. The search results are presented

using Preferred Reporting Items for Systematic Reviews and Meta-Analyses study flow chart (Figure 2.1) which includes a summary of reasons for exclusion at full text stage.

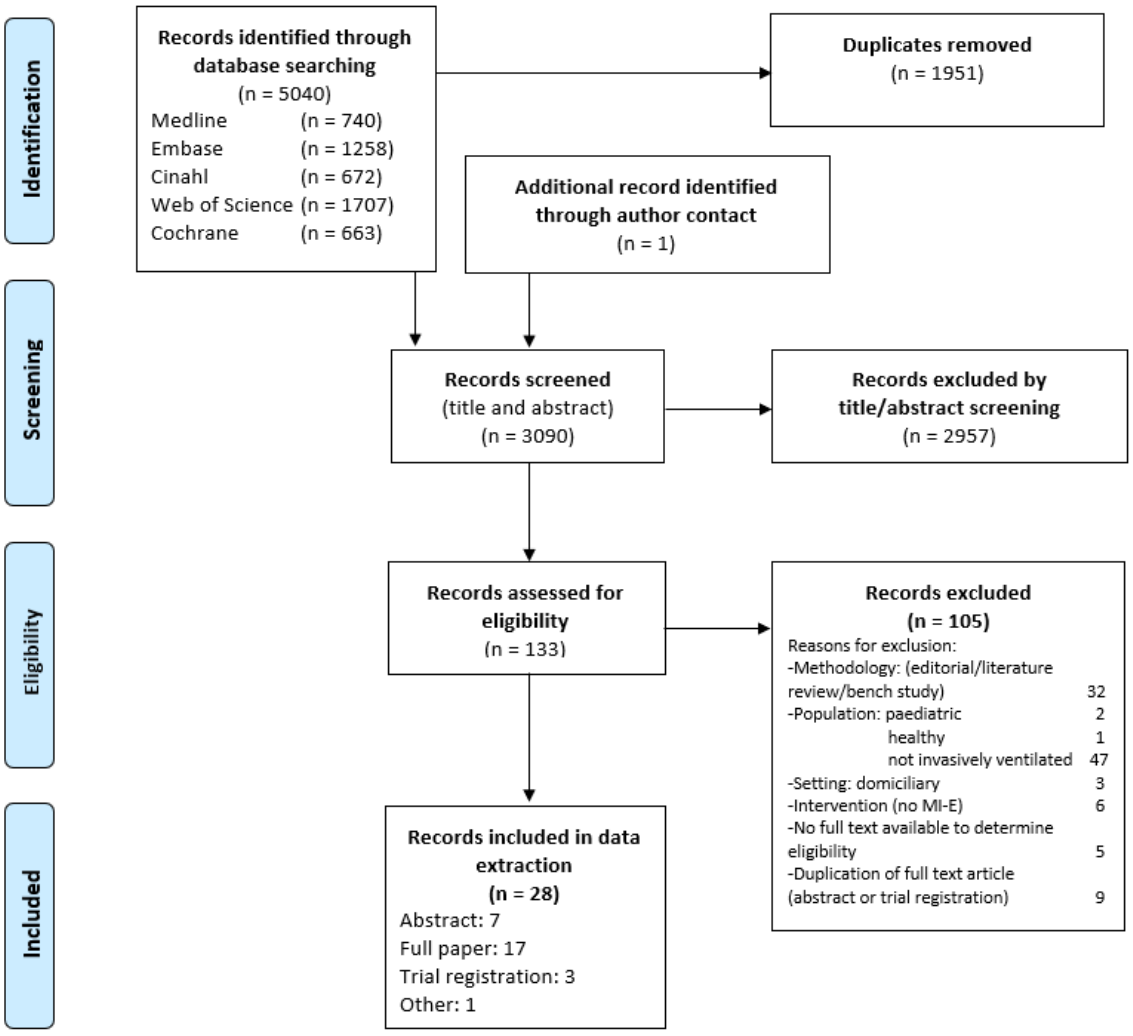


Figure 2.1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses study flow chart

Characteristics of included studies are detailed in Table 2.3. Studies were completed in 13 different countries and used a range of methods. Most studies were RCTs. The MMAT was completed for the 19 full-text publications (Table 2.3). It was not possible to complete a MMAT on the remaining nine studies due to insufficient data and detail of the studies as they were either abstracts or trial registrations. Only 5/19 (26%) studies scored 100% (high quality). Two surveys (Garstang et al., 2000; Bialais et al., 2010) had relatively low response rates (16% and 37% respectively) introducing a risk of selection bias. Additionally, there was a lack of detail across studies about potential confounders (Schmitt et al., 2007; Bialais et al., 2010; Bach et al., 2015; Kuroiwa et al., 2021) and blinding of outcome assessors (Gonçalves et al., 2012; Coutinho et al., 2018; Campos et al., 2019), accounting for lower MMAT scores.

2.5.1 Population

Of the 28 studies, 19 provided information on the ICU population in which MI-E was studied. The remaining nine studies were trial registrations (n=3) and survey data (n=6). The 19 completed intervention studies varied in terms of ICU patient population with a range of reasons reported for intubation/mechanical ventilation. The primary reason for intubation was recorded in 17/19 (89%) and was most commonly acute respiratory failure (n=12). Multiple underlying causes of acute respiratory failure were specified across studies including post-operative respiratory failure; pneumonia; cardiac arrest, acute spinal cord injury and NMD. Duration of mechanical ventilation ranged from 24 hours to 10 days at the time of recruitment (Table 2.3).

2.5.2 Clinical indications and contraindications

Ten different indications for use of MI-E were identified. In the 22 intervention studies (including abstracts and trial registrations) the most commonly reported indication was a presence of secretions and mucus plugging (9/28, 32%), followed by prophylactic airway clearance (7/28, 25%). Contraindications relating to concerns about using high levels of positive pressure (10/28, 36%) were most common. These findings were mirrored in the six survey reports of healthcare professionals (Table 2.4).

Table 2.3: Study characteristics

1st Author & Year of Publication	Citation format	Country	N	Population description	Primary ICU diagnoses/reason for IMV	Interface	Outcomes	MMAT (%)
Randomised controlled trials								
Gonçalves, 2012	Full paper	Portugal	75	General ICU	Acute hypoxaemic and/or hypercapnic RF from a specific etiology	ETT	reintubation; mortality; total ICU LOS; post extubation LOS; NIV failure rates	80
Coutinho, 2018	Full paper	Brazil	43	IMV > 48 hours	Traumatic brain injury; post-operative; polytrauma	NS	secretion clearance; hemodynamics (heart rate, systolic and diastolic blood pressure, mean airway pressure); respiratory mechanics (VT, MV, RR, Crs, Rrs); SpO_2	80
Ferreira de Camillis, 2018	Full paper	Brazil	180	IMV >24 hours	acute RF, decreased level of consciousness, hemodynamic stability, postop, cardiac arrest	ETT	wet aspirated sputum weight; Crs; Rrs; Work of Breathing; adverse ventilator or hemodynamic event	100

1st Author & Year of Publication	Citation format	Country	N	Population description	Primary ICU diagnoses/reason for IMV	Interface	Outcomes	MMAT (%)
Randomised controlled trials continued								
Campos, 2019	Full paper	Brazil	22	IMV>10days; no VAP	Postoperative RF (retained secretions)	ETT	VAP incidence; IMV duration; ICU LOS; mortality, bronchoscopy use; antibiotic use	60
Jprn, 2018	Trial registration	Japan	NS	IMV in ICU >24 hours and expected for 48 hours	NS	NS	ventilator days; ICU days; reintubation; tracheostomy	NA
NCT04149873, 2019	Trial registration	Taiwan	240*	IMV on pressure support mode	Postoperative	ETT	Re-intubation rate; ICU mortality; post extubation LOS	NA
Sanchez Garcia, 2018	Full paper	Spain	120	Critically ill patients	NS	ETT or TT	Safety, tolerance (pain and agitation scores, sedation/responsiveness score)	80
Martínez-Alejos, 2021	Full paper	France, Spain	26	IMV >48 hours	NS	ETT	sputum volume; effects on respiratory mechanics, hemodynamics and safety	100

1st Author & Year of Publication	Citation format	Country	N	Population description	Primary ICU diagnoses/reason for IMV	Interface	Outcomes	MMAT (%)
Observational Cohort								
Bach, 2010	Full paper	USA, Portugal	157	NMD, Critical Care Myopathy	acute RF due to pneumonia and/or surgery	ETT	successful extubation; Vital Capacity, duration on NIV, CPF, pre-intubation NIV experience; total days intubated	100
Soares, 2014	Abstract	Portugal	27	NMD	NMD with RF	TT	CPF	NA
Bach, 2015	Full paper	USA	98	NMD with previous failed extubations	RF (pneumonia)	ETT	successful extubation; SpO_2; CPF; Vital Capacity	80
Farina, 2017	Abstract	Spain	13	NS	NS	ETT and TT	sputum clearance; ventilator/laboratory/ respiratory parameters	NA
Sanchez-Garcia, 2018	Full paper	Spain	13	IMV	Peritonitis, severe pancreatitis, nosocomial pneumonia, RF, coma, severe CAP, bronchospasm, cardiac arrest	ETT and TT	Ventilator modes and parameters, arterial blood gas, hemodynamic parameters, adverse events, secretion clearance, device tolerance	80

Author	Citation format	Country	N	Population description	Primary ICU diagnoses/reason for IMV	Interface	Outcomes	MMAT (%)
Observation cohort continued								
Kikuchi, 2019	Full paper	Japan	10	NMD hospitalised with routine MI-E >1 year	acute RF	TT	CPF	80
Kuroiwa, 2021	Full paper	India	30	IMV patients	RF-medical, post-operative, trauma	ETT and TT	VAP incidence; IMV duration, LOS ICU, mortality, no of VAP/IMV duration; bronchoscopy frequency, bronchoscopy/IMV duration; antibiotic use; antibiotic/IMV duration; bronchial obstructions	80
Crossover study								
ISRCTN25106564, 2013	Trial registration	France	NS	IMV <7 days and expected for >48 hours	acute RF	ETT	Secretion drainage procedures 24hrs AND secretion volume; VAP incidence; extubation failure; hospital & ICU LOS, ICU & hospital mortality	NA

Author	Citation format	Country	N	Population description	Primary ICU diagnoses/reason for IMV	Interface	Outcomes	MMAT (%)
Crossover studies continued								
Sancho, 2003	Full paper	Spain	6	ALS	Respiratory tract infections	TT	SpO_2, peak inspiratory pressure, Paw, work of breathing, wet sputum weight and volume, patient preference for comfort and effectiveness	NA
Case study/series report								
Bialais, 2010	Full paper	Belgium	1	Post-operative	RF-atelectasis	ETT	atelectasis resolution	20
Khan, 2015	Abstract	USA	5	ALS	Emergency intubation due to RF	ETT	Extubation success, interventions used, respiratory muscle strength, bulbar function, cough strength, ICU LOS, hospital LOS, survival, discharge location	NA

Author	Citation format	Country	N	Population description	Primary ICU diagnoses/reason for IMV	Interface	Outcomes	MMAT (%)
Case study/series report continued								
Tan, 2017	Full paper	Malaysia	2	acute spinal cord injury	post op prolonged weaning and prolonged weaning post cervical SCI	ETT and TT	CPF	80
Vokes, 2019	Abstract	UK	1	previously fit and well	aspiration pneumonia	ETT	secretion clearance; FiO_2; arterial blood gas	NA
Guarnieri 2020	Abstract	Italy	23	Cervical SCI	RF	ETT and TT	Extubation failure	NA
Surveys								
Schmitt, 2007	Full paper	USA	86	SCI	NS	NS	device use, patient satisfaction	60
Prevost, 2015	Full paper	Canada	114	Respiratory therapists	NMD, SCI	NS	device use	80
Rose, 2016	Full paper	Canada	157	ICU clinicians	NS	NS	device use	100
Garstang, 2000	Full paper	USA	18	traumatic SCI	RF	TT	patient's experience/preference (pain, preference, fatigue)	60

Author	Citation format	Country	N	Population description	Primary ICU diagnoses/reason for IMV	Interface	Outcomes	MMAT (%)
Surveys continued								
Stilma, 2021	Full paper	Nether-lands	78	ICU professional with expertise in airway care	NS	NS	device use	100
Swingwood, 2020	Full paper	UK	166	ICU Physiotherapists	NS	NS	device use	100

**Sample size mentioned in trial registration Abbreviations: CPF, Cough Peak Flow; Crs, lung compliance; ETT, endotracheal tube; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; MMAT, mixed methods assessment tool; MV, minute volume; N, number of participants; NA, not applicable; NIV, non-invasive ventilation; NMD, Neuromuscular disease; NS, not stated; RF, respiratory failure; RR, respiratory rate; Rrs, Airway Resistance; SCI, Spinal Cord Injury; SpO_2, peripheral oxygen saturations; TT, Tracheostomy Tube; UK, United Kingdom, USA, United States of America; VAP, ventilator acquired pneumonia; VT, tidal volume*

Table 2.4 Reported indications and contraindications for MI-E (n=28)*

	Clinical studies		Survey studies in healthcare professionals	
Indications	**n**	**%**	**n**	**%**
Secretions and mucus plugging	9	32	4	14
Prophylactic airway clearance	6	21	-	-
Reduced Peak Cough Flow or insufficient cough	4	14	2	7
Neuro Muscular Disease or Spinal Cord Injury	-	-	4	13
Previous domiciliary use	-	-	2	7
Weaning failure	4	14	2	7
Atelectasis	3	11	2	7
Respiratory failure	2	7	2	7
ICU acquired weakness	-	-	1	3
Need for endotracheal suctioning	3	11	-	-
Contraindications				
Contraindications to increased positive pressure†	9	32	9	30
Recent surgery (pulmonary/thoracic/abdominal/neuro)	3	11	4	13
Mechanical ventilation settings				
(FiO_2 > 60% or PEEP >10 mmHg or Ppeak >40 mmHg)	2	7	1	3
(Severe) bronchospasm, COPD or asthma	1	7	-	-
Hemodynamic instability	1	7	1	3
Active tuberculosis	1	7	-	-
Increased intracranial pressures (>25 mmHg)	-	-	2	7
Severe COPD or asthma	-	-	2	7
Impaired consciousness				
(inability to respond to direct simple commands)	-	-	1	3
Trauma (facial, cranial, rib fractures)	-	-	1	3
Other‡	6	21	1	3

Data is presented as frequency count and % of 28 studies. *multiple indications/contraindications per study so the total is greater than 100%

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; PEEP, positive end expiratory pressure; Ppeak, peak pressure. †These included: pneumothorax, haemothorax, haemoptysis, emphysema, subcutaneous. ‡Other: palliative care, hemofiltration via jugular catheter, pregnancy, strict dorsal position, contractures, nausea and vomiting

2.5.3 Clinical studies

Figure 2.2 and Table 2.5 provide an overview of described settings of MI-E use in invasively ventilated critically ill patients. All clinical intervention studies (n=22, including abstracts and trial registrations) reported on one or more elements of MI-E device settings. A range of devices were used; 11 (50%) reported using the E70 device (Philips Respironics, Carlsbad, CA, USA) and two (9%) the Emerson Cough Assist device (Emerson Cough Assist, Cambridge, MA). Eleven clinical studies did not specify the model of device used. Eleven (50%) studies reported use via an endotracheal tube, three (14%) via tracheostomy, and six (27%) via a combination of endotracheal tube and tracheostomy. Two studies (9%) did not report on the interface used for MI-E delivery.

For completed studies (n=19, excluding trial registrations), a pressure setting combination of +/-40 cmH_2O was most commonly reported (10/19, 53%). Time settings were reported in 11/19 (58%) studies. Most commonly used inspiratory (Ti) and expiratory (Te) time settings were 3 seconds and 2 seconds respectively, with a pause of 1 second. A pause duration was reported in 8/19 (42%) studies. Five studies (26%) reported use of one insufflation breath prior to an exsufflation breath (not reported in the remaining studies). Flow profile was specified in only three (16%) studies and was set at medium (n =2) or high (n =1). The oscillation setting was applied in three studies. One study applied an oscillation amplitude of 10Hz and frequency of 20Hz, whereas only oscillation frequency was reported in the remaining two studies as 'high' or 16Hz.

Treatment regimes varied across studies with MI-E cycles being repeated most commonly up to once per day but ranging from up to every 20 minutes through to four times a day. Five studies (26%) reported the inclusion of other treatment adjuncts alongside MI-E including side positioning, manual assisted cough and suction. Seven (37%) studies described the individual applying MI-E. This was most commonly a physiotherapist or respiratory therapist, followed by ICU nurses, carers/family and ICU physicians.

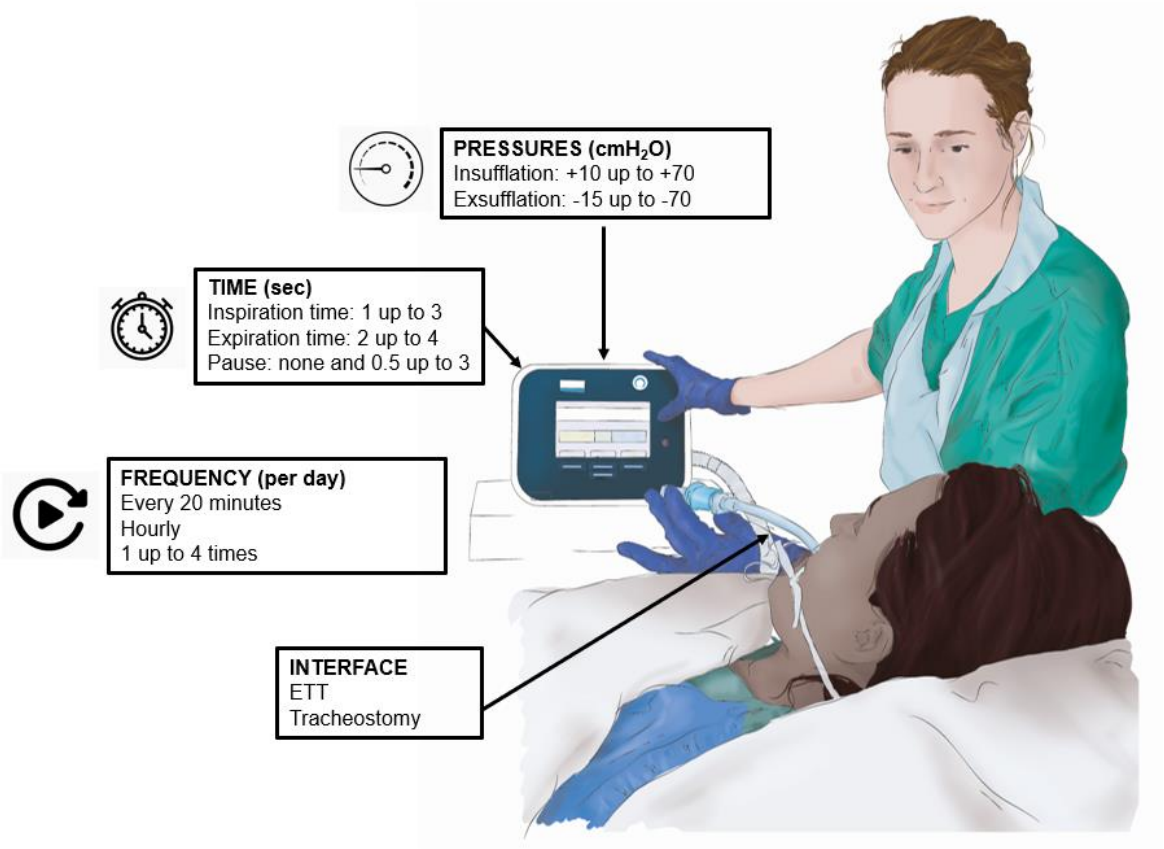


Figure 2.2: Summary of MI-E settings reported across studies.
(Image ownership W.Stilma, used with permission)

Table 2.5: MI-E settings detailed across studies (n=19 completed intervention studies)

1st Author, year	Mode	Insufflation pressure (cmH_2O)	Exsufflation pressure (cmH_2O)	Insuff time (sec)	Exsuff time (sec)	pause (sec)	flow profile	Insuff repeat	Treatment regime
Randomised controlled trials									
Gonçalves, 2012	NS	40	40	3	2	3	NS	1	8 cycles* per session, 3 sessions/day. 1 day whilst intubated, 2 days post extubation
Coutinho, 2018	auto timed	40	40	3	3	0	NS	1	5 repetitions of 4 cycles
Ferreira de Camillis, 2018	NS	40	40	2	3	2	NA	NS	3 repetitions of 10 cycles
Campos, 2019	NS	30	15	2	2	0.5	medium	NS	30 seconds on, 30 seconds off until 5 minutes
Sanchez-Garcia, 2019	NS	50	50	NS	NS	NS	NS	NS	NS

1st Author, year	Mode	Insufflation pressure (cmH_2O)	Exsufflation pressure (cmH_2O)	Insuff time (sec)	Exsuff time (sec)	pause (sec)	flow profile	Insuff repeat	Treatment regime
Randomised controlled trials continued									
Martínez-Alejos, 2021	automatic	40	40	3	2	1	medium	NS	4 repetitions of 5 cycles, with 1-minute rest between repetitions
Observational Cohort									
Bach, 2010	manual	40	40	NS	NS	NS	NS	NS	Up to every 20 minutes to maintain or return pulse oxygen saturation to >95% in ambient air
Soares, 2014	-	30-70	30-70	NS	NS	NS	NS	NS	NS
Bach, 2015	manual	60-70	60-70	NS	NS	NS	NS	NS	hourly whilst awake
Farina, 2017		50	45	3	4				2 cycles per session

1st Author, year	Mode	Insufflation pressure (cmH_2O)	Exsufflation pressure (cmH_2O)	Insuff time (sec)	Exsuff time (sec)	pause (sec)	flow profile	Insuff repeat	Treatment regime
Observational cohort continued									
Sánchez García, 2018	patient triggered	50	-45	3	4	NS	high	1	2 repetitions of 10-12 cycles
Kikuchi, 2019	automatic	40	40	1.5	1.5	2	NS	0	2 repetitions per cycle
Kuroiwa, 2021	-	15-40 (started low and gradually increased, through auscultation and changes in SpO2)	15-40	2-3	2-3	2	NS	NS	2 repetitions of 5-10 cycles
Crossover									
Sancho, 2003	-	40	40	2	3	1	NS	NS	5 cycles
Case study/series report									
Bialais, 2010	manual	40	40	NS	NS	NS	NS	NS	10 repetitions of 5 cycles
Khan, 2015	NS	NS	NS	NS	NS	NS	NS	NS	NS

1st Author, year	Mode	Insufflation pressure (cmH_2O)	Exsufflation pressure (cmH_2O)	Insuff time (sec)	Exsuff time (sec)	pause (sec)	flow profile	Insuff repeat	Treatment regime
Case study/series report continued									
Tan, 2017	NS	25 building up to 40 in increments of 50	26 building up to 40 in increments of 40	NS	NS	NS	NS	NS	6-10 cycles with 20-60sec rest between each cycle
Vokes, 2019	NS	40	45	NS	NS	NS	NS	NS	NS
Guarnieri 2020	NS	NS	NS	NS	NS	NS	NS	NS	4 times a day

Abbreviations: NS, data not supplied

**cycle refers to an insufflation breath rapidly followed by an exsufflation breath*

2.5.4 Outcomes and measures

Of the 28 studies, 22 provided information relating to outcomes and measures, the remaining six were survey-based studies reporting on organisation of care. There were 21 different outcomes measured in the 22 studies that provided this information (Table 2.3 and Table 2.6). Only seven studies (7/22, 32%) clearly specified a primary outcome, which included aspirated/wet sputum, re-intubation rate, suction frequency, number of ventilator/ICU days, incidence of VAP and mortality rate in one year. Five (5/22, 23%) studies reported on one outcome only. These included peak cough flow (n=3), reintubation rate (n=1) and atelectasis resolution (n=1). Pulmonary mechanics were the most frequently reported outcomes overall (n=9). These included measures of tidal volume, minute ventilation, airway resistance, lung compliance and vital capacity. Eight studies (8/22, 36%) reported on extubation failure/success; seven studies (7/22, 32%) reported on secretion clearance or wet sputum weight.

Methods of outcome measurement varied across studies. Secretion clearance was primarily measured by aspirated sputum or sputum weight, most commonly at 5 minutes post study intervention (Sancho et al., 2003; Ferreira de Camillis et al., 2018). When needed 10ml sodium chloride (NaCl) was used to rinse the suction catheter and that weight was extracted from the result (Ferreira de Camillis et al., 2018). Alternatively, in a trial registration, it was proposed that secretion clearance would be measured by frequency of endotracheal suctioning over a 24-hour period (ISRCTN25106564, 2013). VAP incidence was measured throughout the period of intubation, with the frequency of assessment not reported. The definition of VAP provided was ‘pneumonia in a patient who was on mechanical ventilation

for > 48 hours' (Kuroiwa et al., 2021). Reintubation rate or extubation failure was used as an outcome measure in eight (8/22, 36%) studies and defined in 3/8 studies. Definitions of extubation failure varied across studies including '48 hours following extubation' (Gonçalves et al., 2012); 'not needing a tracheostomy during hospitalisation or at any time during follow up' (Bach et al., 2015) and 'discharge without re-intubation' (Bach et al., 2010).

Timepoints for measuring pulmonary mechanics were 5 minutes before and after the intervention, and 1 hour after the intervention. Peak cough flow was measured during and after intubation, mostly using the MI-E device (Soares et al., 2014; Tan et al., 2017; Kikuchi et al., 2019).

2.5.5 Adverse events

Adverse events were addressed in 13/19 (68%) clinical studies. For reporting purposes, adverse events were grouped into three commonly occurring categories, namely 'respiratory', 'hemodynamic' and 'other' (Table 2.7).

Of the 13 studies that reported on adverse events, 10 reported no occurrence of adverse events in relation to MI-E. The remaining three studies (Khan et al., 2015; Rose et al., 2016; Martinez et al., 2021) reported oxygen desaturation (< 85%), haemodynamic variation (increase or decrease of heart rate or blood pressure for > 15-20% from baseline), re-intubation, pneumothorax, mucus plugging, haemoptysis and chest pain.

Table 2.6 Outcomes measured* (n=22)

Physiologic variables	**Frequency (%) of outcome included in studies**
Pulmonary mechanics	9 (41)
Extubation failure/success	8 (36)
Secretion clearance/wet sputum weight	7 (32)
Peak Cough Flow	5 (23)
Pain/agitation score	5 (23)
Adverse event	5 (23)
Device use	3 (14)
Ventilator Acquired Pneumonia incidence	3 (14)
Patient preference	3 (14)
SpO_2	2 (9)
Bronchoscopy use	2 (9)
Antibiotic use	2 (9)
Frequency of bronchial obstructions	2 (9)
Haemodynamic parameters	2 (9)
Work of breathing	2 (9)
Atelectasis resolution	1 (5)
Clinical outcome	
Mechanical Ventilation duration	4 (18)
Non-Invasive Ventilation failure rate	3 (14)
ICU length of stay	7 (32)
Mortality	5 (23)
Discharge location	1 (5)

*Abbreviations: ICU, intensive care unit; SpO_2, peripheral oxygen saturations. *Multiple outcomes reported per study at times*

Table 2.7 Reporting of adverse events (to include definitions when provided) (13/28, 46%)*

1st author, year	Summary of planned adverse events data collection			Summary of adverse event reporting
	Respiratory	**Hemodynamic**	**Other**	
Clinical studies				
Sancho et al., 2003				No untoward effects
Soares et al., 2014				No side effects in relation to high MI-E pressures
Khan et al., 2015	reintubation and pneumothorax			Reintubation 2/5 patients; pneumothorax 1/5 patient
Farina et al., 2017	barotrauma, desaturation, atelectasis, haemoptysis	hemodynamic complications		None detected after MI-E
Coutinho et al., 2018		HR and Mean Arterial Pressure		No significant changes
Ferreira de Camillis et al., 2018	↓ oxygen saturation by 3%	occurrence of Systolic Blood Pressure <90 mmHg		None observed
Sanchez-Garcia et al., 2018	barotrauma (pneumothorax) or atelectasis, desaturation, haemoptysis, other airway complications		tolerance (need for additional sedatives or analgesic medication)	No adverse events observed, well tolerated

1st author, year	Summary of planned adverse events data collection			Summary of adverse event reporting
	Respiratory	Hemodynamic	Other	
Clinical studies continued				
Sanchez-Garcia et al., 2019				Safe and feasible, no adverse effects
Vokes et al., 2019				Safe and feasible, no adverse effects
Guarnieri et al., 2020				No adverse events observed
Martínez-Alejos et al., 2021	pneumothorax, SaO_2 consistently ↓ < 85% or > 10% from baseline	HR, Systolic Blood Pressure or Diastolic Blood Pressure ↑ or ↓ > 20% from baseline		10 episodes of brief desaturations or hemodynamic variations were documented during expiratory rib cage compressions + MI-E.
Surveys				
Prevost et al., 2010				Complications (not defined) rare in Neuromuscular Disease patient, in other patient groups unknown

1st author, year	Summary of planned adverse events data collection			Summary of adverse event reporting
	Respiratory	**Hemodynamic**	**Other**	
Surveys continued				
Rose et al., 2016	Mucus plugging requiring tracheostomy, pneumothorax, haemoptysis	Bradycardia/asystole, hypotension, arrhythmias	Chest pain	Mucus plugging requiring tracheostomy (10/43, 23%); pneumothorax (4/43, 9%); haemoptysis (3/43, 7%); bradycardia/asystole (8/43, 19%); hypotension (7/42, 16%); arrhythmias (6/43, 14%); chest pain (8/43, 19%)

** Remaining articles did not explicitly report on adverse events.*

Abbreviations: HR, heart rate; MI-E, Mechanical In- Exsufflation; SaO_2, arterial oxygen saturations; SpO_2, peripheral oxygen saturation

2.5.6 Barriers and facilitators to MI-E use

There were no qualitative studies identified for inclusion in the scoping review, however three survey studies reported qualitative data collected with open-ended questions (Schmitt et al., 2007; Rose et al., 2016; Swingwood et al., 2020). Themes illustrating barriers and facilitators to MI-E use were grouped under six of the 14 Theoretical Domains Framework domains; knowledge, skills, beliefs about consequences, intention, environmental context and resources, and social influences (Table 2.8). Barriers to MI-E use in the critically ill population included the impact of team culture, a lack of clinical experience, and the need for additional resources and training with the device. Conversely, data illustrated positive intention to use MI-E with this patient group and described positive experiences.

Table 2.8 Reported barriers and facilitators to MI-E use

TDF Domain	Description
Knowledge and Skills	A perceived lack of skills ('skills') and knowledge ('knowledge') were barriers to use, with the suggestion that clinicians may be more skilled using the device via a tracheostomy interface in comparison to an ETT (Rose et al., 2016; Swingwood et al., 2020).
Beliefs about consequences	Expected or potential outcomes ('beliefs about consequences') were focused on positive clinical experiences (Schmitt et al., 2007; Rose et al., 2016; Swingwood et al., 2020).
Intention	A positive intent to practice ('intention') (Swingwood et al., 2020).
Environmental Context and resources	A lack of resources, funding and senior culture ('environmental context') impacting implementation (Schmitt et al., 2007; Rose et al., 2016; Swingwood et al., 2020).
Social influences	Team culture and senior support ('social influences') influencing implementation and illustrating the potential impact of colleagues (Rose et al., 2016; Swingwood et al., 2020).

Abbreviations: TDF, theoretical domains framework

2.6 Discussion

The aim of this scoping review was to describe current and emerging evidence on how MI-E is used in invasively ventilated critically ill adults. Included in the review were 25 completed studies and three trial registrations published between January 1990-April 2021. The modified and updated literature search generated additional references to those included in the earlier Cochrane review (Rose et al., 2017) enabling the advancement in the commentary of the evidence base for the use of MI-E in this specific patient population. Findings of the scoping review are discussed in context of the wider research evidence and then specifically for the subsequent doctoral research.

Results demonstrated that the primary clinical diagnoses for mechanical ventilation as an indication for MI-E were acute respiratory failure with multiple causes (post-operative respiratory failure, pneumonia and cardiac arrest). Nearly half of studies included MI-E use in people with NMD and spinal cord injury, whereas the remaining studies included patients who reflected the heterogenous nature of invasively ventilated ICU patients. With MI-E being traditionally used in a NMD cohort, the inclusion of a range of patients is a strength of this review.

Reported indications for commencing MI-E use included the presence of secretions, mucus plugging and prophylactic airway clearance; these mirror indications previously described (Chatwin et al., 2018). Reported contraindications to MI-E

included the use of increased positive pressure (due to the risk of pneumothorax). During invasive ventilation positive pressure breaths are delivered followed by a passive expiration. In contrast MI-E delivers both positive (insufflation) and negative (exsufflation) pressure breaths. Therefore, it is remarkable that the use of positive pressure was a perceived contraindication, whereas negative pressure was not considered a contraindication or precaution for use of MI-E in invasively ventilated critically ill adults. In the ICU patient, lung recruitment and de-recruitment are important considerations (Brower et al., 2000; Park et al., 2013). Barotrauma (lung damage due to excess pressure) and volutrauma (lung damage due to excess volume) associated with a large tidal volume is well documented, and low volume lung protective ventilation is standard care, particularly for patients with acute lung injury (Brower et al., 2000). However, de-recruitment of lung units can have an equally adverse impact on oxygenation and effective ventilation, whilst attenuating lung injury (Park et al., 2013). To date, no studies have examined the extent of de-recruitment or possible adverse events in relation to a negative pressure exsufflation breath using MI-E.

A range of MI-E devices were used across studies via both endotracheal and tracheostomy interfaces. The review data indicate that MI-E has mainly been studied with insufflation and exsufflation pressures of +/-40cmH_2O. The use of asymmetrical pressure settings and customisation of pressure settings to endotracheal size have not been reported in invasively ventilated critically ill adults. Previous studies in a NMD non-ICU population (Chatwin and Simonds, 2020) illustrated that asymmetrical

pressure settings (that is, pressure settings to enhance the expiratory flow +30: -40cmH_2O) may enhance expiratory flow. One bench study examining the impact of an artificial airway on MI-E flow rates (Guerin et al., 2011), found higher pressures were required to overcome resistance to flow, particularly in narrower endotracheal tube sizes. Recommendations for practice subsequently included the use of a higher-pressure regime for intubated patients. However, this has not been investigated and supported in clinical studies and is therefore an area that requires further investigation.

Detail of flow rates, use of oscillations and timings were reported infrequently and where they were reported there was little consistency between studies. This makes extrapolation of device set up into a clinical setting challenging. It is unclear whether these omissions are simply a lack of reporting detail or whether the full potential of MI-E settings were not used. It should be acknowledged that advanced settings such as oscillations have not been available to clinicians for the duration of the data collection period and would have impacted on the reporting of this feature. The use of oscillations during MI-E has only been examined in an amyotrophic lateral sclerosis population (Sancho et al., 2016; Sancho et al., 2021). The addition of oscillations to MI-E was reported to have no impact on generated cough peak flow, or reduced infection risk, hospital admissions and need for bronchoscopy in this patient group. The impact of oscillations in the intubated, critically ill population therefore remains unknown. Future research should focus on gaining a better understanding on how oscillations may impact the physiological working of MI-E

before considering the efficacy in this patient group. Findings regarding the set-up of MI-E are unique to this scoping review. The previous Cochrane Review only included one study of MI-E which limited the ability to make comparisons across studies. This scoping review has highlighted the importance of recording and reporting the detail of device set up within future research. Data are needed to optimise the physiological impact of MI-E in invasively ventilated critically ill patients and to provide evidence-based guidance for practice of care, training and education.

Across the included studies 21 different outcomes were measured. Methods of outcome measurement and timepoints of measurement varied across studies. This limits the ability to make comparison across studies to determine efficacy of MI-E in this patient group and to make recommendation regarding device implementation. The most common outcomes reported across studies included re-intubation rates, wet sputum weight and respiratory parameters. The appropriateness of wet sputum weight as a primary outcome for examining the efficacy of MI-E is questionable (Berney and Denehy, 2002; Swingwood et al., 2020). Although sputum clearance is important to quantify in invasively ventilated critically ill patients, a linear relationship does not exist between sputum quantity and disease severity (Fahy and Dickey, 2010). The range of outcome measures used across MI-E studies based in ICU is challenging and potentially limits the quality of the overall evidence base. Consistency in the selection of outcome domains and measures across MI-E studies would strengthen the overall evidence base.

Only 13 studies explicitly mentioned adverse events with three of these reporting the occurrence of pneumothoraces, haemodynamic instability and oxygen desaturation. Changes in haemodynamic parameters during MI-E application were transient, reported as non-significant and did not require trial protocol cessation, therefore authors referred to these occurrences as clinically irrelevant (Martinez et al., 2021). In the current scoping review, the reporting of a pneumothorax occurred in 2/28 studies (Khan et al., 2015; Rose et al., 2016). One abstract (Khan et al., 2015) reported a single occurrence of pneumothorax across five amyotrophic lateral sclerosis patients. All patients had had an emergency intubation due to acute respiratory failure, receiving mechanical ventilation via an ETT. Rose et al., (2016) described results from a Canadian National Survey examining cough augmentation techniques in the critically ill. Of the 43 centres reporting MI-E use there were 4(9%) centres that had experienced pneumothorax. Across these two studies no further detail was provided which limits further discussion but it is likely there were other clinical factors present that may have contributed. Occurrence of pneumothorax would be classed as a serious adverse event but in these instances, it is not possible to directly attribute any cause or effect of the pneumothoraces to MI-E use. Case reports of pneumothoraces have previously been described in an adult NMD non-ICU population (Allen and O'Leary, 2018; Suri et al., 2008) following MI-E, and again no causal relationship could be confirmed due to the use of MI-E (Allen and O'Leary, 2018; Suri et al., 2008; McDonald et al., 2019; Yasokawa et al., 2020). It is important to note that across included studies in the scoping review, the recording of adverse events was not always pre-defined which may have led to under-reporting.

Additionally, there was variation between studies in how adverse events were defined limiting direct comparison between studies.

In the current scoping review, MI-E was most frequently provided by physiotherapists. However, the provider of MI-E has been shown to vary by country as shown in previous practice surveys (Rose et al., 2016; Stilma et al., 2021). This is an important consideration for future MI-E education. Analysis of qualitative data from included surveys used the theoretical domains framework (TDF) and demonstrated the impact of knowledge and skills as a potential barrier to MI-E implementation in the ICU setting. Education should consider needs of all clinicians delivering MI-E. Dissemination and implementation of study findings should also consider the breadth of clinicians that need to be reached and influenced.

No qualitative studies were identified for inclusion in the scoping review. Barriers to MI-E use described in data from surveys of practice, included team culture and a perceived lack of skills and knowledge, suggesting an important opportunity for training and education. Conversely, positive experiences of MI-E were described, alongside a positive intention for future use. With MI-E being part of respiratory care, further qualitative inquiry to explore barriers and facilitators in greater detail could provide useful data to inform the optimal clinical implementation of research findings. A further gap to the evidence base that the scoping review highlighted was the lack of patient experience data which is important when considering wider implementation of MI-E.

2.6.1 Strengths and limitations

This review was described as a scoping review as it addressed a broad topic, with descriptive research questions and the inclusion of multiple methodologies to include trial registrations. The scoping review protocol followed methods as outlined by Arksey and O'Malley (2005). Additionally, advancements to this original framework by subsequent authors were considered and included within the protocol to strengthen the methods. A transparent prespecified protocol was developed and subsequently followed. However, the review also followed a systematic approach and included a quality assessment of citations. As such, this work package could be viewed as a systematic review. As previously discussed, the definitions of review methodologies are not exclusive and overlap of terminology and descriptions occurs (Arksey and O'Mallet, 2005; Colquhoun et al., 2014; Munn et al., 2018).

The search strategy had no limitations regarding study design or language restrictions to ensure that a broad range of evidence was considered. The initial database search identified 3090 citations. One complication was inclusion of the term 'exsufflation' as this returned a vast number of studies relating to gastro-intestinal procedures. A key feature of the original framework (Arksey and O'Malley. 2005) is that authors wanted the identification of relevant studies to be an iterative process, meaning search terms and inclusion criteria can be revised as the process is completed. 'Exsufflation' was a key term relevant to this project, being part of the technique name, and so no revisions to the search strategy were made. A potential

limitation to acknowledge is the exclusion of bench studies in the review, which may have provided additional data on MI-E settings to inform future research protocols.

When charting the data, a piloted extraction form was used. The piloting phase included data extraction for five citations by two researchers independently. This was an important process as it ensured consistent interpretation of extraction fields and consistent use of the data extraction form. There were two researchers (ES and WS) screening, reviewing and extracting data which limits bias and enhances the validity of findings within the current scoping review. As recommended all data were managed in Excel and an online citation management software package was used (Arksey and O'Malley., 2005; Levac et al., 2010). This enabled data to be kept in an organised manner, remaining accessible to others within the review team.

Risk of bias and quality assessment scoring is not traditionally part of the scoping review process; however, advancements to the original framework have highlighted concerns about this omission (Levac et al., 2010; Daudt et al., 2013). Authors of these papers have not specified which assessment tool to use, instead recommending use of 'a validated instrument'. A quality assessment process was implemented in this scoping review using MMAT to provide some commentary on the included studies.

When presenting and discussing data a consistent and clear approach was used that followed the specific pre-stated research objectives and questions. For qualitative data relating to barriers and enablers, a theoretical framework was implemented. The sixth stage of the scoping review framework (Arksey and O'Malley et al., 2005) is the consultation phase, the importance of which has been highlighted (Levac et al., 2010). Consultation should occur with all relevant stakeholders including clinicians, patients and researchers. In this regard, the research team was multi-disciplinary and inter-professional which is a strength (Levac et al., 2010). The knowledge and experience of the team was implemented early on in consultation with the PAG when developing the review protocol, ensuring it remained relevant to clinical practice. Evidence and knowledge were acknowledged as lacking and a barrier to MI-E implementation (Swingwood et al., 2020), and the review protocol was designed to help address this gap. The PAG were consulted throughout the scoping review process.

2.6.2 Implications of the scoping review for future research

One of the key purposes of completing the current scoping review was to address the remaining gaps in the evidence base as illustrated from the Cochrane review (Rose et al., 2017). The current search was completed in April 2021 and therefore included an additional five years of publications in comparison to the Cochrane review. With the inclusion of a modified search strategy and broader inclusion criteria results have provided an illustration of how MI-E has been used in research up to 2021 and enabled progression in commentary around the original research

questions. However, there remain areas that require additional exploration which will now be discussed.

Findings from the scoping review have illustrated the importance of, and need for detail in relation to MI-E device set up in future studies to ensure that the interventions can be replicated. The review was not designed to determine optimum device set up but this would be useful information for clinical practice and worthy of future exploration. Knowledge pertaining to MI-E use is currently seen as a barrier to use so the generation of such information may be beneficial to overcoming this. There was a sparsity of qualitative literature within the scoping review exploring both clinician and patient experiences of MI-E in the ICU setting. This would be a valuable future addition to the evidence base.

Development of a core outcome measure set, as recommended by the COMET initiative (https://www.comet-initiative.org/, accessed September 2021) (Williamson et al., 2012; 2017), that specifically focuses on interventions for airway clearance in the invasively ventilated critically ill adult population is warranted. MI-E is just one airway clearance technique available to use in the ICU setting. Rather than narrow the outcome set specifically to airway clearance via MI-E, it would be more useful to generate a core outcome set (to include recommended measures) for airway clearance techniques in the intubated population. This would encourage consistency in outcome selection and reporting for airway clearance techniques, thus enabling studies to be compared and contrasted more easily.

2.7 Conclusion

This scoping review of MI-E use in invasively ventilated critically ill adults reported data on 28 studies. A lack of qualitative data was an apparent gap in the current evidence base. There was little consistency across the included studies in how MI-E was used and reported. This lack of consistency limits the strength of the overall body of evidence and the ability, therefore, to make recommendations about best practice. More studies are required, including transparent reporting of device settings for the invasively ventilated critically ill patient. Additionally, development of a core outcome measure set for airway clearance in this population is needed to promote consistency in outcome reporting in future intervention trials important to patients, clinicians, and researchers.

Chapter 3

Clinician reported barriers and facilitators to the use of Mechanical Insufflation-Exsufflation (MI-E) in intubated patients across adult UK Intensive Care Units

3.1 Introduction

Despite emerging evidence for the efficacy and safety of MI-E in the intubated population, implementation of MI-E as an airway clearance technique across UK ICUs remains slow. A pre-doctoral survey of UK physiotherapists practicing in critical care (Swingwood et al., 2020) found that just over half of respondents (n=86/163, 53%) used MI-E with intubated adult patients. In contrast, 99% of respondents reported that they used MI-E with extubated patients. Of those physiotherapists who did not use MI-E in intubated patients (77/163, 47%), a range of barriers was reported.

Barriers reported in the survey were categorised into three main themes.

1. *The need for training and experience using the device:* Respondents of all grades identified a need for training and experience to use the device specifically in the ICU population. This need was perceived to be greater where MI-E was being used for patients with an ETT, in comparison to patients with a tracheostomy.

2. *Resource availability:* There was a limited number of devices available for specific use in ICU, with units having to share a device across several clinical specialties and clinical ward areas. In some cases, a lack of available funding for more devices was also highlighted as a limitation to solving this problem.

3. *The culture of the ICU:* Where there were negative perceptions or conflicting opinions about MI-E from within the physiotherapy team and wider multi-disciplinary team (including doctors and nurses), it was suggested that this limited use of MI-E in an ICU setting. Some respondents did not consider MI-E to be part of routine care, which was a barrier to use in a wider team setting.

There were limitations to the survey which include the uni-professional group of survey respondents, all of whom were physiotherapists. The nature of a survey also prevented in-depth exploration of the barriers and facilitators. In the UK, physiotherapists have autonomy, and therefore accountability, in relation to clinical decision making, which is not the case in most other countries. However, despite having autonomy, physiotherapists remain influenced by the wider multi-disciplinary team and the associated culture of that team.

Further research is therefore warranted to comprehensively explore the barriers and facilitators to the use of MI-E as an airway clearance technique in the intubated population and to include the opinions and experiences of the wider ICU multi-disciplinary team. The findings of this further work have the potential to inform

future research, education and implementation techniques to enable effective and optimal use of MI-E in the wider ICU population.

At the time of carrying out the scoping review (Chapter 2) no qualitative studies that examined clinician or patient experiences of using MI-E in this acute setting were identified (Swingwood et al., 2022).

3.2 Study aim and objectives

The aim of this study was to explore barriers and enablers for MI-E use as an airway clearance technique in intubated critically ill adults as perceived by ICU clinicians.

3.2.1 Study Objectives

- To explore the impact of ICU culture on MI-E implementation
- To further understand perceived barriers and enablers that are specific to MI-E use via a tracheostomy and an ETT interface
- To compare and contrast professional group beliefs about MI-E use in the ICU

3.3 Approaching the qualitative study

There are several philosophical assumptions underpinning qualitative research which include the researcher's stance towards the nature of reality (ontology); how the researcher knows what they know (epistemology); the role of values (axiology) and

the methods used in the research process (methodology) (Creswell, 2003). These are considered below within the context of this specific study.

3.3.1 The ontology continuum; 'the researcher's stance'

The ontology continuum has many variations which range from a view of *relativism*, whereby reality is dependent upon human interpretation and knowledge resulting in multiple realities, through to *realism*, where reality refers to one single truth and is independent of such influence and interpretation (Braun and Clarke, 2013). In between lies *critical realism* which recognizes that knowledge exists but perception can be influenced by social interactions and experiences.

3.3.2 Epistemological assumption and axiology

It is well documented that the researcher plays an active role in the research process. It is important to therefore consider the relationship between the researcher and the topic being researched. The researcher also has influence over the research as they bring independent views based on past experiences and therefore another unique reality.

The researcher should acknowledge their personal views, knowledge and experience. Furthermore, the researchers influence on development of the research questions, methodological choices, analysis approach and development of onward theory should be considered. The qualitative paradigm used by a researcher will vary depending on the experiences and biases that they bring to a study. There are four

key paradigms that inform qualitative research; post-positivism; constructivism; advocacy/participatory and pragmatism (Creswell, 2003).

Post-positivism takes a scientific and logical approach to research often focusing on empirical data collection and a cause and effect relationship. This approach is often employed by those researchers with prior and extensive quantitative research. A post-positivist approach does acknowledge the existence of multiple realities and perspective from participants but eventually seeks out a single truth or reality (Creswell, 2003; Braun and Clarke, 2013).

In contrast, a participatory approach to qualitative research focuses on marginalised groups or individuals so that the researcher becomes the voice for these participants. Often, participants are an integral and active collaborator in the research process to ensure they are not marginalised further. Outputs from this approach focus on an action plan to address required changes to practice (Creswell, 2003).

Pragmatism comes in many forms but as with a participatory approach, is outcome focused. Researchers focus on the problem and research question to be examined, often employing multiple methods (quantitative and qualitative) of data collection and focusing on the research implications and why the research needs to be completed (Creswell, 2003).

Constructivism acknowledges that individual realities are impacted and therefore dependent upon factors such as culture and past experiences, therefore each research participant may have different realities which co-exist and, in some cases, some shared understanding may exist between individuals. This is in contrast to a post-positivist approach of a single reality. Furthermore, a constructivist approach acknowledges the impact of the researcher in the research process. The researcher focuses on complexity of meaning rather than trying to narrow meaning into a few categories providing a deeper understanding of the phenomenon which can then be used to develop practices and/or policies.

The aim of this study was to explore barriers and enablers for MI-E use in intubated critically ill adults as perceived by ICU clinicians. Participants were from different professional groups (physiotherapists, doctors and nurses), with differing levels of clinical and MI-E experience. Additionally, clinicians were from different hospitals across the UK with varying experiences. Differences between participants were particularly important in the context of this study which investigated an emerging technique in a unique patient group. It was anticipated that there were likely to be multiple realities across and within professions and, in some cases, a shared understanding between participants. It was important to investigate participants' views using broad, open-ended questions and report the various realities using multiple quotes across all participant groups. A post-positivist approach would not enable this broad approach. A pragmatic approach with a focus on consequences of enquiry and 'what works' did not seem appropriate due to the topic being an emerging area. Consequently, a constructionist approach was adopted to

acknowledge the impact of the researcher whilst enabling a broad overview of the multiple realities, relevant to each of the different professional groups, occurring concurrently.

3.3.3 Reflexivity (positioning of the researcher)

My background and experiences will have shaped how I generated, interpreted and drew conclusions from the data; therefore, my position as the researcher was important to acknowledge. It was also important to critically reflect on the knowledge generated through qualitative research and the role of the researchers in that process.

Building on previous descriptions of my researcher position (Chapter 1), I am passionate about the exploration of airway clearance techniques and patterns of practice in the acutely intubated population. MI-E forms part of an airway clearance toolbox and despite emerging evidence for its use in the intubated population, I wanted to consider if MI-E was being used to its full potential. In the decade prior to commencing the research there had been a shift of focus away from research on airway clearance and towards rehabilitation and early mobilisation in this patient group.

Additionally, due to past experiences and previously completed research, I was interested in exploring why clinicians used MI-E and wanted to understand their rationale informing device set up. I believe all clinicians should feel confident and competent and that use of MI-E should not be linked to clinician hierarchy. On many

occasions during educational events, I have observed that delegates have been predominantly band 7 physiotherapists who manage a team of clinicians and were not representative of the wider workforce.

Embarking on the interviews, I believed it was likely that I would know some participants (irrespective of profession) either through direct working relationships or through previous educational events and social media presence. There was a possibility that these relationships may have affected the participants' willingness to speak openly. To mitigate this, my role as the researcher, the process of data anonymisation and assurance of confidentiality were clearly explained at the start of each interview.

3.4 Methodology

3.4.1 Methodological Frameworks

As illustrated in the pre-doctoral UK survey (Swingwood et al., 2020), MI-E implementation in the intubated ICU population remains in its infancy, despite emerging evidence. Awareness of the potentially low level of MI-E use is an important starting point when considering implementation of the MI-E technique as an intervention. The application of evidence-based practice and the success of implementation is dependent upon behaviour change. There are multiple models available to help understand the influences of behaviour. These influences can be manipulated to have a direct impact on the behaviour output and resultant implementation of the evidence base.

In 2011, Michie et al., completed a review of current behaviour change frameworks through which 19 were identified. These frameworks were evaluated against three criteria: comprehensiveness, coherence and links to a model of behaviour. The 19 frameworks covered nine intervention functions and seven policy categories to enable the interventions. Framework quality assessment was based upon pre-defined criteria which included the need for a framework to be comprehensive, coherent and linked to behaviour change models. On evaluating these frameworks, Michie et al (2011) concluded that none covered the full list of intervention functions or policies. Furthermore, only a small number of frameworks were deemed to be coherent and/or linked to a current behaviour model.

Behaviour Change Frameworks need to capture the range of mechanisms involved in change. However, the quantity of potential behaviour change frameworks available makes selection challenging. Furthermore, it is not feasible to select multiple frameworks as this will be time consuming and chosen frameworks may still not consider relevant influences and integral information may be missed. These omissions are likely to have an impact on the resulting success of implementation (Michie et al., 2011).

Michie et al., (2011) went on to develop a new framework for behaviour change with the aim of meeting their three quality criteria (comprehensiveness, coherence and links to a model of behaviour). At the centre of the framework that they developed is a 'behaviour system', composed of three conditions; capability, opportunity and motivation (*COM-B system*). Around the COM-B system are nine intervention

functions and then seven policy categories. Together this is named the '*behaviour change wheel*'.

3.4.2 The COM-B system

The COM-B system illustrates the interactions of three key conditions; capability, opportunity and motivation and the impact of these interactions on resultant behaviour (Figure 3.1).

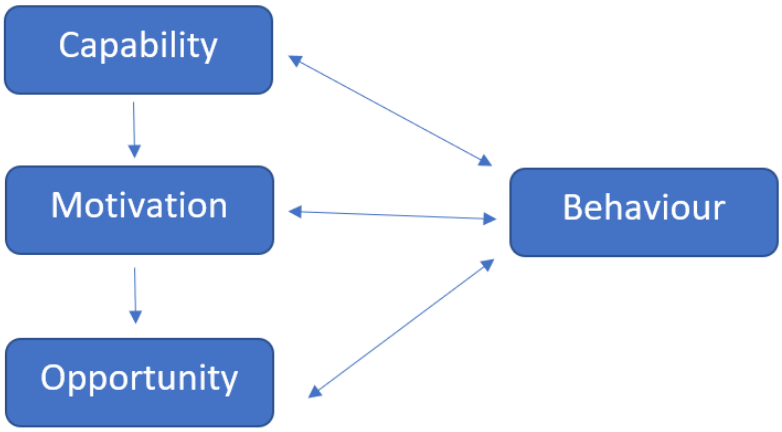


Figure 3.1: The COM-B system

The COM-B conditions are further defined, providing additional detail and six sub-components. Capability encompasses the *physical* and *psychological* capacity to engage in relevant thought processes and activities. Motivation includes both reflective (planning) and automatic (emotion) processes, with opportunity being divided into the physical and cultural impact of how individuals think. It is important to consider that for each individual, the interaction between components will differ. Additionally, the causal links across components will have an impact.

3.4.3 Behaviour change wheel (BCW)

The BCW framework (Figure 3.2) is based on existing frameworks and developed to overcome their acknowledged limitations as previously discussed (Michie et al 2011). The BCW has three distinct layers which include sources of behaviour (COM-B system); nine intervention functions (aimed to address deficits) and seven policy categories (intervention enablers). The model is not linear, but instead aims to illustrate all interactions across and between the separate component layers. The reliability of the BCW has since been tested with positive results gained (Michie et al., 2011).

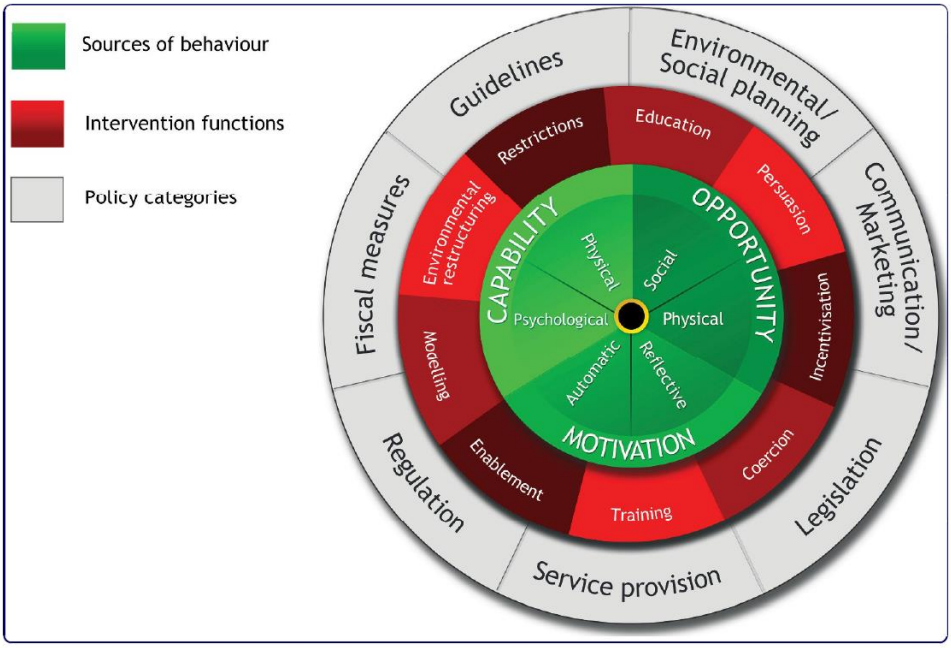


Figure 3.2: Behaviour Change Wheel (Michie et al., 2011)

3.4.4 Theoretical Domains Framework

This clinician interview study was based on the TDF which was initially developed in 2005 (Michie et al., 2005) and later updated in 2012 (Cane et al., 2012). It is a

comprehensive framework previously used for research in healthcare settings to systematically identify factors influencing clinical behaviours through the consideration of individual, social and environmental factors (Phillips et al., 2015; McGowan et al., 2020).

The refined TDF (Cane et al., 2012) comprised 14 domains: Knowledge, Skills, Social/Professional Role and Identity, Beliefs about Capabilities, Optimism, Beliefs about Consequences, Reinforcement, Intentions, Goals, Memory, Attention and Decision Processes, Environmental Context and Resources, Social Influences, Emotions, and Behaviour Regulation. Within the domains there were 84 component constructs (Table 3.1 for full version).

These 14 domains allowed for the assessment and explanation of barriers and enablers that could inform the design and implementation of interventions (Cane et al., 2012; Atkins et al., 2017). Such detail was important for subsequent implementation processes such as the use of MI-E in an ICU patient group. Since development there had been a steady increase in the number of studies using the TDF; the majority involving healthcare professionals rather than patients or service users (McGowan et al., 2020). An earlier mixed methods study used interviews and surveys to explore ten health professionals' experiences of using the TDF (Philips et al., 2015). They identified three main themes: 1) reasons for using the TDF, which described perceived increased confidence in generated results due to a broad perspective and use of theoretical underpinning; 2) challenges of using the TDF,

which included time and resources; and 3) future use of the TDF, which focused on user training and the potential generation of an instrument for evaluation.

Advice for use of the framework highlights the importance of TDF integration throughout planning, development, and analysis of qualitative research (Atkins et al., 2017). A recent systematic review of TDF based qualitative studies aimed to quantify and describe the use of TDF within qualitative research, and ways to optimize TDF use in such studies (McGowan et al., 2020). The authors highlighted potential problems associated with using a purely deductive approach and inflexible use of the TDF which included topic guide questions, structure, language used, and the approach of analysis and results presentation. For an emerging intervention it was important to gain breadth of information from participants, using the TDF flexibly. As an example, using topic guides flexibly, with the participant the flow of conversation, allows participants to talk about what was important to them. In contrast when the topic guide has a specific order of questions that is non-changeable, conversations could be disjointed and repetitive, with key information lost. This emphasized the need to integrate the TDF in a flexible manner in the interview study.

The refined framework domains have been validated against the COM-B (Cane et al., 2012). Three experts in behaviour change independently mapped TDF domains onto the COM-B segments. They had 100% agreement throughout, leading authors to confirm validity of the refined TDF (Cane et al., 2012).

As previously discussed, there are many psychological theories of behaviour change and therefore as a researcher it is challenging to select the most appropriate theory. With the interviews focusing on an emerging intervention (MI-E) and views being sought from individuals representing three professions, there was likely to be a wide variation of findings. The multiple theories in the TDF would allow consideration of a wider range of behavioural determinants in comparison to a single theory, which could subsequently facilitate implementation of MI-E in clinical practice.

Table 3.1 Theoretical Domains Framework

DOMAIN	CONSTRUCT
Knowledge: an awareness of the existence of something	knowledge (including knowledge of condition/scientific rationale); procedural knowledge; knowledge of task environment
Skills: an ability or proficiency acquired through practice	skills; skills development; competence; ability; interpersonal skills; practice; skill assessment
Social/professional role and identity: a coherent set of behaviours and displayed personal qualities of an individual in a social or work setting	professional identity; professional role; social identity; identity; professional boundaries; professional confidence; group identity; leadership; organisational commitment
Beliefs about capabilities: acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use	self-confidence; perceived competence; self-efficacy; perceived behavioural control; beliefs; self-esteem; empowerment; professional confidence
Optimism: the confidence that things will happen for the best or desired goals will be attained	optimism; pessimism; unrealistic optimism; identity

Beliefs about consequences: acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation	beliefs; outcome expectancies; characteristics of outcome expectancies; anticipated regret; consequents
Reinforcement: increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	rewards; outcome expectancies; punishment; consequents; reinforcement; contingencies; sanctions
DOMAIN	**CONSTRUCT**
Intention: a conscious decision to perform a behaviour or a resolve to act in a certain way	stability of intentions; stages of change model; transtheoretical model and stages of change
Environmental context and resources: any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour	environmental stressors; resources/material resources; organisational culture/climate; salient events/critical incidents; person x environment interaction; barriers and facilitators
Social influences: those interpersonal processes that can cause individuals to change their thoughts, feelings or behaviours	social pressure; social norms; group conformity; social comparisons; group norms; social support; power; intergroup conflict; alienation; group identity; modelling
Emotion: a complex reaction pattern, involving experimental, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event	fear; anxiety; affect; stress; depression; positive/negative affect; burn-out
Behavioural Regulation: anything aimed at managing or changing objectively observed or measured actions	self-monitoring; breaking habit; action planning

3.5 Methods

3.5.1 Study design

Semi-structured interviews were conducted with staff to explore the barriers and enablers for MI-E use in intubated critically ill patients as perceived by three clinician groups (physiotherapists, medical doctors, nurses) working in an ICU setting.

Focus groups had initially been proposed to enable data collection from multiple participants simultaneously, whilst allowing interaction between participants. However, in discussions with the SAG during study planning, it was clear that some clinicians were uncomfortable with this format as they did not feel they (or colleagues) would talk openly in front of all colleagues. As a result, semi-structured interviews were used to collect data. This enabled consistent questioning across participants, whilst allowing scope for divergent views to be reported.

Due to the data collection coinciding with the COVID-19 pandemic all interviews were conducted remotely, using an online meeting platform, rather than face to face. Prior to the COVID-19 pandemic face to face interviews were deemed the gold standard approach (Novick, 2008) with virtual interviews often viewed as an inferior substitute. Concerns have been previously raised about online and telephone interviews due to a potential lack of visual cues and loss of non-verbal data, compromising rapport between the participant and researcher and ultimately impacting the quality of data collected (Novivk, 2008; Lo Lacono et al., 2016). However, virtual interviews are now used frequently with a range of potential

benefits reported (Lo Lacono et al., 2016; Keen et al., 2022). These include convenience for participants as they can choose their location and are therefore not limited by geography (Lo Lacono et al., 2016; Keen et al., 2022); potential for larger sample sizes due to the elimination of travel time and the inclusion of participants who are less confident to participate face to face. It was important to gather information that followed up on results from the UK survey, therefore factors such as geographical spread, hospital type, profession and clinical experience were all necessary considerations. Virtual interviews provided the flexibility to maximise the variation in the sample of participants in a timely manner.

The topic guides were based on the TDF and developed with input from the supervisory team and the study participant group. There was consideration of language used to ensure there was no profession specific jargon which the PAG supported with and inclusion of open-ended questions to encourage in depth and detailed responses. The final topic guide was subsequently piloted with two physiotherapy clinicians with and without MI-E expertise (appendix 5). Following this pilot phase, a final question was added to provide opportunity to participants to add any further information that they felt was pertinent to the discussion. There was no set order of questions within the topic guide, instead the flow of conversation guided the order of questions asked.

3.5.2 Recruitment

The sample comprised UK ICU staff across three clinician groups: physiotherapists, medical doctors and nurses. The intention was to complete approximately 10-15

interviews per clinician group. As previously discussed, themes such as 'culture' had been highlighted through the UK survey so it was important that participants were from a mix of professions and had a range of clinical experiences. It was important that sufficient data were collected across each clinician group to ensure a representative sample was achieved. However, the target sample size was also a pragmatic decision based on time and resources, balanced with information power.

Clinicians working as a permanent staff member in a UK ICU setting with awareness and/or experience of MI-E use in the intubated population were eligible. Clinicians who had not worked within the ICU environment within the previous 6 months were excluded.

Study advertising occurred through e-mail distribution and social media directed towards ICU specific special interest groups including The British Association of Critical Care Nurses, The Association of Chartered Physiotherapists in Respiratory Care and The Intensive Care Society, alongside regional critical care networks (Appendix 6).

The doctoral fellow was responsible for advertising the study and following up interested potential participants. The doctoral fellow's email address was provided with all advertising materials. Clinicians were asked to make contact if they were interested in participating in the study. Once a clinician was deemed eligible all study information (Appendix 7) was sent to them. Potential participants were given the opportunity for further clarification via email and/or phone. If, at two weeks

following study information being sent to potential participants there had been no response, a reminder email was sent. If a further two weeks passed they were considered as not willing to be recruited into the study and no further contact was made. Within the 4-week period of initial contact, if an individual confirmed study inclusion the doctoral fellow arranged a mutually convenient date and time for an interview.

3.5.3 Interview process and data collection

Participants were requested to provide verbal informed consent at the start of each interview (Appendix 9). Clinician demographic data were recorded which included clinical profession, years qualified, years working in a static ICU post and highest educational level obtained.

Interviews were completed by the doctoral fellow via a virtual platform (Microsoft Teams) and recorded. A University approved supplier transcribed interviews verbatim and a data processing agreement was in place. No corrections or amendments were made to the transcripts to capture the way in which participants expressed themselves. Transcripts were checked for accuracy and pseudonymised.

3.5.4 Data analysis

Demographic data collected at the start of each interview were summarised using descriptive statistics. Data from clinician interview transcripts were analysed using content analysis (Braun and Clarke, 2013) where all utterances were assigned deductively to TDF domains through first level coding. Links and relationships across

domains were considered. This deductive approach to analysis with the TDF has been found to be most commonly used (McGowan et al., 2020).

NVivo software (NVivo 12 QSR International, Melbourne, Australia, 2018) was used to support the analysis process. A sample of coding was checked by a doctoral supervisor (SV) with queries and discrepancies resolved with other members of the supervisory team. Responses that were thematically similar were grouped in a process of data reduction to compare and contrast across transcripts. Tables were produced to highlight key thematic content, barriers and enablers within each TDF domain. Following review of participant quotes, study specific definitions for each TDF domain were developed. Domains were identified as salient based on their frequency of inclusion and potential strength of impact.

3.5.5 Ethical and Regulatory Considerations

A risk assessment was completed as part of the UWE ethical approval process. There were no anticipated risks to participating in the interviews. However, in the unlikely event that any interview participant experienced any distress through issues raised, the information sheet provided details of how to access appropriate support. Participants were able to withdraw from the study up to the point of data pseudonymisation (once audio file sent for transcription).

Health Research Authority (HRA) approval was not required for this study as staff were not recruited via the National Health Service (NHS). Approval of the research protocol and associated documentation was gained from the UWE Research Ethics

Committee (REC) (UWE REC REF No: HAS.21.03.121). No research activities were initiated until all research approvals were obtained and there were no protocol amendments during the study.

3.5.6 Patient Advisory Group (PAG)

The Patient Advisory Group (PAG) was made up of previous ICU patients and their relatives. PPI occurred in the planning of the overall doctoral fellowship and during the development of the protocol for the semi-structured interviews with healthcare professionals. PAG members supported the use of semi-structured interviews and shared experiences of completing meetings and interviews online. Many PAG participants highlighted challenges of an online format which mostly related to the lack of non-verbal communication such as body language. Therefore, time was allocated at the start of the interview for open, more social conversation which aimed to put participants at ease. For the interview guide, PAG members were particularly interested in the impact of culture and educational needs of clinicians on the subsequent use of MI-E. As such these topics were covered within the interview guide. During data analysis it was particularly helpful to understand how PAG members prioritised results.

3.5.7 Data protection and patient confidentiality

The doctoral fellow complied with the requirements of the Data Protection Act 2018 and GDPR with regards to the collection, storage, processing and disclosure of personal information and upheld the Act's core principles. A study specific UWE Data Management Plan was completed. The research data management provides detail of

the processes for looking after and protecting all the research data, research participants, and the researcher. This covers the entire duration of the study from before research data is collected and continues beyond the end of the study to include data preservation, sharing, and data disposal.

Video files were deleted immediately after interview completion, with audio files being saved onto the UWE OneDrive using a participant number to pseudonymise the dataset. These were stored separately to the identifiable data. Following transcription audio files were also deleted.

3.6 Results

3.6.1 Participant demographics

There were 29 interviews completed across the three professions: 18 physiotherapists; six medical doctors and five nurses, offering sound geographical spread of the UK with representation from England, Scotland and Wales. Clinicians had been qualified for a median [interquartile range (IQR)] of 12 (2-32) years with 7 [1-21] years in a static ICU position. Thirteen clinicians held post-graduate qualifications at Masters level or equivalent. The median[range] interview duration was 31[16-52] minutes. Participant demographics are detailed in Table 3.2.

3.6.2 Codes

In total, 1137 codes were generated from the interview transcripts which covered all TDF domains (Table 3.3).

Table 3.2: Participant demographics

Participant ID	Profession	Years qualified	Banding*/ Grade	Years static in ICU	Qualifications
1	physiotherapist	11	6	7	BSc
2	physiotherapist	10	7	4	BSc
3	physiotherapist	16	8a	12	MSc
4	physiotherapist	6	6	1	BSc
5	physiotherapist	6	7	1	BSc, MSc modules
6	physiotherapist	9	6	1	BSc
7	doctor	10	ST5	2.5	BSc
8	physiotherapist	12	6	4	BSc
9	physiotherapist	20	7	12	BSc
10	physiotherapist	6	7	4.5	BSc
11	physiotherapist	20	7	14	BSc, post-graduate diploma
12	physiotherapist	2	6	1	BSc
13	physiotherapist	23	7	19	BSc, MSc modules
14	physiotherapist	14	7	5	MSc
15	nurse	6	5	1	BSc, MSc modules
16	physiotherapist	9	7	5	BSc, MSc modules
17	physiotherapist	4	6	1	BSc
18	physiotherapist	13	7	10	BSc
19	doctor	20	consultant	17	MBChB
20	physiotherapist	11	7	5	BSc
21	physiotherapist	12	7	10	BSc
22	nurse	7.5	6	5.5	BSc
23	doctor	14	CTF	6	BSc
24	nurse	18	7	17	MSc
25	doctor	28	consultant	15	MB BS
26	nurse	7	5	1	BSc, post-graduate diploma
27	doctor	32	consultant	21	MB BS
28	doctor	9	CTF	5	MBB S, BSc
29	nurse	4	5	4	BSc

Abbreviations: BSc, Bachelor of Science; CTF, core trainee fellow; MBBS/MBChB, Bachelor degree of Medicine/Surgery; MSc, Master of Science

*AfC, agenda for change banding

Table 3.3: Frequency of interview quotes assigned to TDF domains

TDF Domains	Frequency
Knowledge	344
Skills	186
Social/professional role and identity	148
Beliefs about capabilities	30
Optimism	4
Beliefs about consequences	64
Reinforcement	3
Intentions	68
Goals	1
Memory, attention and decision processes	25
Environmental context and resources	181
Social influences	45
Emotion	18
Behavioural regulation	20

Abbreviations: TDF, theoretical domains framework

The findings are presented below according to the 14 TDF domains and with a relevant study specific definition. These definitions are also provided in a single document in Appendix 9. Some domains were further divided into sub-themes to link with the study specific domain definition. The order of TDF domain presentation is based on frequency of representation and potential strength of impact, interaction and influence with other domains. The results are presented in three main parts. Part one presents the most richly represented TDF domains and those domains with the highest interaction with other TDF domains. Part two follows with description of TDF domains that covered internal and external influencers of MI-E use. The results conclude with part three covering the remaining TDF domains not previously discussed.

3.6.3 Part 1: Knowledge and Skills

This section initially presents the domains of *knowledge* and *skills* as these were the most frequently populated TDF domains (344 and 186 quotes respectively), with interaction and association with most other TDF domains. Extensive interaction occurred with TDF domains *environmental context and resources* and *social and professional role and identity* which were also highly populated (Figure 3.3).

3.6.3.a. TDF Domain: Knowledge

Study specific definition: *"Description of current knowledge; perceived knowledge and expectations of others; methods of acquiring knowledge; and experience and the influence of knowledge on the use of MI-E".*

Descriptions of current knowledge

Descriptions of current knowledge focused on the indications and contraindications to initiate MI-E with the intubated population. There was also recall of specific patient groups that was used with on ICU. Common indications for MI-E included sputum retention (often linked to the prevention of re-intubation), poor oxygenation, reduced cough strength (particularly when linked to a NMD or spinal cord injury) and prolonged use of sedation and/or paralysis. Frequently mentioned contraindications included high PEEP requirements (with a focus of 10-12cmH_2O as an upper limit), cardiovascular instability with or without the use of inotropes, bullae presence, undrained pneumothorax, unexplained haemoptysis, unstable intracranial pressure and flail rib segments.

Perceived knowledge and expectations of others

In addition to their own knowledge participants discussed their perceptions of others' knowledge, in terms of current knowledge base and expected knowledge base. Common topics included knowledge for the practical, hands-on use of the device, awareness of when to initiate and cease MI-E, a working understanding of the ventilator (for disconnection and reconnection) and how to manage an acutely deteriorating patient.

Differences in perceived knowledge base across professions were often associated with variation in device exposure during education and in the clinical setting, and to profession specific roles in ICU. Roles are further explored within the *Social/professional role and identity* domain. The doctors particularly focused on patient safety, referring to common ICU practices such as protective lung ventilation rather than knowledge related to the MI-E device itself.

"I think they are just quite unfamiliar with it, certainly our consultant group, because it isn't something that's … that's been routinely used on our unit" (Participant 20, Physiotherapist).

There was a difference in the expected knowledge across professions. Both nurses and doctors expected physiotherapists to have rounded knowledge (patient, ventilator and device). In contrast, when the physiotherapists were describing the level of knowledge required by nursing staff there was a limit which very much focused on the practical application of the device.

Methods of acquiring knowledge

Two main types of learning were described: evidence-based practice and experiential learning. When discussing the evidence base for MI-E use in the intubated, critically ill population, clinicians either highlighted a weak evidence base or were unable to recall specific studies or literature relevant to the topic.

"I'm blissfully ignorant. I think most people are probably fairly ignorant of it" (Participant 7, Doctor).

"I think we've all tried to have a look for it, I know it's quite a weak…evidence base in that there's not been a lot of research done on it" (Participant 12, Physiotherapist).

Some clinicians presumed that the evidence base existed because they were using MI-E.

"…I haven't read that much about it, I'm assuming there's some good evidence out there…I hope that's the case….it seems silly to be using something that's not evidence based that we're just going, okay, that's fine, it might work" (Participant 15, Nurse).

Most participants, across all professions stated a desire to increase their awareness and knowledge of the relevant evidence base but simultaneously referred to limiting factors such as time. Experiential learning referred to hands-on practical use of the device with patients; this is considered further in the TDF domain, Skills.

Influence of knowledge on the use of MI-E

When providing description of existing knowledge and associated indications and contraindications for MI-E in the ICU population there were some grey areas which were stated as precautions rather than specific contraindications. This meant clinicians would approach the use of MI-E with more caution. Clinical presentations considered to be precautions included rib fractures, asthma exacerbations, the risk of vomiting and diagnosis of severe Acute Respiratory Distress Syndrome when considering the timing of MI-E initiation rather than absolute use of MI-E.

Several participants discussed the balance of clinical risk and clinical benefit linked to knowledge and consideration of contraindications and precautions. Frequently, communications with medical colleagues were referred to; this is considered further within the *Social/professional role and identity* domain.

"…but I don't think there's a specific group of patients that I'm thinking, oh, I would definitely not use it with. I think it's just kind of weighing everything up and like anything just thinking about the risk versus benefit" (Participant 12, Physiotherapist).

Some clinicians described the influence of experience (years of experience and seniority) on their own knowledge base or the knowledge base of others. This experience subsequently facilitating and/or determining the outcome of risk benefit discussions.

"we've had quite a lot of times where we're being pushed a little bit on our boundaries of what we, we determine is contraindications and I think that is more, would, chances

would be taken a bit more with the senior group than the junior group of staff" (Participant 10, Physiotherapist).

The importance of not using MI-E straight away, but ensuring treatment selection was reasoned and based on assessment findings came across as an important point.

"I was always trying to ensure that as physiotherapists we were not going to just be using this device to kind of hoover people out and not be thinking about, erm, other techniques that would potentially be beneficial and potentially less invasive" (Participant 13, Physiotherapist).

In contrast some participants described a treatment hierarchy which often placed MI-E at the end of the list once other treatment options had been exhausted and the use of MI-E became more reactive in response to a deteriorating patient or other treatment options that were not having sufficient response.

"And so you think right, I've literally tried everything, I'm just going to cough assist them" (Participant 3, Physiotherapist).

Clinicians highlighted how experiential learning influenced their practice and confidence when using the device to deliver MI-E.

"I don't remember the exacts of how it started but there was just one day where we had somebody who was really poorly and gave it a go, got incredible results very

quickly and kind of from them we've really just started picking a bit more into kind of what settings we use, which patients are appropriate" (Participant 1, Physiotherapist).

Participants described how knowledge and experience from other patient groups such as NMD was used to influence and guide their practice in an ICU setting. Linked to indications and contraindications was discussion related to potential side effects of using MI-E in the ICU patient group. This knowledge was gained primarily from experience but also from other methods such as teaching sessions. Gaps in knowledge were also specified which related to optimal patient choice, timing of intervention and MI-E treatment prescription.

"I think definitely kind of the adjustment of regimes, and pressures and kind of when to start it, like is it better if you start it early to prevent these problems occurring or can you not justify the risk, I think things like that would be interesting to, to know" (Participant 1, Physiotherapist).

3.6.3 b. TDF domain: Skills

Study specific definition: *"Practical skills to enable the application of MI-E; training methods for skill development; and the assessment of skills through competencies".*

Practical skills

Discussions about the practical application of MI-E were intertwined with key topics of the *knowledge* domain including a working knowledge of physiology and

associated clinical reasoning. Interestingly general device use was not deemed as a challenging skill by interviewees but the importance of frequent hands on practice to maintain confidence was emphasised across professions.

"I do think the hands on, hands on experience is definitely, in this, in this environment, is, is a big factor" (Participant 17, Physiotherapist).

Additional skills such as appropriate patient selection and patient-clinician communication were deemed important and influential in the success of MI-E application.

"how that's communicated and how it's kind of taught initially, can really make or break that experience for them, because it is such an odd feeling and it's a very different feeling to the pressures that they get from the vent" (Participant 20, Physiotherapist).

The perceived skillset requirements described, varied across professions. It was suggested that a comprehensive clinical skillset was required for appropriate device set up and initiation, subsequent treatment prescription adaptations and MI-E cessation. This level of skills was mostly associated with physiotherapists.

"I think, clearly competence with the device itself, and the skills to be able to manipulate that and to assess patient response to treatment….so being able to identify actually when that patient needs to go back onto a vent, or to stop treatment altogether" (Participant 20, Physiotherapist).

Differences in skill set requirements were rarely highlighted between MI-E use via an ETT or tracheostomy tube although some physiotherapists identified MI-E via an ETT as an advanced competency. Clinicians focused on whether the patient was initiating their own breaths, as this would determine device set up. For physiotherapy participants, differences in skills were also highlighted and linked to past experiences of MI-E and clinical banding.

The majority of nursing participants had no previous experience of delivering MI-E independently. Physiotherapists reported a desire for nurses to develop skills to use the device according to protocol and once a treatment plan was already in place. A reported barrier to MI-E delivery in the nursing group was a lack of clinical skills (and knowledge) to be able to manipulate treatment settings and clinical time, with concerns that an additional task would deviate from other core patient care needs. However, when nurses were able to use MI-E this was seen as an advantage by the physiotherapy group. In particular, the ability for nurses to use MI-E out of standard working hours could reduce call outs. There was acknowledgement that the important skill for nurses in this instance would be the ability to recognize when a physiotherapist was required, for example when adaption to a treatment prescription was required.

"..assessment, to know that we are safe and that we were aware of, like, the risks benefits, what can go wrong, um, and the types of patients that are best to use it on, when we would use it, so when we would, when it's safe for us as a nurse to use it,

whereas, potentially, when you might need to escalate it to, um, to a physio.." (Participant 15, Nurse).

None of the participants included in the study alluded towards a requirement for doctors to have practical MI-E skills to use the device but instead awareness of the technique was seen as important (see *knowledge* domain (section 3.6.3.a.)).

Skill development and assessment of competence

Different methods of maintaining and assessing competence were highlighted including competency documents, peer supervision sessions, e-learning, simulation and teaching sessions. For the physiotherapy group all methods were identified as established within practice. For nurses, training and competency checks (when in place) occurred via 'on the job' training in real time with patients. Often competency documents were for general MI-E use rather than being specific to either use with/without an artificial airway or specific to a disease process. It was rare for a competency process to be in situ for nurses but when documents were present they were different to those used by physiotherapists.

"I think the nurse one will be slightly less involved in that they won't be altering settings so they'll sort of be using the settings that physios have set up" (Participant 15, Nurse).

The maintenance of competencies was highlighted as a challenge and was linked to infrequent MI-E use, for example with rotational staff members or due to a fluctuating caseload.

3.6.3.c. TDF domain: Environmental context and resources

Study specific definition: *"The impact of team culture; infrastructure; and physical resources (on the use of MI-E)"*

Culture

The culture within physiotherapy and the wider multi-disciplinary team was highlighted as influential to MI-E use in the ICU setting. Within physiotherapy, a hierarchy was apparent with more senior staff members influencing and dictating the introduction and initiation of MI-E in ICU. There were multiple positive examples where seniors had encouraged others to develop new skills. In contrast some participants highlighted the negative impact of senior staff. Firstly, by preventing the introduction of MI-E within ICU physiotherapy practice and secondly preventing clinicians with knowledge and experience from using MI-E and potentially developing ICU practice. At times this was perceived to be due to gaps in the knowledge base of the more senior staff.

"…it wasn't that they'd heard about it and thought, well no, we can't do that, it was that they didn't know people were doing it… from a Band 7 that had been in the role previously and had been in place for kind of 15 years" (Participant 1, Physiotherapist).

Having senior staff with the relevant experience to influence in a positive manner was viewed as important by participants.

"my sense has been that the physios themselves have been nervous about it, because you need leaders who...who truly…who have experience" (Participant 27, Doctor).

Participants also highlighted the impact of the wider MDT. In many cases relationships across the MDT were positive towards physiotherapy and MI-E use.
"we don't come across any issues with kind of convincing people that it's the right thing to do or kind of any barriers from the medical team" (Participant 1, Physiotherapist).

Some interviewees also described how the MDT could have a negative impact on the autonomy of the physiotherapy role and the resultant use of MI-E. These quotes illustrated the importance of time required to build positive relationships and cohesive attitudes for the use of MI-E in ICU.
"so it's sort of been a bit of a process of sort of, sort of gaining trust of the consultants and the nurses um on what we're doing" (Participant 18, Physiotherapist).

"when you come to a new unit, you're new, and I don't know if it's the culture of the unit and I think our physio team have had to, over the years, build up I think more trust with some of the consultants to get us to do a bit more" (Participant 6, Physiotherapist).

Infrastructure

Staffing resources were highlighted primarily by the physiotherapy participants, illustrating a moral conflict when considering the whole clinical caseload. Problems occurred when a patient required MI-E on a frequent basis (multiple times a day), utilising staffing resources and potentially limiting the ability to fulfil treatment

requirements for others, such as those requiring rehabilitation. Interviewees highlighted how positive patient experiences and outcomes have the potential to create unrealistic expectations on physiotherapy regarding patient management. *"we've made a rod for our own back, with our success in a way, that's put other patients at risk, um, because it's seen that we can provide that treatment, we can provide that care, but you can't be in two places at once"* (Participant 11, Physiotherapist).

Additionally, patient complexity was discussed and interviewees highlighted how at times patient MI-E treatment sessions would require more than one therapist to enable the utilisation of additional treatment strategies, thus stretching staffing capacity further. The staffing infrastructure was further emphasised as a barrier to MI-E when considering training needs of staff. Concern was highlighted by nurse participants regarding the number of nurses who would require training for initial competence and how competence would subsequently be maintained. The maintenance of competence was relevant to both the nursing and physiotherapy participants due to the number of rotational staff in many teams.

Physical resources

The role of equipment referred to the MI-E device but also included MI-E consumable funding and associated storage facilities. There was variation in MI-E device provision with no consistency in how devices and associated consumables were funded across Trusts.

3.6.3.d. TDF domain: Social and professional role and identity

Study specific definition: *"The MI-E decision-making process and ICU task orientated roles"*

Decision making

The decision-making process for MI-E initiation was predominantly led by physiotherapists. Some participants spoke about the influence of physiotherapy hierarchy, where senior clinicians viewed MI-E as an advanced skill and therefore part of a senior role. Other physiotherapy participants suggested that this limited the ability of less experienced clinicians being involved in decisions relating to MI-E and associated development opportunities in clinical practice.

"It tends to be more experienced staff. I wouldn't expect, like, a new Band 5 to feel confident in making those decisions" (Participant 16, Physiotherapist).

Doctors were involved in the decision-making process for the more complex patients where physiotherapists would initiate discussions around the balance of risks and benefits of MI-E. Comments from physiotherapists highlighted the importance of such a conversation in the decision-making process. In contrast doctors were open to discussion but acknowledged their lack of knowledge and experience with MI-E, viewing physiotherapists as the experts.

Task orientated roles

Roles regarding the use of MI-E were consistent, with physiotherapists being referred to as the main user of the technique across professions. Some

physiotherapy participants felt strongly that the use of MI-E should be a protected role. Frequently, justification of this role linked back to knowledge and skills that the physiotherapy profession holds.

"I quite strongly feel that is, that is our role and we've achieved that and we should always be kind of supported and encouraged that it is a physiotherapy role" (Participant 1, Physiotherapist).

Some participants (across professions) felt that MI-E use should primarily be a physiotherapy role, with some seeing potential benefits to other professions applying the technique. Further to this, some participants were open to other professions using MI-E where suitable training and competencies were in place. The nursing role created more debate. Generally, MI-E use was not commonplace amongst nurse participants with some conflicting views. There were some instances where nurses reported using MI-E in ICU but this role was less established, with users often reporting previous MI-E experience in other patient groups. There were also defined boundaries to MI-E use by nurses which involved the continuation of MI-E that had already been prescribed and established with patients by a physiotherapist. Nurses did not have a role in MI-E initiation or prescription adaptation.

"…with the nurses we don't, we don't let them like change the settings at all. Um and like they would never start a patient on MI-E" (Participant 18, Physiotherapist).

There were no reports of doctors being involved in the clinical application of MI-E.

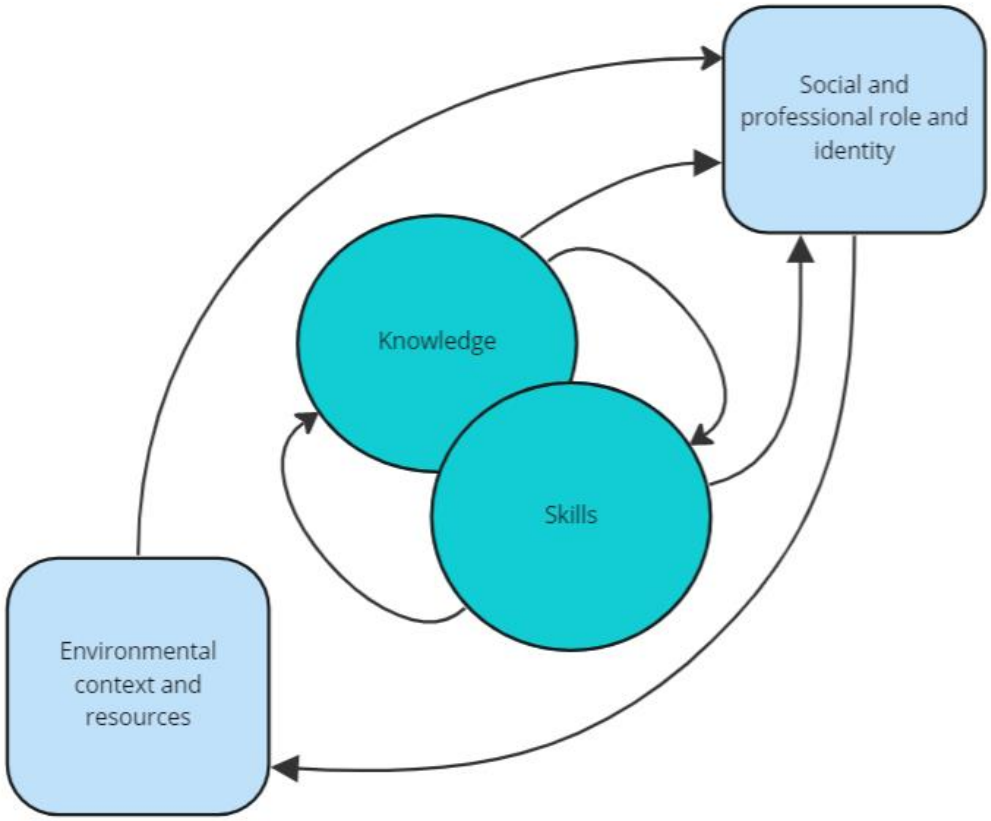


Figure 3.3: Illustration of most populated TDF domains and interactions across domains (Part 1). Arrows represent interaction across domains; although interaction and influence across domains was bi-directional, arrows illustrate the dominant direction of interaction and influence.

3.6.4 Part 2: Internal and external influencers

This section includes six TDF domains split into internal and external influencers.

Internal influencers include the domains *beliefs about consequences*; *intentions;* and *beliefs about capabilities*. External influencers include domains *behavioural regulation; memory, attention and decision processes;* and *social influences* as illustrated in Figure 3.4.

3.6.4.a. TDF domain: Beliefs about consequences

Study specific definition: "Outcomes and experiences following MI-E use/non-use and the impact of such experiences"

Outcomes and experiences

Clinicians, particularly physiotherapists, drew upon past experiences of using MI-E, referring to both positive and negative consequences. Positive consequences related to potential treatment outcomes including secretion clearance, improved cough strength, a reduction in oxygen requirements and bronchoscopy use, and the prevention of re-intubation. In some cases, the use of MI-E was compared to other interventions, where it was viewed as a more favourable treatment choice in terms of negating adverse effects for the patient or negating the need for medical intervention.

"I don't think I've actually seen any adverse effects…the patient was much more settled afterwards. And I mean, we were considering just giving him a little bit of sedation to kind of help with his chest, so actually we avoided that…..I think sometimes obviously people are very quick to do a lot of suctioning….you end up trauma, you know, maybe a bit of blood stains secretions, so maybe it would help a bit more if we can give them the deep breath to make them cough better" (Participant 22, Nurse).

When discussing the perceived benefits of MI-E over other treatment strategies, participants often referred to the inclusion of negative pressure (exsufflation).

"…it's more the exsufflation that we then would think, oh, we would rather use the cough assist than the manual hyperinflation because it'll give us that negative

pressure that we're not getting by using the bag or using IPPB [intermittent positive pressure ventilation]" (Participant 12, Physiotherapist).

Frequent concerns about the use of MI-E in the ICU setting included the impact of larger inspiratory volumes in relation to protective lung ventilation and cardiovascular instability as a negative outcome to MI-E use.

Impact of experiences

Negative experiences appeared to impact subsequent use of MI-E. Clinicians raised concern about negating previous positive experiences of others and subsequent change regarding MI-E utilisation.

"at that point I was like, oh God, like we're going to take a two-year step back here now…" (Participant 1, Physiotherapist).

Concerns about using MI-E related to potential adverse events and included episodes of desaturation, lung de-recruitment, pneumothoraces and cardiovascular instability. Despite clinicians listing and highlighting negatives consequences, they did not always have first-hand experiences of them when using MI-E.

Differences between MI-E use via an ETT and tracheostomy tube were identified such as the additional challenge of tracheostomy patients being awake. These differences did not prevent MI-E being used in either patient group. Instead clinicians more frequently raised additional considerations for optimizing treatment outcomes when using MI-E in a tracheostomised patient group. Clinicians stressed

the importance of communication with the patient in these situations to optimise use of MI-E.

"I think it's probably harder if they are more awake, but I haven't seen many problems with sort of fighting it, or desynchrony" (Participant 10, Physiotherapist).

The use of MI-E by a nurse, was generally viewed positively as it had the potential to prevent the need to call out a physiotherapist outside core hours.

At times clinicians demonstrated anxiety and a lack of confidence, linked to past experience, when deciding whether to use MI-E. Concerns were raised regarding a lack of control over potential adverse clinical consequences as a result of using MI-E. This is further explored in the *Emotion* TDF domain.

"I really wanted to cough assist him but I didn't feel, just didn't, I just thought I could quite easily make this situation worse….but obviously I could have made it better" (Participant 1, Physiotherapist).

3.6.4.b. TDF domain: Intentions

Study specific definition: "*Stages of change linked to device use in an ICU setting"*

This domain encompassed the stages of change linked to MI-E implementation that were experienced on an individual clinician level, by profession specific clinical teams and the wider MDT. Across the interviews, variability in MI-E implementation was illustrated. Some clinicians were aware of MI-E and keen to know more but did not

have hands on experience. In contrast there were some clinicians who had a wealth of skills and experience with the technique.

"I want to know more, in fact I want to know, like, how it works and things" (Participant 15, Nurse).

"Through additional experience gained er, you know, the more you use it, the more you realise the benefits" (Participant 27, Doctor).

"I think it's something that I've become more aware of in the last er, probably two or three years, um, before that it wasn't something that I would normally have … have gone to as a treatment option" (Participant 20, Physiotherapist).

MI-E implementation also linked to an individual's definition of standard care and what was 'normal' for them, often linked to confidence. Common treatment interventions listed as part of standard care included manual hyperinflation, manual techniques, suctioning and positioning.

"we'll go for what we know and what we are comfortable with and that is likely to be bagging, shakes, repositioning" (Participant 14, Physiotherapist).

It was acknowledged that change to 'standard care' required time but in general there was a positive feeling towards MI-E use with some participants wanting to use it more and learn more about the technique.

"So it takes like time for, you know, the whole on-call team to um feel happy doing it, you know, to feel um like whenever you start something new it's sort of a journey of

um, but they yeah, seem a lot, a lot um happier, and a lot clearer on what they're doing now" (Participant 18, Physiotherapist).

3.6.4.c. TDF domain: Beliefs about capabilities

Study specific definition*: "Capabilities of self, other professions and the MI-E device"*

There were links to the domains of knowledge and skills regarding capabilities of self and that of the other professions. When discussing the practical application of MI-E self-confidence varied amongst participants.

"I'm quite conservative and I worry about doing things wrong, and I constantly go home and think well, have I gone too high pressure, or have I done the right treatment for that person? That's my nature" (Participant 4, Physiotherapist).

Physiotherapists were perceived as the experts (most capable) in MI-E application by all professions. A range of views were provided regarding the ability of nurses to use the device effectively. Consensus was present around general device use by a nurse when already set up with a treatment prescription in place. In contrast, the initiation and prescription of a treatment regime was not considered an appropriate task for nurses to be completing, which was linked to perceived competence.

"And I think that again, sort of highlights the difference between us and the nursing staff, you know, they will quite happily follow a prescription, but it has to be exact. Whereas the physios will just trouble shoot what you've asked them to do" (Participant 11, Physiotherapist).

"Um, so it's because any high-risk machine has got to be adapted or got to be you know, got to be treated by somebody who really knows what they're doing. I wouldn't be expecting Band five bedside nurses to be taught how to do cough assist, to be changing pressures" (Participant 24, Nurse)

Perceived benefits of using MI-E related to positive treatment outcomes which were based on both previous clinical experience and/or knowledge gained through training. This has been discussed in detail within the TDF domain *beliefs about consequences*.

3.6.4.d. TDF domain: Behavioural regulation

Study specific definition: "*Describes a change of clinical approach (behaviour) and the introduction of something new (that is, MI-E)"*

This domain had consistent links with the *Intentions* domain. Participants described external influences which included other team members either as MI-E adopters or non-adopters; patient clinical status and a lack of formal guidance documentation. Where other clinicians felt confident with the MI-E this was viewed as helpful and provided support for the less experienced clinicians.

"I can imagine if you're in a back end of nowhere kind of trust, where you don't get to keep up to date with current practice, and you don't get to go to conferences, and you don't have a clinical specialist there challenging you, I can't imagine they will adopt it,

because it's just how will they access that information, um and how will they see that that's something to do?" (Participant 3, Physiotherapist).

Where the clinical status of a patient was deemed as higher risk, participants frequently reported that this would deter them from MI-E use and more towards what they referred to as standard care. This pattern of behaviour was seen to reinforce the use of 'standard care'.

"…it's almost a bit of a chicken and egg situation in that the caseload puts me off doing it, and therefore I don't do it as often, so those patients that maybe are on the borderline, you might lean towards something else first, just because that confidence and that regular use isn't there" (Participant 20, Physiotherapist).

In contrast some participants referred to high-risk clinical examples and highlighted how such exposure with positive outcomes had positive influence on subsequent MI-E use in this specific patient group.

3.6.4.e. TDF Domain: Memory, attention and decision processes

Study specific definition: "*The decision-making process and associated communication pathways for MI-E use in the intubated population"*

Physiotherapists were viewed as the predominant decision-maker regarding the use of MI-E in the intubated population. However, some participants described situations where patients were deemed more complex, including clinical situations of increased PEEP, cardiovascular instability, head injury patients with intracranial pressure monitoring in situ and undiagnosed pneumothoraces. With more complex

patients and potentially higher clinical risk, this would often trigger a discussion with the medical team to consider risk-benefit.

"…so I do like to have, not permission from them, but they're, kind of, just reason it through with them and check they're on side" (Participant 21, Physiotherapist).

This conversation was frequently emphasised by the physiotherapists. The doctors also shared that the conversation was often two-way where they would highlight patients that they had concerns with, particularly involving reduced cough efficiency and increased retained secretions.

3.6.4.f. TDF domain: Social influences

Study specific definition: "*The impact of culture, hierarchy and collaborations"*

Influences within this domain had positive and negative impact on MI-E use. Culture was a strong theme illustrated in this domain, both within professions and across the wider MDT. For physiotherapy participants the hierarchy of the team influenced whether MI-E was used. In multiple examples, when the more senior clinician did not use MI-E, this resulted in it not being used by the rest of the team. At times this would prevent more junior clinicians from using MI-E despite having the necessary knowledge and skills.

"And I think there's still quite a lot of hierarchy within the team that I work with, like despite the fact that I have the experience I have now, and I've kind of proved almost proved myself from a clinical point of view over the last few years. I think there is still

that, well I can't ask somebody who is more junior than me for help" (Participant 1, Physiotherapist).

A similar pattern of experiences was reported about the other professions, where hierarchy influenced and prevented a change in practice.

"some of the junior nurses were … were really on board with this, and were yeah, this is so easy, I can deliver this. I think it was more the senior established nurses, well this is new, this is different clinical practice, we don't normally do this, why … why are we doing it now?" (Participant 11, Physiotherapist).

At times, participants alluded to a reluctance or lack of awareness of changes to practice on a wider scale. This was linked to hierarchy and culture, as more senior clinicians would not be seeking new knowledge from outside of their working environment, such as, networking across the hospital or attendance at conferences.

"And I think that's what you get from going to conferences and things, and if you've not been supported in your job to go on conferences and join specialist groups, and join discussions, then you probably don't keep up to date with the way that practice is changing" (Participant 3, Physiotherapist).

The importance of MDT collaborations was illustrated by all professions with shared decision making having a positive impact on MI-E use and the generation of new skills and knowledge for staff.

"I think the other thing, the other thing where you need the get the balance right is … is that it's got to be multi professional hasn't it? It's got to be er, you know, still probably physio lead, but er, as you've … as you've implied, you know, engaging nurses

as well as … as well as medics, so … so that everyone is … is well versed in the fact that this is … this is generally a good thing" (Participant 27, Doctor).

"whereas here there's lots of different people with lots of experience, so you have to balance things a bit more. You can't just say this is what we do and why, because actually everyone's got their own clinical reasoning behind it" (Participant 3, Physiotherapist).

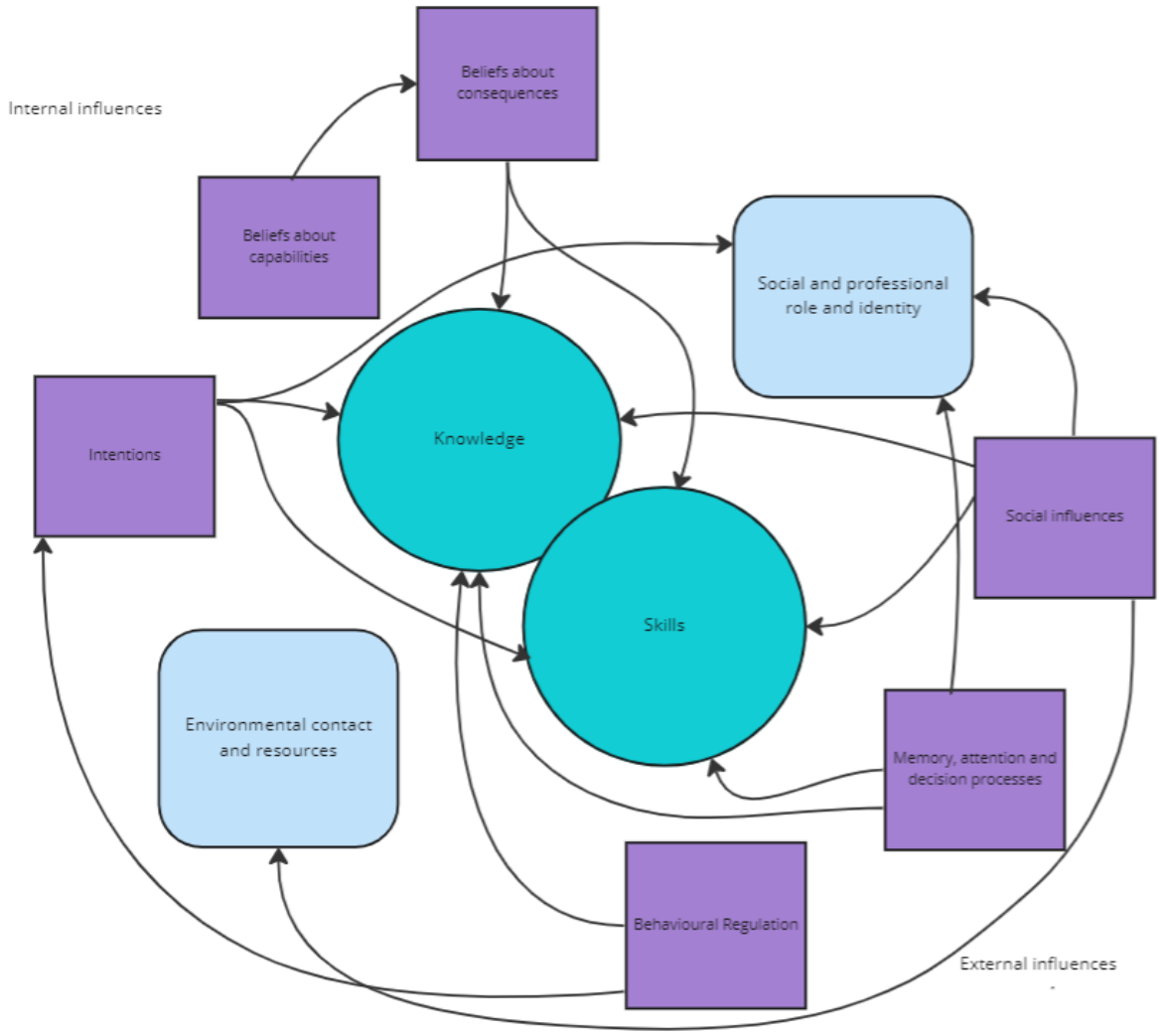


Figure 3.4: Illustration of TDF domains representing internal and external influencers, and interactions across domains (Part 2). Arrows represent interaction across domains; although interaction and influence across domains was bi-directional, arrows illustrate the dominant direction of interaction and influence.

3.6.5 Part 3

The final TDF domains were less populated compared to the previous domains, with less interactions (Figure 3.5). These domains of emotions, reinforcement, optimism and goals did however raise some important points.

3.6.5.a. TDF domain: Emotions

Study specific definition: "*Feelings of clinicians and patients that impact on device use"*

Reported emotions often had a negative impact on the use of MI-E. Frequently reported emotions linked to MI-E use were confidence and anxiety. These were often associated with stages of behaviour change regarding MI-E use in the intubated population. A lack of confidence was mentioned by individual clinicians and reference was also made to confidence of the wider team regarding MI-E adoption. It was apparent that confidence was linked to frequency of use of MI-E.

"I guess the other is just clinician confidence, to be honest, you know, there are probably plenty of those patients that it would be safe and appropriate to use it for. Um, but without doing it regularly, it's harder to identify those ones where you … where the risk benefit balance kind of tips in favour of using MI-E" (Participant 20, Physiotherapist).

Some participants also reported a lack of confidence and anxiety about deviating from traditional and established standard care. Again, this was linked to frequency of MI-E use and the subsequent experience of positive outcomes from its' use.

"There … there may be an element where um, from the nursing perspective, there's always an anxiety about going slightly off piste. So um, and I don't know if the same rings true for physiotherapy, it maybe it does" (Participant 25, Doctor).

3.6.5.b. TDF domain: Reinforcement

Study specific definition: "*Outcomes that influence future MI-E device use (positively and negatively)"*

Positive and negative clinical outcomes were referred to by participants which were described as having impact on subsequent MI-E use. In particular, patient outcomes reinforced clinical reasoning skills to determine MI-E use or not based on assessment findings.

"we had somebody who was really poorly and gave it a go, got incredible results very quickly" (Participant 1, Physiotherapist).

One participant also discussed how they gained reinforcement from a senior colleague in developing reasoning skills which aided clinician confidence.

"Yes, 100%, especially working with Band seven, Band eight at the moment, um, yes, she's really good at explaining the reasoning for it, and actually working … it's more coaching" (Participant 4, Physiotherapist).

3.6.5.c. TDF domain: Optimism

Study specific definition: "*A positive outlook on current and future MI-E use"*

This domain was not highly populated, with no links to other domains, but covered views from nurses and physiotherapists who focused on a positive outlook for MI-E use.

"But you know, I like … I like using it, I think it's really good" (Participant 22, Nurse)

"I think it's definitely seen positively" (Participant 5, Physiotherapist).

3.6.5.d. TDF domain: Goals

Study specific definition: "*Goals and aspirations for future MI-E practice"*

Goals was the least populated domain with a single quote. This quote has links to the *Intentions* domain but when considered in context of the interview discussion, it was most suited to the *Goals* domain. This discussion focused on goals for the future and aspirations for future practice which included the use of competency documents and MI-E adoption.

"we do have competencies and it's … on our, kind of, to do list, to roll them out to all the seniors in the team to make it more of something that's, kind of, in our toolbox" (Participant 2, Physiotherapist).

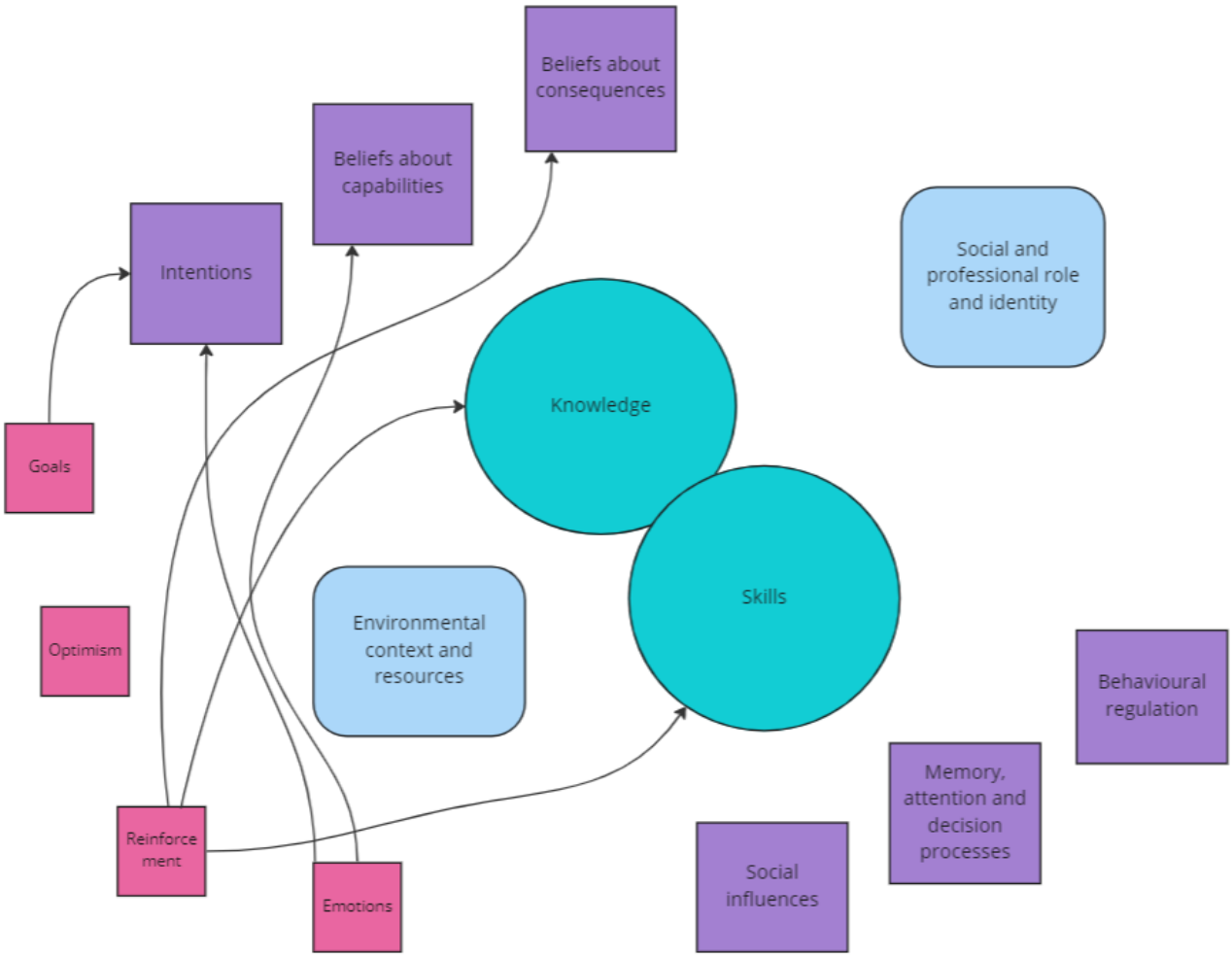


Figure 3.5: Final TDF domains (Part 3). Arrows represent interaction across domains; although interaction and influence across domains was bi-directional, arrows illustrate the dominant direction of interaction and influence.

3.7 Discussion

This qualitative study aimed to investigate the barriers and enablers to MI-E use in acutely intubated ICU patients from a multi-disciplinary perspective through the completion of semi-structured virtual interviews. This discussion is based around the three study objectives, with study strengths and limitations discussed latterly.

Implications of the study results are considered for future research including those specific to subsequent studies reported within the thesis.

Knowledge and skills were important determinants of MI-E initiation, with differences across professions regarding current and perceived knowledge base and skill ability apparent. This impacts the role different professions play in MI-E use in the ICU setting. Profession specific roles were important in the decision-making process and the practical application of MI-E. Some conflict of opinion arose regarding profession specific roles in the practical application of MI-E. Practical use of MI-E was dominated by physiotherapists which is in contrast to previous studies where multiple professions have been reported to be involved in MI-E provision (Rose et al., 2017; Stilma et al., 2021). A Canadian survey (Rose et al., 2016) reported cough augmentation techniques to be completed by respiratory therapists, physiotherapists and nurses in the ICU setting. Although the survey was not specific to MI-E, similar barriers were identified including clinician expertise and knowledge, with respondents highlighting the need for further evidence for cough augmentation techniques in this patient group. Notably, as emphasised in the current interviews, the need for more robust evidence remains several years later, despite a number of publications in this area since. The recent scoping review (Chapter 2) included 28 research papers, of which 14 were published after the Canadian survey, illustrating the growth in the evidence base specific to MI-E in the ICU. It is apparent from the current interviews that there is a delay in research implementation into practice, partly due to a lack of awareness of current research in some clinician cases. However, it is also possible that the current research is not fully addressing the

perceived evidence gap. These gaps between research publications and the implementation into practice warrants further exploration.

The findings from the current study concur with a recent focus group study with 35 clinicians which highlighted the impact of knowledge on MI-E use in the ICU setting (Stilma et al., 2022). Specifically, the focus group data emphasised the impact of knowledge on current and future adoption of MI-E. The focus groups were interprofessional with participants mostly from the Netherlands but also included some international clinicians. Despite the mixed cohort, nurses were reported as the expert users of MI-E in the ICU setting. Profession specific roles were also evident with nurses initiating MI-E use, overseen by medical consultant colleagues. Some of these differences in profession specific roles for MI-E use could be explained by the difference in the organisation and delivery of healthcare in the UK and across Europe and the associated differences in clinical practice, roles and responsibilities.

It should also be noted that there are no standardised requirements for training, competence and qualifications for physiotherapists working in the ICU. As a result, the role and the scope of ICU physiotherapists is likely to vary across hospitals nationally as well as internationally. The need for education to enhance clinician skills and knowledge has been highlighted in the current study and is supported by recent literature (Stilma et al., 2022). It is apparent that each clinical profession has a different role in the use of MI-E in the ICU setting. As a result, education strategies may need to differ for each profession or be tailored to baseline knowledge, level of capability and the expected role in delivering the intervention. However, it could be

argued that profession specific education would further divide and exacerbate the professional differences in MI-E knowledge and skills, and subsequent roles in the practical application of MI-E in this patient group. These are important considerations in context of education for wider MI-E implementation beyond this study.

Challenges to the use of MI-E via an ETT and tracheostomy were identified, with the use of MI-E via an ETT viewed as an advanced skill by some interviewees. Participants reported that these challenges could be overcome with appropriate knowledge and skills (device use, communication). MI-E has traditionally been used in people with NMD and spinal cord injury, with extensive evidence supporting its efficacy (Chatwin et al., 2018). Studies in the NMD population, examining the use of MI-E include self-ventilating patients with a patent airway and those who require a tracheostomy (Garstang et al., 2000; Sancho et al., 2003; Miske et al., 2004; Pillastrini et al., 2006). It is possible that previous application of MI-E via a tracheostomy in other patient groups such as NMD, leads to clinicians' feeling more confident and viewing the ETT as the complex component.

Twose et al., (2019) completed a three round Delphi study, to determine minimum-standards of clinical practice for physiotherapists working in ICU. A total of 107 items of knowledge and skills were deemed essential to clinical practice which included MI-E (85% consensus during round 1). The current interviews demonstrated that despite MI-E being viewed as a core skill within the Delphi study, it is still not widely implemented, particularly with an ETT. Participants of the Delphi study were highly

experienced physiotherapists. In comparison, interview participants in this study had a much wider spectrum of experience which may account for the differences in opinion. Authors of the Delphi study (Twose et al., 2019) emphasised the importance of implementing findings to help standardise training both within higher education institutions and the wider health service. However, to date there is no published guidance specifically for the practical application of MI-E in this patient group.

The definition and understanding of the term 'standard care' for airway clearance techniques was also challenged by participants and viewed as a potential barrier to future MI-E use. As such, it should be questioned whether a generic definition of 'standard care' exists for airway clearance in the ICU setting. Clinicians (mostly physiotherapists) described a treatment hierarchy depending on patient clinical need, with MI-E often considered as a last resort or other techniques being chosen over MI-E because of familiarity. It is likely that there is a spectrum of current implementation with some centres using MI-E on a regular basis and others not using it at all. This is supported by previous findings from the UK survey which illustrated a range of reported frequency of use (Swingwood et al., 2020) and more recently in a survey based in The Netherlands which demonstrated few (22%) ICUs using MI-E with their invasively ventilated population (Stilma et al., 2021). Heterogeneity in airway care techniques were reported across the 72 Dutch units surveyed; with heated humidification (58/72, 81%), nebulisation (72/72, 100%) and manual hyperinflation (58/72, 81%) reported to be used more frequently that MI-E. These findings suggest that MI-E is not yet considered part of standard care despite emerging evidence and the recommendation for MI-E to be included as a minimum

standard of clinical practice for UK ICU physiotherapists (Twose et al., 2019). Interestingly, in the current interview study, MHI was frequently highlighted by clinicians as either the preferred treatment option or an alternative treatment option to MI-E. Both treatment techniques utilise positive pressure as a means of gaining volume to precede a cough, but only MI-E delivers a negative pressure breath. Participants who were already MI-E users, perceived one strength of MI-E was the negative pressure breath used to influence expiratory flow rates and therefore augment cough. Respondents in this study, and previous surveys, have expressed the wish for more evidence relating to MI-E. However, evidence relating to MHI and other airway clearance techniques has quality issues (Tronstad et al., 2022) and it could be questioned if there is any difference per se in the strength of evidence for or against the use of different airway clearance techniques. The delay in incorporation of research evidence into clinical practice is documented and not specific to the ICU setting or physiotherapy (Worral et al., 2016; Frastsve-Howley and Rindel, 2019). What could also be influential therefore in the choice of airway clearance technique is the impact of clinician's tacit knowledge, including clinical experience and discussions with colleagues. The interaction and influence of research evidence and past experiences on MI-E use was also highlighted in a series of Dutch focus groups (Stilma et al., 2022) and is worthy of further exploration. This may enhance understanding of the clinical reasoning associated with MI-E use, which can subsequently be considered for future education and implementation of the technique.

Culture was influential in the introduction and ongoing use of MI-E in the ICU setting, having both positive and negative effects. This was evident within single professions

and across the wider MDT. The impact of hierarchy within professional groups tended to have negative consequences on MI-E implementation, exposure to the technique and subsequent development of skills and knowledge of others across the MDT.

Culture has been previously reported as a barrier to MI-E use (Rose et al., 2017; Swingwood et al., 2020; Stilma et al., 2021; Stilma et al., 2022) and more generally the impact of ICU culture on implementation has been previously documented. For example, studies examining the implementation of early mobilisation and rehabilitation in the ICU setting have emphasised the impact of culture on clinician behaviour (Dafoe et al., 2015; Messer et al., 2015; Dubb et al., 2016). Dubb et al., (2016) completed a review of 40 studies based around early rehabilitation. Culture was shown to be a key determinant of successful implementation across the included studies. Further to this, Worral et al., (2016) discussed how to improve uniformity in the delivery of lung protective ventilation across ICU. They highlighted challenges that impacted the implementation of change including 'unit culture', 'authority hierarchy' and 'variation between multiple autonomous practitioners'.

More recently, Schumann et al., (2023) described the introduction of 'weaning boards' to guide ventilation weaning plans in the ICU setting. Again, ICU workplace culture was stated as a key determinant of implementation success. It appears from the literature that the impact of culture could be key to success and sustainability of MI-E implementation and ongoing use. A collaborative approach was identified as important in the current interviews, to enable clinical progression and change

regarding the use of MI-E in the ICU setting. Such collaboration may be key to overcoming any negative impact of culture.

When overlaying all the TDF domains and highlighting the interactions across domains, the result is complex. This is an important consideration for future MI-E implementation because there appear to be numerous influencers, both positive and negative, on technique initiation, ongoing use and cessation.

3.7.1 Study strengths and limitations

Interviews were completed with 29 participants across three different clinical professions, with differing levels of MI-E exposure to gain a breadth of perspectives. Participants were predominantly physiotherapists which may have biased the findings and subsequent discussion points. When discussing sample sizes within qualitative research, the term 'data saturation' is no longer a key determinant. Instead the focus is gaining data that is 'information rich' and the sample size is determined according to the breadth of the research question and the depth of knowledge held by participants (Malterud et al., 2016; Braun and Clarke, 2021). Findings from the current study demonstrated agreement across professions on key themes. However, a purposeful recruitment approach to achieve a more evenly balanced multi-professional cohort may have provided additional insight. All participants were based in the UK so findings may not be reflective of MI-E use in other countries. Interviews were completed virtually which enabled a geographical spread of participants that may not have occurred if the interviews had been face to face. The use of an online format for interviews was employed to negate common

challenges of in-person interviews such as travel time and costs. This was a strength of the research in relation to inclusivity (Lo Lacono et al., 2016; Keen et al., 2022). However, participation was voluntary and it is possible that the sample were therefore biased towards those that had positive beliefs about MI-E.

The TDF was used prospectively to develop interview guides and informed the data analysis; this framework provides a systematic approach and a strong theoretical basis (Phillips et al., 2015). Previous studies have highlighted the benefits of TDF implementation across study phases, enabling a breadth of information to be gathered, particularly about behaviour determinants (Atkins et al., 2017; McGowen et al., 2020). With MI-E being an emerging intervention, it was important to gain breadth of information. Previous recommendations made by McGowen et al., (2020) were followed which included using the interview topic guides in a flexible manner. Throughout, interviewees (who did not have sight of the topic guide) dictated the flow of conversation to allow important points, as perceived by the interviewee, to be raised.

From an analysis perspective, the deductive use of the TDF limited the potential for unwarranted assumptions and researcher bias. However, by using the TDF in such a manner, information may have been missed, particularly if it was not viewed as aligning with a TDF domain during analysis. Reassuringly, data illustrated different behaviours across professions and a different emphasis of potential barriers to the use of MI-E in the ICU setting. This suggests that the TDF did enable detailed information on a professional and organisational level to be highlighted.

Finally, interviews were completed by the doctoral fellow. Interview responses may therefore have been influenced where the doctoral fellow was known by the interviewee. Time was spent at the start of each interview to assure confidentiality and explain the role of the doctoral fellow to minimise the impact of this potential bias.

3.7.2 Implications of the interview findings for the wider PhD programme of research

Results from the current interview study have highlighted the strong influence of knowledge and skills in determining MI-E use in the ICU setting. Profession specific differences were shown in baseline skills and knowledge and in the roles of MI-E delivery which needed to be taken into consideration when designing the education of clinicians in the subsequent feasibility intervention trial. Further to this, theoretical knowledge and practical skills for MI-E were identified that would need to be incorporated into an education package. It was apparent that clinician confidence in using MI-E was dependent upon the interface (ETT versus tracheostomy tube). Training would therefore need to cover both theory and practical skills for both interface options, particularly as interview respondents highlighted less familiarity for using MI-E via an ETT.

The impact of culture on MI-E use was highlighted with a collaborative approach appearing to be favourable for implementation. This was an important factor to consider in developing the training and for future implementation. For example, the provision of collaborative education and dissemination of findings via specialty

specific (ICU) routes rather than restricting the information to profession specific audiences.

3.8 Conclusions

This qualitative interview study exploring barriers and enablers of MI-E use in the ICU setting was the first study of this nature in the UK. The study has highlighted barriers to MI-E use consistent with previous literature. Knowledge and skills were identified as important determinants of MI-E application in the intubated population. Education strategies should consider learning needs and profession specific roles. MDT culture and hierarchy can limit or facilitate initiation and ongoing MI-E use. A collaborative MDT approach was viewed as important to optimise future MI-E implementation outcomes.

Future work should focus on confirming efficacy and safety of MI-E in the ICU population, alongside optimal treatment strategies, that is, timing of intervention and device settings, to optimise outcomes. Further consideration for implementation strategies of findings into the clinical setting are important to overcome described barriers and to optimise future use of MI-E in the ICU setting. This thesis will continue with the presentation of a feasibility study exploring the use of MI-E to promote extubation success.

Chapter 4

Feasibility study to explore the use of Mechanical Insufflation-Exsufflation to promote extubation success in adult intensive care: The MERIT Study Methods

4.1 Introduction

As demonstrated in Chapter 2, there is a growing body of evidence exploring the use of MI-E as an airway clearance technique in ICU. Individual studies have demonstrated effectiveness of MI-E across a variety of outcomes including volume of aspirated sputum weight, static lung compliance, airway resistance and work of breathing. However, the review identified variation in MI-E device set up and presented protocol detail across studies. The variation in how MI-E has been delivered, combined with the wide variation in patient outcomes such as promoting weaning success, reducing extubation failure, and safety; limits the ability to make practice recommendations to support implementation.

The previous scoping review (Chapter 2) and clinician interviews (Chapter 3) highlighted key gaps to be investigated and uncertainties in the evidence base which are limiting MI-E implementation. The scoping review demonstrated inconsistent reporting regarding the safety of MI-E in the ICU population although where adverse events were reported it was found to be safe (Farina et al., 2017; Ferreira de Camillis

et al., 2018; Sanchez-Garcia et al., 2018). The importance of evidence relating to safety was emphasised within the clinician interviews during which participants highlighted the need for more robust evidence regarding the efficacy and safety of MI-E in the ICU setting. The lack of consistency between studies in the outcomes used to determine MI-E effectiveness is a further limitation. To date there remains no published evidence regarding economics of MI-E use. This may be an important consideration as resource availability linked to device costs have been described as a potential barrier to MI-E in the ICU setting (Swingwood et al., 2020).

The technique of MI-E can be considered a complex intervention. A recently updated framework for the development and evaluation of complex interventions by the Medical Research Council (MRC) describes complex intervention research across four phases; development, feasibility, evaluation and implementation (Skivington et al., 2021). Evaluation of a complex intervention should not simply consider whether an intervention works or not for its intended purpose, but also consider additional factors such as intervention value, how the intervention is working and the wider impact on system change. Before additional studies of MI-E efficacy are undertaken, it is important to consider feasibility of trial design (Skivington et al., 2021). Feasibility trials are vital to investigate the uncertainties around trial design and conduct to establish whether a definitive multi-centre RCT is feasible and to optimise the design of such a trial. Furthermore, acceptability forms an important part of feasibility testing which can be considered through both quantitative and qualitative

processes. As such, this study will examine the feasibility of using MI-E as an airway clearance technique, as part of a weaning protocol, to promote extubation success.

4.2 Aims and objectives

The aim of this study was to determine the feasibility of a RCT of the airway clearance technique MI-E to promote extubation success in critically ill, intubated adults on ICU.

This feasibility study addressed the following objectives:

1. To determine trial feasibility based on feasibility end points (Table 4.1)
2. Whether it was possible to recruit and retain participants throughout the study duration
3. Whether it was possible to collect outcome data (to include follow up data) and to examine dataset completeness
4. To determine the acceptability of MI-E as an airway clearance technique to patients and members of the interprofessional team including doctors, nurses and physiotherapists
5. To identify the information that patients and relatives (making decisions) want for a future trial
6. To determine how clinicians set up MI-E and to ascertain if there are differences in set up across intubated and extubated patients
7. To provide a description of 'standard physiotherapy care' on ICU

4.3 Feasibility endpoints and outcomes

Feasibility outcomes are illustrated in Table 4.1. Feasibility was subsequently assessed by pre-defined progression criterion (Table 4.2).

Table 4.1: Feasibility outcomes

Feasibility outcome	**How measured**
Proportion of eligible patients approached, consented and randomised	Screening log and randomization records
Proportion of MI-E treatment sessions completed	Case report form
Proportion of recruited patients with all outcome measures recorded	Case report form
Attrition (participant withdrawal and loss to follow up)	Case report form and withdrawal records
Acceptability of trial processes to participants and clinicians	Qualitative interviews Acceptability of intervention measure (AIM)/Intervention appropriate measure (IAM)/feasibility of intervention measure (FIM)
Acceptability of outcome measures to participants and clinicians	Qualitative interviews

Abbreviations: MI-E, Mechanical Insufflation-Exsufflation

Table 4.2: Progression criteria (based on feasibility parameters)

	Summary	Action required
Go (green)	**Recruitment**: >70% expected recruitment target **Follow up:** >75% data completeness **Adherence:** >75% adherence to intervention	Continue to main trial
Amend (amber)	**Recruitment:** 50-70% of expected recruitment target **Follow up**: 65-75% data completeness **Adherence:** 65-75% adherence to intervention	Identify remediable factors, discuss with trial management group
Stop (red)	**Recruitment**: <50% of expected recruitment target **Follow up:** <65% data completeness **Adherence:** <65% adherence to intervention	Do not progress to main trial, unless there is a strong case that unanticipated remediable factors have been identified and can be addressed after further discussion with the trial management group

4.4 Trial design

The protocol was accepted for publication in Trials and Feasibility (Swingwood et al., 2023) (Appendix 10). This study was a single centre, individual parallel group, randomised, feasibility RCT with economic scoping and nested qualitative study.

There were 2 stages to the study:

1. Feasibility intervention trial with economic scoping (single site)
2. Qualitative investigation of the acceptability of MI-E as an airway clearance technique and the associated study protocol

The study took place in a general 21 bed adult ICU, within a large NHS teaching trust. The unit had approximately 1250 admissions annually and admitted adults (>16

years of age) with any condition except cardiac surgery or neurosurgery, which was representative of most UK general adult ICUs.

4.4.1 Participant Eligibility Criteria

Findings from the scoping review (Chapter 2) illustrated that studies included patients that did not always reflect the heterogenous ICU population. It was therefore important that the current study attempted to reflect a UK general ICU population. The inclusion criteria and associated rationale for the feasibility intervention trial are listed in table 4.3. Exclusion criteria and associated rationale are listed in table 4.4.

Table 4.3: Study inclusion criteria

Inclusion criteria	Rationale
Adult >16 years	Admitting age of patients to the study site/adult UK ICUs.
Expected to require IMV for >48hours	Patients who have required IMV <48hours have low risk of extubation failure. After 48hours, risk of retained secretions and ICU associated weakness increases, impacting extubation success.
Clinician identified pre-extubation problems with secretion management defined as poor/weak cough effort (cough peak flow <60L/min) and/or secretion load that is difficult to clear with usual airway clearance management (as assessed by the treating clinical team)	Clinical indications for the use of MI-E (supported by scoping review and clinician interview findings).
Identified as 'ready to wean or weaning' by the treating clinical team (on a spontaneous mode of ventilation for example CPAP ASB, PSV, APRV with spontaneous effort)	At a time point in clinical care where extubation is being planned, therefore timely to consider the optimisation of airway clearance strategies at this stage in order to promote extubation success.

Abbreviations: APRV, Airway Pressure Release Ventilation; ASB, Assisted Spontaneous Breathing; CPAP, Continuous Positive Airway Pressure; ICU, Intensive Care Unit; IMV, invasive mechanical ventilation; L/min, Litres per minute; MI-E, Mechanical Insufflation-Exsufflation; PSV, Pressure Support Ventilation; UK, United Kingdom

Table 4.4: Study exclusion criteria

Exclusion criteria	Rationale
PEEP >10	Disconnection from the ventilator will eliminate the impact of PEEP, therefore predisposing a patient to lung de-recruitment and risk of deterioration.
FiO_2 >0.7	It is only possible to entrain approximately FiO_2 0.4 oxygen through the MI-E device (even with a flow rate of 15L/min). Reducing the oxygen delivered may therefore increase the risk of patient deterioration.
Hemodynamic/Cardiovascular instability (for example noradrenaline >0.25mg/kg, arrhythmias requiring intervention);	During MI-E there are swings/changes in intrathoracic pressure which will impact the cardiovascular system. If a patient already has cardiovascular instability (with or without inotropic support), these additional changes may not be well tolerated and put the patient at an increased risk of deterioration.
Recent undrained pneumothorax (admission with no chest drain in situ);	The use of positive pressure with an undrained pneumothorax will likely worsen the pneumothorax and place the patient at an increased risk of deterioration
Unable to continue to use MI-E post extubation (for example contraindications to facemask use-facial/cranial trauma, recent facial surgery; active upper gastrointestinal bleeding/uncontrolled vomiting; recent upper abdominal/thoracic surgery with at risk anastomosis)	The protocol requires the use of MI-E whilst the patient is intubated and after they are extubated. If there are reasons a patient would not be able to receive MI-E post extubation then the protocol will not be completed.
Pre-existing neuromuscular respiratory condition	Known benefits in this patient group therefore inclusion may skew results
Pre-existing routine use of MI-E in the community	Known benefits in this patient group therefore inclusion may skew results
Patients with pre-existing permanent tracheostomy	Patients would not be aiming to wean off ventilation for extubation/decannulation
Treatment withdrawal expected within 24hours or not expected to survive	Not suitable for active treatment as extubation may not be planned
Re-admission to ICU following index admission	To prevent introduction of bias to results
Previous MERIT trial participation	To prevent introduction of bias to results

Abbreviations: FiO_2, Fraction of inspired oxygen; MI-E, Mechanical Insufflation-Exsufflation; PEEP, Positive End Expiratory Pressure

4.4.2 Participant identification

All ICU patients were screened against the eligibility criteria using the daily caseload sheets by either the doctoral fellow, the research nurse or delegated clinician (Good Clinical Practice (GCP) trained) from the Physiotherapy team. Once deemed eligible, an individual study identification number was generated through the study RedCap database.

4.4.3 Co-enrolment to other studies

Patients in the trial were eligible for co-enrolment in other studies. This was decided on a case-by-case basis by the Trial Management Group (TMG), in keeping with standard UK national approaches to co-enrolment in critical care research (Felton et al., 2020). The Clinical Trials Unit (CTU) and study sponsor were informed when co-enrolment was being considered, co-enrolment agreements where applicable were stored in the Trial Master File (TMF), and details of co-enrolment with studies documented in the Case Report Form (CRF). Prior to opening to recruitment, all current live studies with the study site were contacted with details of the planned trial.

4.4.4 Consent

The study was conducted with ethical principles from the Declaration of Helsinki. The study team member taking consent (doctoral Fellow, Research Nurse or a member of Physiotherapy team) was GCP trained and had this duty delegated to

them on the study delegation log. On initial enrolment into the trial patients were sedated and ventilated due to the nature of their illness. They therefore lacked capacity and were unable to provide informed consent to study involvement. The Mental Capacity Act, 2005 (sections 30-34) refers primarily to long term cognitive impairment but also covers short term occurrences for example when participants are unconscious. In line with this guidance, participation was discussed with a personal or nominated professional consultee prior to enrolment. Participants were approached for informed consent if/once they regained capacity (section 4.4.4.c) (Figure 4.1).

4.4.4.a Personal Consultee

The doctoral fellow or delegated GCP compliant study team member took reasonable steps to seek opinion from a personal consultee as to whether the patient would wish to participate.

For the purpose of the current study (based on The Mental Capacity Act, 2005), a 'personal consultee' was defined as a partner, friend or carer who was not seeking renumeration or acting in a professional manner. This person did not provide consent on behalf of the patient but instead provided 'informed advice' for inclusion/exclusion into the trial. Once identified the consultee was provided with a 'consultee information form' (appendix 11) and appropriate Declaration Form (appendix 12). Provision of the 'informed advice' was documented on the study specific recruitment log.

4.4.4.b Nominated professional consultee

At the time of requiring consent, if a personal consultee was not available (for example, where no family member or friend was willing or able to act as consultee, or where the family or friend lived a long distance away, and/or were unable to at least discuss the information sheet(s) within adequate time), and/or a personal consultee became unavailable during the study, or was no longer willing to undertake the role, then a nominated professional consultee was approached to advise the researcher about the participation of the person who lacked capacity. For the purpose of the current study, a nominated professional consultee was defined as an individual who was independent of the project. For the purposes of this trial a 'nominated professional consultee' was a health professional at the trial site who was appointed by the doctoral fellow. This could have included a member of the care team as long as they were not directly connected with the project to avoid potential conflict.

The Nominated Professional Consultee was provided with the Consultee Information Sheet (appendix 11) and Consultee Declaration Form (appendix 12); agreement was sought in the same way as noted above, for the Personal Consultee.

If the Personal or Nominated Consultee advised the research team that the participant should be withdrawn from the study, the research team were required to withdraw them.

4.4.4.c Participant consent on regaining capacity during the trial

On regaining capacity, the patient was informed of their participation in the trial and informed consent sought. Participants were provided with a 'participant information sheet' (appendix 13) and consent form (appendix 14). If they did not wish to remain in the study, they were withdrawn. In the situation of a patient not consenting to ongoing participation then permission to use data collected to that point would have been requested. Unless the patient gave permission for data collected to that specific timepoint to be kept and used within the analysis, it would have been destroyed.

4.4.4.d Participant death during the trial

If a patient died during the study period, permissions for study inclusion approved use of data that had been collected up to that point.

4.4.4.e COVID-19 considerations

Visitor restrictions imposed during the COVID-19 pandemic meant that there were either no visitors within the hospital, or that patient visitors had restricted visiting opportunities. It was unknown on study opening whether there would be ongoing restrictions impacting patient visitors during trial recruitment. To facilitate timely and appropriate participant recruitment a decision was made to initially approach professional consultees for consent as described above and then to approach personal consultees when possible.

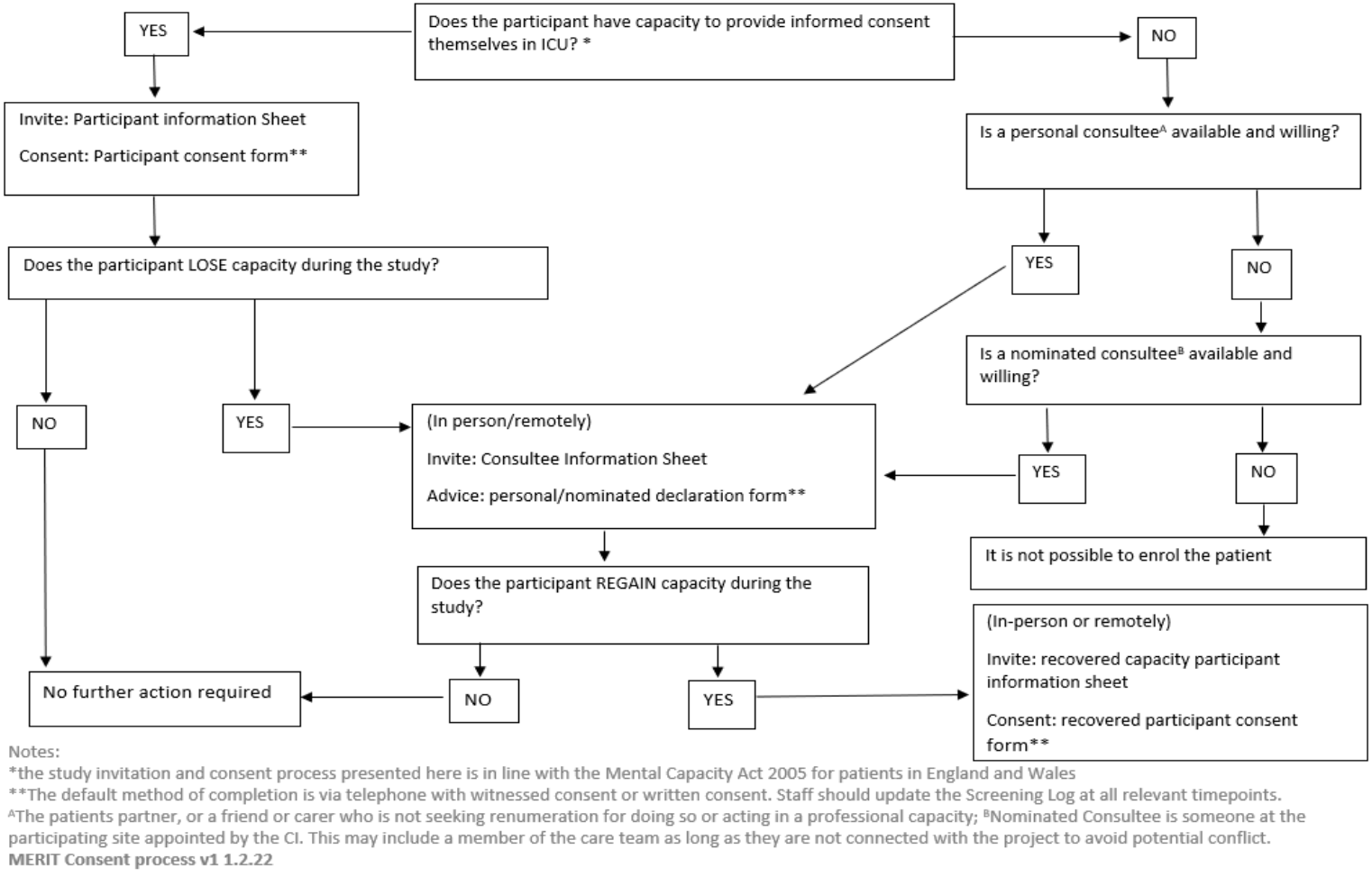


Figure 4.1: Consent process

4.4.5 Randomisation

Randomisation to a study arm took place once consent for study participation had been obtained. Participants were randomised with a 1:1 allocation to either (A)-control arm (standard care) or (B)-intervention arm (MI-E plus standard care).

An online randomisation system was used, with the randomisation sequence generated by the company "Sealed Envelope™". To randomise a participant, the recruiting staff signed into the online randomisation system and entered brief participant details (including unique study identification (ID) and date of informed consent/advice). Once the online randomisation process was complete, the computer screen indicated the group to which the participant had been allocated. "Sealed Envelope™" automatically sent an email to study team users that had 'notifications enabled' confirming the randomisation. A member of the research team placed a record (electronic and print out) and pre-prepared 'treatment allocation group' sticker in the patient's records and on the electronic health record system. The doctoral fellow was responsible for ensuring this process was completed. Blinding of participants and clinicians was not possible due to the nature of the intervention.

4.4.6 Baseline demographic data

Following randomisation, the doctoral fellow or delegated member of the research team collected baseline demographic and clinical characteristic data from the electronic medical record. These data were collected to allow the patient population to be described. This included:

- General demographics (included age, gender, estimated body weight, history of chronic lung disease (chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis), smoking history)
- Reason for intubation (COPD exacerbation; congestive heart failure; Community Acquired Pneumonia (CAP); Hospital Acquired Pneumonia (HAP); post-operative respiratory failure; acute lung injury; thoracic trauma; sepsis; cardiac arrest; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2))
- Date of hospital and ICU admission
- Date of intubation
- Acute Physiology and Chronic Health Evaluation Score (APACHE II): The APACHE II is the most commonly used disease severity score in ICU. It is made up of 12 physiological variables and two disease related variables. Each variable is assigned a score resulting in an integer score of 0-71 with an increasing score illustrating an increased mortality risk and poorer hospital outcomes (Godinjak et al., 2016; Czajka et al., 2020). It has been shown to accurately predict hospital mortality in an acute inpatient setting (Czajka et al., 2020).
- Baseline ventilator settings at time of recruitment into the study (mode of ventilation, pressures, volumes, times, respiratory rate as appropriate)
- Airway type and size

4.4.7 Recruitment log

As recommended by Consolidated Standards of Reporting Trials (CONSORT), a trial specific recruitment log was completed based on the SEAR framework (Wilson et al., 2018) to record the flow of potential participants through the trial whilst identifying recruitment obstacles thus facilitating improvements in a future recruitment process.

There are four stages to the recruitment pathway within the SEAR framework; Screening, Eligibility, Approached and Randomized. The trial specific screening log required the following information: unique study ID, patient name, hospital number, patient date of birth, date of screening, eligibility status, date of consent, type of consent/advise obtained, date of randomisation, date of participant-consent (where applicable) and date for follow up completion. When provided, reasons for non-participation and non-eligibility were included. All screened patients and their subsequent eligibility and consent status was recorded on EDGE (global clinical research management system) in real time.

4.5 Trial treatments

The trial treatment arms were as follows:

4.5.1 Control arm (standard care)

Patients received standard care including ventilation, weaning, standard physiotherapy techniques such as positioning, manual techniques, manual/ventilator hyperinflation, suctioning, and nebulisers. At the time of starting the trial, MI-E in the intubated population was not routine clinical care at the study site. Respiratory physiotherapy treatments varied between patients at the discretion of the treating physiotherapist based on individual assessment rather than a set protocol. Decisions to extubate and re-intubate were made by the attending physician with reason(s) documented.

4.5.2 Intervention arm (MI-E plus standard care)

The intervention under investigation was MI-E. In this study the MI-E device, Clearway 2 (Breas Medical LTD, Stratford-Upon-Avon, Warwickshire, UK) was used in addition to standard care (as described above). The device is reusable between patients with single patient use circuits, filters and interface (mouthpiece, facemask and flexible catheter mount).

Whilst intubated, treatment for those in the Intervention arm included a minimum of two MI-E sessions via the endotracheal tube (with cuff inflated) following

randomisation and prior to extubation. Post extubation (and up to 48hrs), Intervention arm participants received MI-E delivered via facemask or mouthpiece up to twice per day. MI-E settings (mode, pressure, timings, flow) were individualised to each patient based on ventilator settings/respiratory support, patient tolerance, chest expansion and secretion clearance (as assessed by the treating physiotherapist) (see Appendix 15).

As illustrated in Chapter 2, the most common MI-E pressure settings used across studies were +40:-40cmH_20. Previous trials had used a predefined device set up with positive outcomes enabling replication of device set up in the clinical setting. Despite this, use remains low in the intubated patient population (Swingwood et al., 2020). Recent interviews (chapter 3) indicated that clinicians were concerned about the safety of using high pressures and believed that the evidence base did not adequately support implementation. It was deemed important to ascertain how clinicians set up the MI-E device and if there were differences in set up across intubated and extubated patients. In relation to MI-E application there is variation between studies with limited evidence to suggest optimal settings nor how the device settings should be individualised to the patient. No studies to date have investigated an MI-E protocol where clinicians determine device set up and treatment prescription. Reproducibility of methods with clinician determined device set up could be challenging to investigate which further supported the need for a feasibility study. This information could enable further exploration of implementation of the evidence base into clinical practice.

4.6 Trial measurements

Clinical outcomes were collected to understand feasibility of collection to inform the conduct of a definitive trial and not to conduct hypothesis testing related to causation. Clinical outcomes and their associated measurements are summarised in Table 4.5.

Clinical data collection occurred during physiotherapy intervention sessions in the 24 hours preceding extubation and up to 48 hours post extubation. Following baseline demographic data collection (section 4.4.6), outcomes were measured during and after physiotherapy intervention for all participants. Findings from the scoping review (Chapter 2) highlighted a vast array of outcomes measured to date in the investigation of MI-E with no agreed core set. Outcomes were therefore based on the core outcome measure set for critical care ventilation trials (Blackwood et al., 2019) with reference to measures used previously. Table 4.6 provides a summary of all outcomes measured and the timepoint of measurement.

Table 4.5: Clinical outcomes collected within the feasibility study

Outcome	**Measurement method (source data)**	**Timepoint of measurement**
Re-intubation rate	Electronic health record	Defined as reintubation within 48 hours after extubation
Duration of first episode of invasive mechanical ventilation	Electronic health record	Intubation (if available) or time from randomisation and extubation timepoints (hours)
Requirement and duration of non-invasive ventilation	Electronic health record	Post extubation
Requirement and duration of High Flow Oxygen Therapy post extubation	Electronic health record	Post extubation
Need for tracheostomy	Electronic health record	During ICU stay
ICU LOS (to include post extubation LOS)	Electronic health record/demographic data	ICU admission and discharge timepoints
Mortality	Electronic health record	60 days from randomisation
Patient reported pain/discomfort	Numeric rating scale /Critical Care Pain Observation Tool	Pre, during and 5 mins post intervention
Cardiovascular parameters	-HR and rhythm -SBP and DBP	Pre, during and 5 mins post intervention
Ventilator parameters	-Compliance (for ventilated patients) -Resistance (for ventilated patients)	Pre and 5 minutes post intervention
Respiratory parameters	-Lung Ultrasound Score -Respiratory rate -SpO_2	Pre and 5 minutes post intervention
Health Economic Scoping -Quality of life	EQ-5D-5L	6/12 post end of intervention

Outcome	Measurement method (source data)	Timepoint of measurement
Health economic scoping -Resource use	Resource use (treating clinician(s); duration of treatment; equipment used; on-call physiotherapy use (planned and unplanned), suction frequency over 24hours)	During intervention period
Adverse events	Occurrence frequency of the following: -HR, SBP, DBP increase/decrease >20% baseline -Arrhythmia (requiring intervention) -Pneumothorax -Acute desaturation to SpO_2<85% or >10% below baseline -Accidental extubation -Cardiopulmonary arrest	During intervention period
Acceptability	Feasibility of intervention measure/Acceptability of intervention measure/Intervention appropriateness measure	Post intervention

Abbreviations: DBP, diastolic blood pressure; ICU, Intensive Care Unit; LOS, length of stay; SBP, systolic blood pressure; SpO2, peripheral oxygen saturations

4.6.1 Clinical Outcomes

Physiotherapy treatment interventions completed for each patient: These data were used to inform a description of 'standard care' in the ICU setting. Detail regarding the treatment prescription, such as frequency or intensity of any additional interventions was not collected, just that they had occurred.

Use of additional respiratory support: This included hours of NIV, HFOT and tracheostomy use per 24-hour period of data collection.

Lung Ultrasound Score: The lung ultrasound score (LUS) is a semi-quantitative scoring method used to illustrate pulmonary aeration (Soummer et al., 2012). A framework for practical application of the LUS at the ICU bedside was followed (Via et al., 2012). The framework describes six areas of interest per lung with each hemithorax being divided into anterior, lateral and posterior regions and each region having an upper and lower position. There is one representation point per area scanned and scored between 0 and 3 as part of this framework. Total scores range between 0 and 36. LUS was obtained pre and post intervention.

Pain score: This was measured using either the 'numeric rating scale' (NRS) (Krebs et al., 2007) or the Critical Care Pain Observation Tool (CPOT) (Gelinas et al., 2006). The NRS is a self-reported measure where patients rate their pain on a scale from 0 to 10. The ratings can be categorised as follows; 0-no pain; 1-3 mild pain; 4-6 moderate pain; 7-10 severe pain. The NRS is simple to use and highly reproducible with high sensitivity to small change. It is easy for patients to comprehend facilitating its use

across different cultures, languages and reduced mental capacity (McLean et al., 2004; Devlin et al., 2018; Karcioglu et al., 2018). In current clinical practice guidelines for the prevention and management of pain, the NRS was highly favoured by ICU patients (Devlin et al., 2018). The 0-10 oral NRS (NRS-O) and the 0-10 visually enlarged laminated NRS (NRS-V) were compared in a study of 111 critically ill adults based in a medical/surgical ICU (Chanques et al., 2010). The patients in the study were alert and able to follow simple commands. The findings supported use of the NRS-V in the ICU setting (Chanques et al., 2010).

In the situation that a patient was unable to rate their own pain (due to impaired consciousness or communication difficulties) the CPOT was used by the treating physiotherapist. The CPOT was specifically developed for the ICU setting (Gelinas et al., 2006). It contains four indicators; facial expressions, body movements, compliance with the ventilator or vocalisation and muscle tension. Each indicator is scored between 0 and 2 providing a maximum score of eight, with a higher score representing greater pain. Studies have demonstrated the CPOT to have strong inter-rater reliability in both intubated and extubated, unconscious and conscious ICU critically ill patients (Gelinas et al., 2006; Gelinas and Johnson, 2007). In a sample of 105 critically ill patients, CPOT was measured at rest and during and post turning (Gelinas et al., 2006). Significant associations with patient self-report of pain (criterion validity) and high discriminant validity when comparing CPOT scores during two timepoints (during turning and at rest) were demonstrated (Gelinas et al., 2006). A subsequent study mirrored these findings in a smaller cohort of 55 (conscious and unconscious) critically ill adults (Gelinas and Johnson, 2007).

In the current feasibility study, pain was scored pre and post intervention using CPOT and/or NRS-V. The inclusion of both a patient reported and clinician reported measure of pain was discussed with the PAG and SAG. Patient members of the PAG and SAG suggested that it was important for participants to have the opportunity to indicate how they felt during the MI-E intervention. The patient view has not previously been included in studies as reflected in the scoping review (Chapter 2).

Cardiovascular and respiratory parameters: These included heart rate, SBP and DBP which were measured pre, during and post intervention. During the intervention the highest/lowest change and/or new arrhythmia onset was recorded. In all patients SpO_2 and respiratory rate pre, during and post intervention with the highest/lowest change were recorded. These timepoints were included to illustrate and determine if potential changes were transient in nature or related to a safety issue. Previous interviews (Chapter 3) indicated that MDT clinicians had concerns about the safety of MI-E therefore differentiating between transient changes and those that may have placed the patient at risk was deemed important. Whilst safety issues could result in MI-E cessation, transient changes could reflect a need to adapt settings and, in some cases, may not be of any concern.

Ventilatory parameters: In intubated patients' ventilator settings, airway resistance and lung compliance pre and post intervention were recorded.

Clinician acceptability: As previously discussed, acceptability of the intervention and associated trial processes is an important part of feasibility testing (Weiner et al.,

2017; Skivington et al., 2021). Three key outcomes were used in the current feasibility study; Acceptability of Intervention Measure (AIM); Intervention appropriate measure (IAM) and feasibility of intervention measure (FIM) (Weiner et al., 2017). These implementation outcomes, consisting of 12 items (four items per measure) which are scored from 1-5 on an ordinal scale; 1 = completely disagree, 2 = disagree, 3 = neither agree or disagree, 4 = agree and 5 = completely agree. Items are totalled and averaged, with a mean score of ≥4 providing a positive (acceptability) response. A higher score illustrates greater acceptability, appropriateness and feasibility. These outcomes (AIM, IAM, FIM) were shown to have strong psychometric properties during their development with sound validity, reliability and responsiveness to change when tested by 326 mental health professionals (Weiner et al., 2017). The relevance of these measures could therefore be questioned for the current ICU based feasibility study. Authors of the outcomes acknowledged that at the time of development, further testing with other health care professionals would have provided useful information regarding generalisability of the measures. However, Weiner et al., (2017) have highlighted benefits of the AIM, IAM and FIM as they require no formal training to administer, score or interpret the results, and there is no cost associated with use. Additionally, due to the general wording used within the measures, it is suggested that the measures could be used across implementation studies regardless of the setting and disease being investigated (Weiner et al., 2017). These measures of acceptability have been used successfully in previous studies based in the ICU (Istanbulian et al., 2022).

Table 4.6: Summary of outcomes and measurements during study period

Data		Baseline	Pre-intervention	During intervention	5 mins post intervention	Duration of ICU stay	6 months follow up
Baseline demographic outcome	Demographics	X					
	Reason for intubation	X					
	Date of hospital and ICU admission	X					
	Date of intubation	X					
	Ventilator settings	X	X		X		
	Airway type and size	X					
	APACHE II score	X					
Clinical outcomes	Use of HFOT, NIV, tracheostomy					X	
	Use of physiotherapy interventions			X			
	LUS		X		X		
	Patient pain/discomfort		X		X		
	CVS parameters		X	X	X		
	Ventilator parameters		X		X		
	Respiratory parameters		X		X		
Health economics	-resource use -QOL via EQ-5D-5L			X			X
Safety	Adverse events			X	X	X	
Appropriateness	FIM/AIM/IAM				X		

Abbreviations: AIM, Acceptability of Intervention Measure; APACHE II, Acute Physiology and Chronic Health Evaluation; CVS, cardiovascular system; DBP, diastolic blood pressure; FIM, Feasibility of Intervention Measure; HFOT, High Flow Oxygen Therapy; HR, heart rate; IAM, Intervention Appropriateness Measure; ICU, Intensive Care Unit; LUS, Lung Ultrasound Score; NIV, Non-Invasive Ventilation; QOL, quality of life; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, peripheral oxygen saturations

4.6.2 Nested Health Economic Evaluation

The economic benefits of critically ill patients being treated and cared for in the ICU has been previously established (Ridley and Morris, 2007). With an ever-increasing ICU survivorship, the ongoing quality of life (QOL) and morbidity status of this patient group is of high importance (Lau et al., 2021). However, there is not an infinite resource supply and as a result there must be consideration of resource use, ensuring value for money is demonstrated both with regard to actual monetary cost and to the health consequences for patients (Drummond et al., 2005; Kahn, 2021).

Health economic evaluation can be purely descriptive where the resource under examination is not compared to another, and information is reported about either the consequences or the cost of that resource. Evaluation can become more detailed through the addition of a comparator resource and/or a partial evaluation of either efficacy or cost analysis. The most detailed form of economic evaluation involves resource comparison and an analysis in terms of costs and outcomes. There are four main types of full economic evaluation; cost-minimisation analysis; cost-effectiveness analysis; cost-utility analysis and cost-benefit analysis (Drummond et al., 2005; Brazier et al., 2007; Kyeremanteng et al., 2016).

Cost-minimisation analysis is used when outcomes of interventions or treatments are similar, allowing comparisons of costs to ascertain the least costly option (Drummond et al., 2005). This method of comparison assumes that the alternatives

being compared are equally as effective and does not consider the impact of secondary outcomes or risk of the intervention in question (Kyeremanteng et al., 2016). This method can therefore be challenging in the ICU environment as patients have multi-factorial and complex presentations with individual outcomes often differing. As such it is not recommended for use in the ICU and complex medical domains (Kyeremanteng et al., 2016).

Cost-benefit analysis provides a comparison of costs versus benefits of interventions or treatments. Monetary values are assigned to health benefits to enable decisions of whether intervention costs are outweighed by intervention outcomes. This method has been challenged in the ICU setting as it is not viewed as being patient centred. Additionally, potential ethical issues have been highlighted regarding the assignment of monetary values to health situations such as morbidity and mortality (Kyeremanteng et al., 2016).

Cost-effectiveness analysis examines costs and health outcomes of one or more interventions or treatments. It then provides an estimate on how much a particular intervention or treatment would cost to gain a specified unit of health, for example deaths prevented, life years gained or number of ICU admissions (Kyeremanteng et al., 2016). A strength of cost-effectiveness analysis is the inclusion of different types of costs beyond the initial direct intervention costs to include factors such as clinician time, patient impact, such as, pain and productivity. However, as with cost-benefit analysis, cost-effectiveness analysis does not consider the patients QOL

which is particularly important when considering the lifelong sequalae of an ICU stay. Furthermore, cost-effectiveness analysis does not provide comparison across illnesses, populations or interventions (Lau et al., 2021).

Cost-utility analysis combines both health related QOL and length of life, resulting in benefits being presented as quality adjusted life years (QALYs). A benefit of including QALYs as the common denominator in evaluation is that they allow comparison across different treatments, populations and disease states. This method of analysis is widely used in medical literature and is validated in the general population and some health conditions such as COPD and heart failure (Kahn, 2021; Lau et al., 2021). It has not specifically been validated in the critically ill population but despite the challenges in implementing such a technique, it has been previously recommended as the analysis of choice for the ICU setting (Kyeremanteng et al., 2016; Kahn, 2021).

Each method of full economic evaluation explores a different dimension of 'value' and there is no hierarchy to these methods, therefore selection depends on the resource being examined and the purpose of evaluation. A review of economic evaluation techniques showed preference towards the primary use of cost utility analysis or cost effectiveness analysis in the ICU setting due to the consideration of QOL within the measures and due to the high costs and complex patient presentations (Kyeremanteng et al., 2016). However, a more recent publication illustrated the wide variation in methodological quality across studies that included cost-utility analysis, recommending that standardisation in the implementation and

reporting of economic evaluation was of utmost importance for the future (Lau et al., 2021). Prior to commencing the current feasibility study there had been no economic evaluation of MI-E across any patient population. From the pre-doctoral UK survey and from interviews with healthcare professionals (Chapter 3), the initial cost of an MI-E device and the ongoing costs of consumables was identified as a potential barrier to its use clinically. For a future definitive evaluation study MI-E would need to be compared to standard care. Resource consideration would need to be more detailed than just the monetary value of the MI-E device and include the delivery of the treatment, the clinicians involved and the impact on the patient.

This part of the study focused on establishing the most appropriate economic outcomes for future evaluation within a definitive trial and to determine the ability to collect relevant data in order to complete such evaluation. To assess the feasibility of collecting relevant data the following were collected for each participant:

a) QOL via the EQ-5D-5L
b) Resource use associated with care

The EQ-5D-5L (EuroQol, 1990) is a validated general health related QOL questionnaire which measures patient health across five domains (mobility, self-care, usual activities, pain, and anxiety/depression). It is primarily designed for respondent self-completion, but a 'face-to-face-interview' version is also available, which can be used if the patient is unable to read and/or write independently. This

measure is recommended by NICE for use in health economic evaluations (Wilson et al., 2018). QOL outcomes were collected at six months post ICU discharge.

Resource use during the index admission was identified through hospital records/case notes directly into the study specific database. MI-E device associated resource use included staffing requirements (time duration, Agenda for Change pay band), consumable use and the cost of obtaining and maintaining the device. Patient related resource use included suction frequency (over a 24-hour period), antibiotic use, physiotherapy on call use (planned and unplanned), ICU LOS, ICU re-admission and hospital LOS.

4.7 Statistics and data analysis

4.7.1 Sample size calculation

As this was a feasibility trial a formal sample size calculation based on statistical power to detect a specified treatment effect size was not appropriate (Tickle-Degnen, 2013; Eldridge et al., 2016; Sim et al., 2019). The sample size of 50 patients was determined as adequate for assessment of the feasibility parameters with adequate precision.

The Trust ICU data illustrated approximately 1250 admissions annually (pre COVID-19 data) with 4-5 new eligible patients per week, (a minimum of 200 per year).

Recruiting 50 patients over a 12-month period in this study was deemed achievable, with an estimated recruitment rate of 0.25 and a confidence interval width of 0.12.

4.7.2 Statistical analysis plan

This study was not powered to carry out hypothesis testing and as such no inferences were made. Where appropriate point estimates with a confidence interval (CI) and relative risk values (CI) were presented to aid description of results. Descriptive statistics for the patient baseline demographics were reported overall and by treatment group as means or medians with measures of dispersion for continuous outcomes (as appropriate given the form of their distribution) and frequencies and percentages for categorical outcomes. A CONSORT flow diagram illustrated the flow of patients through the research study. Patient demographics were used to assess comparability of the randomised groups. Patient reported and clinical feasibility outcomes were assessed for completeness of data. For the feasibility study the analysis was not blinded.

4.8 Safety

The inclusion of safety reporting was an essential part of this study from a governance perspective. In addition, the previous clinician interview study (Chapter 3) highlighted knowledge and perceived evidence related to the safety of MI-E use in the intubated population as lacking. The detail therefore of safety data and associated clinical outcomes was important to address this gap. Definitions for safety

reporting used within the study as listed below in Table 4.7, alongside definitions to determine the intensity classification of a safety event (Table 4.8) and definitions for relatedness and causality of safety events to the trial (Table 4.9).

4.8.1 Definitions

Table 4.7: Definitions for safety reporting*

Safety Reporting Term	Definition
Adverse event	Any untoward medical occurrence in a subject to whom a medicinal product/medical device/intervention has been administered, including occurrences which were not necessarily caused by or related to that product. An adverse event was therefore any unfavourable and unintended sign (including abnormal lab results), symptom or disease temporally associated with the use of the medicinal product/medical device/intervention, whether or not considered to be related to the medicinal product/medical device/intervention. Not all adverse events were adverse reactions but all adverse reactions were adverse events.
Adverse reaction	Any untoward and unintended response in a subject to an investigational medicinal product/medical device/intervention which was related to any dose administered to that subject. Any adverse event judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product/medical device/intervention qualified as an adverse reaction; and/or there was evidence or argument to suggest a causal relationship. All adverse reactions were adverse events.
Unexpected adverse reaction	An adverse reaction, the nature and severity of which was not consistent with the information set out in the Reference Safety Information, which may have been: (a) the summary of product characteristics (for a product with a marketing authorisation); (b) the investigator's brochure (for any other investigational medicinal product) or (c) other document containing equivalent information, for example the study protocol. This applied to the medicinal product/medical device/intervention in question. When the outcome of the adverse reaction was not consistent with the reference safety information this adverse reaction was considered as unexpected. All unexpected adverse reactions were adverse events.

Safety Reporting Term	Definition
Serious adverse event, serious adverse reaction or unexpected serious adverse reaction	An adverse event, adverse reaction or unexpected adverse reaction was defined as serious if it: (a) resulted in death; (b) was life-threatening*; (c) required hospitalisation or prolongation of existing hospitalization; (d) resulted in persistent or significant disability or incapacity. *Life threatening in the definition of an serious adverse event or serious adverse reaction referred to an event in which the subject was at risk of death at the time of the event; it did not refer to an event that hypothetically might have caused death if it were more severe. Medical judgement was exercised in deciding whether an adverse reaction/adverse event was serious. Serious adverse events/serious adverse reactions that were not immediately life-threatening or did not result in death or hospitalisation but may have jeopardised the subject or required intervention to prevent one or the other outcomes listed in the definition above, were also be considered serious.
Suspected serious adverse reaction	Any serious adverse reaction that was suspected (possibly or probably or definitely) to be related to the investigational medicinal product/medical device/intervention.
Non-IMP SUSAR	A serious adverse event that occurred in a non-IMP trial and was: • "Related" – that was, possibly, probably or definitely resulted from administration of any of the research procedures, and • "Unexpected" – that was, the type of event was not listed in the protocol as an expected occurrence.

Abbreviations: IMP, investigational medicinal product; SUSAR, suspected unexpected serious adverse reaction

**reproduced with permission from sponsor guidance with study specific terminology included*

Table 4.8: Definitions for intensity classifications*

Intensity classification	Definition
Mild event	An event that was easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that was sufficiently discomforting to interfere with normal everyday activities
Severe event	An event that prevented normal everyday activities

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Table 4.9: Definitions for relatedness and causality*

Relatedness/causality term	Definition
Relatedness Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, was not reasonable or another cause could by itself explain the occurrence of the event.
Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, was unlikely and it was likely there was another cause which could by itself explain the occurrence of the event.
Possibly related **	Temporal relationship of the onset of the event, relative to administration of the intervention, was reasonable but the event could have been due to another, equally likely cause.
Probably related **	Temporal relationship of the onset of the event, relative to administration of the intervention, was reasonable and the event was more likely explained by the intervention than any other cause.
Definitely related **	Temporal relationship of the onset of the event, relative to administration of the intervention, was reasonable and there was no other cause to explain the event, or a re-challenge (if feasible) is positive.

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***where an event was assessed as possibly/probably/definitely related the event is an adverse reaction*

4.8.2 Operational definitions for (Serious) Adverse Events

A list of serious adverse events (SAE) that could have been expected during the trial, or within the included patient population are listed below; other factors such as participant history was not considered.

- Accidental extubation during the intervention
- Pneumothorax as a result of the intervention
- Sputum plugging during the intervention
- Pulmonary complications such as pneumonia, which may cause death

4.8.3 Identification of Adverse events

Due to the vulnerable nature of the target population adverse events (AE) were likely to occur during the feasibility trial. AEs could be reported by the participant or detected by the doctoral fellow or a member of the research team through questioning or observation, during either the index hospital attendance or the follow-up contact. The doctoral fellow and associated research team were responsible for assessing *all* AEs that they became aware of during the trial, that is those occurring from the point of consent until the end of study follow up. All AEs were categorised as to whether they were serious, expected and/or related by the ICU lead research consultant. All AEs were assessed and reported in accordance with the study sponsor Standard Operating Procedure (SOP).

4.8.4 Responsibilities of recording and reporting safety adverse events

It was the responsibility of the sponsor, doctoral fellow and delegated individuals to ensure that the dignity, rights, safety and well-being of research participants were given priority at all times and appropriate action was taken to ensure their safety. The recording and reporting of a SAE, serious adverse reaction (SAR) and suspected unexpected serious adverse reaction (SUSAR) was in accordance with GCP Guidelines and the study sponsor research safety reporting SOP.

4.9 Clinician training

Preceding interviews (Chapter 3) indicated a need for education to enhance clinician skills and knowledge. Differences in skills and knowledge were identified which impacted professional roles in MI-E delivery. In planning clinician training for the current study, the doctoral fellow considered the different roles within the study and what knowledge and skills were required for each. This enabled role specific education and training to be developed rather than one generic training package.

Physiotherapists were responsible for delivering MI-E in the feasibility trial. However, nurses and doctors were involved in the study and therefore included in the education sessions. The different baseline levels of MI-E knowledge and skills across the professions needed to be considered when developing the education material. Education for both the doctors and nurses focused on a general overview of the study and what they could expect. It was important that both professions had awareness of the study as they had daily

responsibility for the patient either as their bedside nurse or as their attending physician. The doctors had additional information on the consent process for the study as this was one of their specific planned roles if a professional consultee was required. Training for both nurses (Appendix 16) and doctors (Appendix 17) were completed as bedside teaching in a face to face manner. Additionally, teaching slides were circulated to each professional group.

Group training for physiotherapists to deliver MI-E was provided at the start of the study through face to face teaching (Appendix 18). Standardised education materials developed by the research team were distributed to all physiotherapists (Appendix 19) with the additional opportunity to practice MI-E set up and delivery using simulation. Standardised training for physiotherapists included how to set up/perform the following:

- Lung ultrasound score (this was completed by FUSIC competent physiotherapists only)
- MI-E device set up to include connection and disconnection when using with an ETT and tracheostomy
- CRF completion via RedCap database

4.10 Semi-structured Qualitative interviews

4.10.1 Rationale

It is important that feasibility testing includes both a quantitative and qualitative element (Skivington et al., 2021). Inclusion of qualitative research can provide an important

contribution to a feasibility trial (O'Cathain et al., 2015), in this case to determine acceptability of MI-E and the associated study protocol. Acceptability is an important consideration as an individual's stance may impact subsequent engagement and/or commitment to an intervention (Sekhon et al., 2017). The scoping review (Chapter 2) demonstrated a lack of qualitative evidence pertaining to patient and clinician experience of using MI-E, thus reinforcing the decision to collection qualitative data on acceptability within the current feasibility study.

4.10.2 Theoretical Framework

Previous interviews informing the feasibility trial (Chapter 3) used the TDF as a basis for study design and analysis. The TDF is a multi-component behaviour change framework. This part of the study aimed to examine acceptability of MI-E as an airway clearance technique and the associated protocol, rather than behaviour change. As such the TDF was not appropriate to use.

For the exploration of acceptability, a deductive approach using the Theoretical Framework of Acceptability (TFA) was used (Sekhon et al., 2017). This framework defines acceptability as 'a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention'. The TFA has seven component constructs; affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs and self-efficacy. Each of the seven constructs are summarised

in Table 4.10. The TFA is used to consider acceptability from the perspective of the intervention deliverer and recipient either prospectively, concurrently and/or retrospectively. The ability of this framework to consider acceptability from multiple perspectives is a strength as it was important to consider views of clinicians and patients.

Table 4.10: The Theoretical Framework of Acceptability constructs and associated definitions (adapted from Sekhon et al., 2017)

Theoretical Framework of Acceptability constructs	**Construct definition**
Affective Attitude	How an individual feels about the intervention
Burden	The perceived amount of effort that is required to participate in the intervention
Ethicality	The extent to which the intervention has good fit with an individual's value system
Intervention Coherence	The extent to which the participant understands the intervention and how it works
Opportunity costs	The extent to which benefits, profits or values must be given up to engage in the intervention
Perceived Effectiveness	The extent to which the intervention is perceived as likely to achieve its purpose
Self-efficacy	The participant's confidence that they can perform the behaviour(s) required to participate in the intervention

4.10.3 Aims and Objectives

The aim of the qualitative component of the feasibility study was to explore acceptability of the study training, study protocol and intervention (MI-E as an airway clearance technique) for clinicians, patients and families (as appropriate).

The objectives were to carry out semi-structured interviews to investigate:

- The acceptability of the study training, study protocol and intervention for clinicians, patients and families (as appropriate)
- Potential barriers to conducting a full trial
- The choice of outcome measures
- Any issues with recruitment and intervention

4.10.4 Study design

Semi-structured qualitative interviews were completed with patients, families and clinicians to explore the acceptability of the intervention and enrolment in the trial. Initially, focus groups had been considered for this stage of work. However, previous doctoral work highlighted the potential negative impact of culture and hierarchy on the use of MI-E in the ICU setting. It was therefore considered that using a design such as focus groups may limit the richness of data generated if clinicians did not feel able to speak openly in front of colleagues. Furthermore, discussions with the PAG and SAG highlighted the sensitivity of topics to be discussed as they related to an individual patient or family's experience of a critical illness. One to one interviews were viewed as less challenging and prevented patients being placed in a position of vulnerability.

Patient and family interviews were completed by the doctoral fellow and took place within 4-6 weeks of ICU discharge (either with the patient remaining in hospital or when they had returned home). Interviews were also conducted with clinicians which included doctors,

nurses and physiotherapists. Interviews were completed by the doctoral fellow and occurred concurrently to the intervention trial but within a 4-week period of active trial involvement.

Interview topic guides (Appendix 20) were based on findings from previous work (Chapters 2 and 3) and the TFA (Sekhon et al., 2017) and were initially developed with input from the supervisory team. It was felt important to cover all TFA constructs in order to ensure a breadth of acceptability was gained.

Previous doctoral work illustrated the impact of clinician confidence on MI-E use in this specific patient group and variety in protocols used across studies. Topics included in the interview guide therefore focused on gaining insight into experiences of the protocol differences between the current study and previous relevant publications highlighted through the scoping review, for example MI-E prescription and outcomes measured (Chapter 2 and 3). PAG members reviewed the topics to be discussed and the wording of questions and prompts for the family interviews.

Pilot interviews were completed with the aim of checking the flow of questions and detail of answers gained, to include whether participants understood what was being asked. Participants for the pilot interviews included physiotherapists with experience of study involvement who had subsequently left the clinical team. Due to the time that had passed since trial involvement the clinicians were not eligible for participating in the interviews

making them ideal candidates to contribute to the pilot interviews. One specific change was made to the clinician interview guide which was the addition of a preliminary question where participants were asked to detail their role in the study. This was viewed as a non-threatening question and allowed the participant to settle into the interview. The study role information was then used to provide context for subsequent questions.

4.10.5 Sample and recruitment

Inclusion and exclusion criteria are described in Table 4.11.

Table 4.11: Interview study inclusion and exclusion criteria

	Inclusion criteria	**Exclusion criteria**
Clinician interviews	Clinicians (physiotherapist, nurse, doctor) working as a permanent staff member in the study ICU setting at the time of interview and active participation in the feasibility trial (defined as delivering the intervention of MI-E or standard care and/or involved in consent process and/or involved in care of patient)	Clinicians who had not worked on the study in the previous 4 weeks
Patient/family interviews	Patient deemed eligible and randomised to the intervention treatment arm of the study or a Consultee (of an eligible patient from the Intervention treatment arm) who had been approached for informed advice regarding patient inclusion in the trial	Non-English speaking or impaired understanding, limiting ability to participate in an interview. No recall of ICU stay or MI-E intervention

4.10.6 Sampling strategy

Participants were recruited from the three clinician groups (physiotherapy; nursing; doctors) and patients and family members. Purposive (theoretical) sampling of 10-15 participants was used to recruit to this study. Clinicians were selected based on factors relevant to achieving a maximal variation sample, for example a range of clinical experience and study roles to ensure all areas of acceptability could be considered. Patients and family members were approached based on their inclusion in the Intervention arm.

4.10.7 Recruitment

The doctoral fellow was responsible for advertising the interview study (Appendix 21) and following up with interested potential participants. Study advertising was directed towards the NHS Trust ICU clinicians and occurred through e-mail distribution and study posters. The doctoral fellows email address was provided with all study information materials. Additionally, the doctoral fellow contacted clinicians/patients/family if they had participated in the trial and approached them for inclusion into this part of the study. Once a clinician was deemed eligible, all study information (participant information sheet (Appendix 22) and consent form (Appendix 23)) was sent to them. Eligible patients were also sent all study information (patient participant information sheet (Appendix 24) and consent form (Appendix 23)).

Potential participants were given the opportunity for further clarification at the participants request via email and/or phone. If, at two weeks following study information being sent to

potential participants there had been no response a reminder email was sent. If a further two weeks passed, the participant was considered as not willing to be recruited into the study and no further contact was made.

Within the 4-week period of initial contact, if the participant confirmed they wanted to be included in the study the lead investigator arranged a date and time for an interview with the participant.

4.10.8 Consent

The doctoral fellow summarised the study information at the start of the interview, providing participants another opportunity to ask any outstanding questions. Participants provided verbal informed consent at the start of each interview.

4.10.9 Qualitative data collection and analysis

Clinician demographic data were recorded (profession and years working on ICU). Patient demographic data recorded included age, sex, duration of ICU LOS.

All interviews were completed virtually via an online platform (Microsoft Teams) and digitally recorded. All interview recordings were stored as audio files only. A University approved supplier transcribed interviews verbatim. The transcripts were checked for accuracy and pseudonymised. All interview transcripts were latterly uploaded into NVIVO software (NVivo 12 QSR International, Melbourne, Australia, 2018) which was used to support the analysis process.

The doctoral fellow initially went through a process of data familiarisation by reading and re-reading individual interview transcripts. Data were then analysed deductively using TFA domains through first level coding. Responses that were thematically similar were grouped in a process of data reduction and compared across transcripts for each participant group (physiotherapy, nursing and medical clinicians, patients and families) and then considered as a whole group. Time was taken to ascertain similarities and differences within and between participant groups. Tables were produced to highlight key thematic content within each TFA domain, supported by relevant participant quotes. Domains were identified as salient based on their frequency of inclusion and potential strength of impact across other domains. All analysis was completed by the doctoral fellow.

4.11 Withdrawal criteria and processes

A participant was free to withdraw from any element of the study at any time without providing a reason. This was from the date of verbal consent (at the time of interview) up to the point interviews were transcribed. Unless specifically stated by the individual, data collected up to that point were still used for analysis.

4.12 End of trial

Patient participant involvement in the trial ended at the six months follow up time period. Patient participants completing an interview would have done so within this follow up time period and so 'trial end' was not altered by their participation. If an interview was undertaken, clinician participant involvement ended following the interview. Data collection

for the whole study was deemed complete when the final randomised patient completed the six months follow up and all qualitative interviews were complete. The study ended once follow up had been completed, all data queries resolved, the database locked and data analysis complete. The sponsor was notified about the trial ending. An end of trial report was sent to the REC and copied to the sponsor for information, along with requested funder (NIHR) annual and end of study reports.

4.13 Data Management

4.13.1 Source data and documentation

Source data was the first place that data was recorded and was contained within source documents. Source data for this trial consisted of paper copies of consent form(s) (plus recorded verbal consent for qualitative interviews with patients and people with carer responsibilities), participants completed questionnaires (paper and/or electronic), paper CRFs designed specifically for the study, and audio-recordings of interviews. Where data were recorded first in the patient's medical records that remained the primary source data. Any specifically designed CRFs were considered supplementary source data.

4.13.2 Document identification

All participants were assigned a unique study ID at the point of being eligible for the study. Participants were identified in all study-related documentation by this study ID. A record of trial participants' and consultee names, contact details, hospital numbers and assigned trial numbers was retained by the doctoral fellow and stored securely for administrative

purposes. Personal data were entered directly into the password protected database and maintained on a Microsoft® SQL Server database system within the University of Bristol. This was only accessible to relevant members of the research team. Any data stored on laptops were encrypted.

Participants were informed via the participant/consultee information documents and consent forms that personal information such as name, email address and phone number would be stored on the secure database with the central trial team (study office, University of Bristol). Furthermore, for the purpose of conducting the trial randomisation only, participant information (unique study ID) was entered into the secure online randomisation system provided by Sealed Envelope™. All data entered on to the Sealed Envelope™ system was done so via secure sockets layer connections and stored on secure servers located in the UK and Ireland that complied with both UK and European Union (EU) regulations on data privacy. User-access to the system was managed by the central trial team (University of Bristol study office), who in turn generated password-protected user-accounts for authorised staff.

Data recorded on paper were entered onto the password protected database by the doctoral fellow. Information capable of identifying individuals and the nature of treatment received was held in the database with passwords restricted to trial staff. These data were not made available in any form to those outside the trial, with the exception of inspection purposes by the sponsor and/or other regulatory authorities. Consent forms and clinical

letters (and any other documentation) with personal identifiable data were stored in a locked filing cabinet (or locked equivalent).

All audio-recorded data were stored on OneDrive maintained by UWE. Audio-recordings were transcribed by an approved UWE University-approved transcription service. Audio-recordings and transcripts were labelled with a unique study ID, edited to ensure respondents were pseudonymised (only participant type (clinician profession, patient or relative documented)), and stored securely adhering to the UWE data storage policies.

Participants were asked to provide consent for quotations and parts of voice-modified recordings to be used for training, teaching, research and publication purposes for the feasibility trial and future studies. At the end of the study, anonymised data (including transcripts of audio-recordings) were stored in a secure research data storage facility, alongside the other study data; see sections 4.13.4.

4.13.3 Data handling and record keeping

The database and randomisation system were designed to protect patient information in line with the General Data Protection Regulation Act (2018). Study staff ensured that the participants' anonymity was maintained through protective and secure handling and storage of patient information at the study site in line with the Ethics approval. All documents were stored securely and only accessible by study staff and authorised personnel. Data were collected and retained in accordance with General Data Protection Regulation.

Data were recorded directly into CRFs and questionnaires (paper and/or online), and where applicable, were entered into a trial specific database by the doctoral fellow. When applicable a random sample of 10% of CRFs were checked, by the doctoral fellow against entries within the database and with the source data for quality purposes. If a significant error rate had been found, the percentage checked would have increased.

The online questionnaires were completed via the REDCap database system (see below for REDCap details), which was securely accessed via the internet. All administrative and clinical study data were stored in a REDCap database. REDCap is a secure, web-based electronic data capture system designed for the collection of research data. The system has been developed and supported by Vanderbilt University. The Bristol Trials Centre (BTC), has set up its own infrastructure so that all systems are hosted at and supported by University of Bristol.

The study specific online CRF (hosted on REDCap) was developed in preparation for the study with a BTC Research Projects Manager. All planned data fields (Table 4.6) were initially collated into an excel spreadsheet. Additional detail included names of variables, units and timepoints of measurements and how the data would be presented, for example as a number value, a dropdown box or as a tick box selection. Additional information for the research projects manager was also detailed which included any rules and question/answer logic within the CRF. This information was transcribed into REDCap to develop the CRF. A clinical validation plan (appendix 25) was completed to establish CRF capability and ease of

use. The final CRF was subsequently tested on different electronic devices including a laptop, tablet and smart phone to ensure accurate formatting.

4.13.4 Archiving

An archiving plan was developed for all trial materials. Data were held in compliance with the Sponsor's SOPs. Study documents (paper and electronic) were retained in a secure location during and after the study finished. All essential documents, including patient records and other source documents will be retained for a period of 5 years following the end of the study. As per study site processes, all hard copy medical records were uploaded onto an electronic patient database and paper records destroyed. Where electronic records were used, the study site Trust policy was followed.

4.14 Monitoring, audit and inspection

This study was conducted in accordance with the principles of GCP, as set out in the International Conference for Harmonisation of Good Clinical Practice guidelines (Dixon, 1998) and The UK Policy Framework for Health and Social Care Research (Health Research Authority, 2023).

The study was monitored in accordance with the sponsors SOPs. All study related documents were made available on request for monitoring and audit by the study sponsor, the relevant REC and for any other regulatory authorities.

4.15 Ethical and regulatory considerations

4.15.1 Research Ethics Committee review & reports

The study was performed following authorisation from all necessary regulatory bodies. Table 4.11 illustrates study specific authorisations and registrations with associated dates of confirmation. Approval was obtained prior to the start of the study. If any substantial amendments had been required, review by the REC would have occurred and changes implemented only once the REC granted a favourable opinion for the trial.

Confirmation was obtained from Medicines and Healthcare Products Regulatory Agency and agreed by the study sponsor (dated 17/2/22) regarding the classification of the study (E/2021/3947). Notification to the Medicines and Healthcare Products Regulatory Agency was not required for the study as the MI-E device was confirmed as being CE marked for the purpose under investigation.

It was the responsibility of the doctoral fellow to produce annual reports for the REC as required. The doctoral fellow also notified the REC of the end of the trial. If the trial had ended prematurely, the doctoral fellow would have notified the REC, including reasons for the premature termination. Within one year after the end of the trial, the doctoral fellow will submit a final report with the results, including any associated publications/abstracts, to the REC and study sponsor. All correspondence with the REC is retained in the TMF and archived as per sponsor policy.

Table 4.12: Study specific regulatory authorisations and registrations

Regulatory body	Reference and (date of authorisation)
Study sponsor	DT/2020/7038 (1/2/22)
IRAS	Project ID: 303674
REC	22/YH/0042 (11/4/22)
HRA and Health and Care Research Wales (HCRW)	(11/4/22)
Capacity and capability and green light to commence recruitment from sponsor	(27/5/22)
UWE Faculty of Health and Applied Sciences Ethics Committee	HAS.22.06.123 (24/6/22)
CPMS ID	52178
ISRCTN ID	24603037

4.15.2 Peer review

The proposal for this trial was peer-reviewed through the NIHR peer-review process, which includes independent expert and lay reviewers. The PAG was actively involved in the development of the protocol. Their involvement continued during the design and development of trial-specific patient information resources, consent documentation, topic guides for interviews and methods for enhancing recruitment and follow-up rates.

The PAG were consulted during the data analysis phases of the study. Findings were presented in lay terms at PAG meetings. The group's interpretation of the findings was considered to ensure the patient voice was evident throughout. Copies of study manuscripts that had been accepted for publication were also distributed to the PAG for member led discussion at PAG meetings. The PAG were also consulted in relation to lay dissemination routes and the best format for this communication.

The PAG met on six occasions over the course of the protocol development and trial delivery to advise the doctoral fellow. PAG members had their travel expenses and meeting time reimbursed either with vouchers or a meeting payment based on INVOLVE guidance.

4.15.3 Protocol compliance

All staff involved in the study were GCP trained so the risk of any breaches to the study protocol were minimal. In the event of deviation or breach, it was planned that all activities were recorded and reported to the sponsor and required corrective/preventative actions taken. The Sponsor would make an informed decision whether the deviation/breach required further reporting to the REC.

4.15.4 Indemnity

This was an NHS-sponsored research study. In the situation of negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity would cover NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and was unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may have been considered in the case of a claim arising.

The following Chapter reports the results of the feasibility study.

Chapter 5

A feasibility study examining the use of Mechanical Insufflation-Exsufflation to promote extubation success in adult ICU: Results

This chapter describes findings from the feasibility study reported in Chapter 4. The main focus is the pre-determined feasibility outcomes but includes presentation of the exploratory clinical findings. Results are presented in two main sections; section one relates to the quantitative data and section two presents the findings from the qualitative investigation. The chapter concludes with a discussion of the findings, where quantitative and qualitative findings are considered separately and then together, within the context of determining feasibility. Implications and recommendations for future research are also considered.

5.1 Quantitative results of the feasibility intervention study

5.1.1 Sample

Patients were recruited between 11th July 2022 and 10th July 2023 (inclusive) with follow up completed in January 2024. Patient flow through the trial is illustrated in the CONSORT diagram (Figure 5.1).

A total of 1017 patients were screened during the recruitment period. There were 115 participants assessed further for eligibility, with 56 (49%) deemed eligible to participate. The

most common reasons for participant exclusion (n=59) were contraindications to the use of MI-E (n=26) and expected survival less than 48 hours at the time of assessment (n=21) (Table 5.1). Nine eligible patients were not consented due to the consent window being missed (n=6) or they were recruited to another research study which did not have a co-enrolment agreement in place (n=3).

In total 47 participants (84% of those eligible; 41% of those assessed for eligibility) were consented. All participants were initially consented using a professional consultee, with one personal consultee also providing consent. Ten participants provided informed consent once capacity was regained. Participants were randomised to either the MI-E Intervention arm (n=22) or Standard Care arm (n=25) (Figure 5.1). Most participants were male (35/47, 76%) with a participant median [interquartile range (IQR)] age of 61 [52-70] years. The mean (SD) APACHE II score at the time of recruitment was 19 (7). The most common reasons for intubation were cardiac arrest (n=18, 38%) and post-operative respiratory failure (n=11, 23%). At the time of study enrolment, all participants were ventilated via an endotracheal tube (ETT) with CPAP as the most common mode of ventilation (n=24, 51%). Detailed demographic and baseline participant data are provided in Table 5.2.

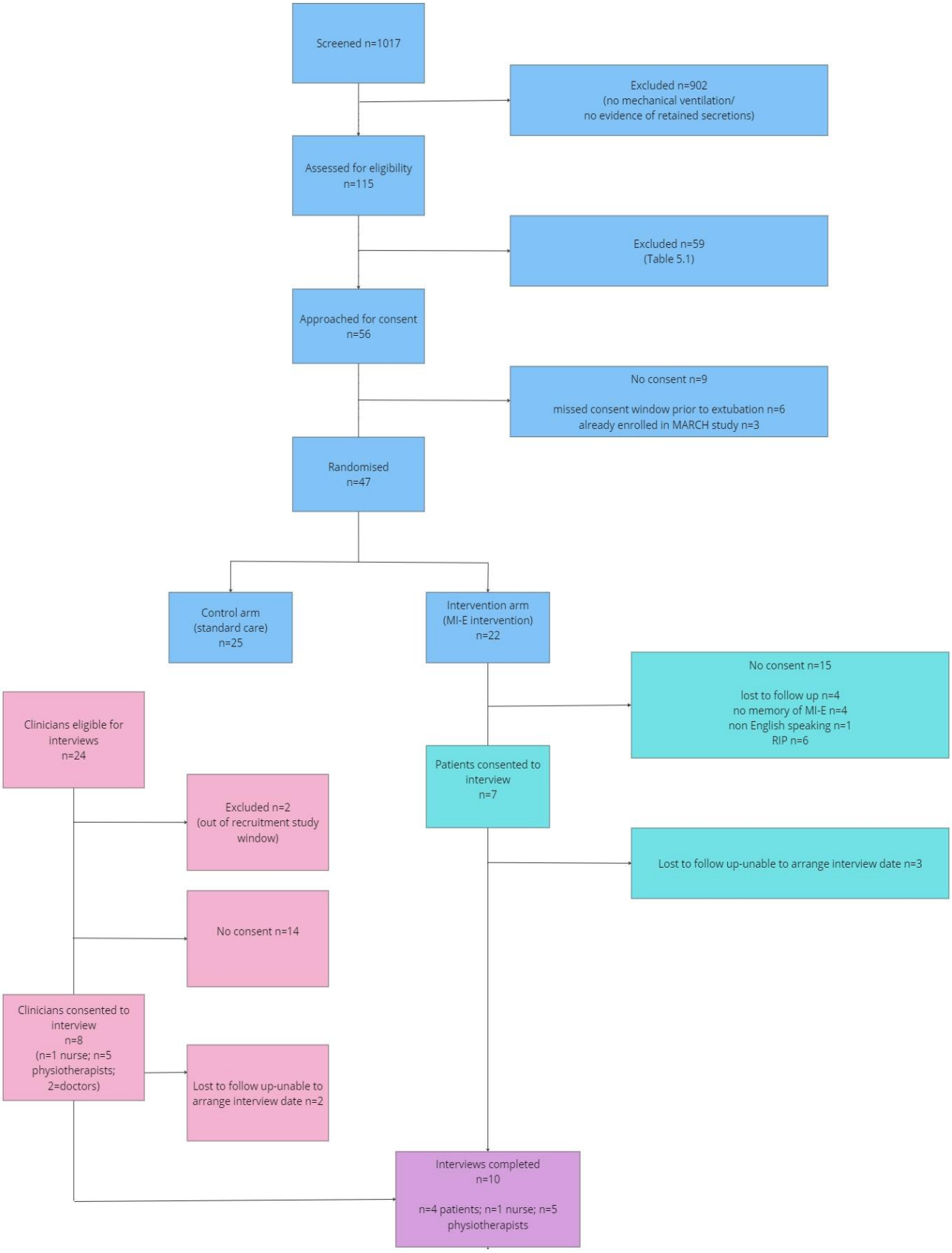

Figure 5.1: CONSORT diagram

Abbreviations: MI-E, mechanical insufflation-exsufflation; n, number of; RIP, patient death

Table 5.1 Reasons for participant exclusion at screening

Exclusion criteria	Number (%) of participants with reported exclusion criteria
Contraindications to MI-E use:	26 (44)
Not specified	7 (12)
Perforated oesophagus	4 (7)
Complex upper airway anatomy	3 (5)
Post cardiac surgery	2 (3)
Complex cancer (mediastinal, throat and larynx)	2 (3)
Extensive bullae/emphysematous changes	2 (3)
Severe bronchospasm	2 (3)
Unexplained stridor	1(2)
Tracheal injury	1 (2)
Multiple rib fractures with flail segments	1 (2)
Trachea-oesophageal fistula	1 (2)
Expected survival less than 48 hours	21 (36)
CVS/haemodynamic instability	12 (20)
PEEP >10cmH_2O	9 (15)
Neuromuscular condition	6 (10)
Recent undrained pneumothorax	3 (5)
FiO_2 > 0.7	2 (3)
Pre-existing MI-E routine use in community	2 (3)
Previous study participation	2 (3)
Pre-existing permanent tracheostomy	2 (3)
Readmission to ICU	1 (2)

Results are presented as frequency of occurrence n (%) for each exclusion criteria. Clinicians were able to record multiple exclusion criteria; therefore, the total percentage exceeds 100% (86 responses from 59 excluded participants).

Abbreviations: CVS, cardiovascular system; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; MI-E, mechanical insufflation-exsufflation; PEEP, positive end expiratory pressure

Table 5.2 Participant demographic and baseline data

Characteristic	**Overall** (n=47)	**Intervention** (n=22)	**Control** (n=25)
Age (years) (median[IQR])	61 [52-70]	58 [52-74]	62 [52-67]
Sex			
Female	11 (23)	4 (18)	7 (28)
Male	35 (74)	18 (82)	17 (68)
Missing	1(2)	0	1(4)
Weight (kg) (median[IQR])	80 [68-90]	79 [68-92]	80 [68-90]
History of chronic lung disease			
Yes	13 (28)	6 (27)	7 (28)
COPD	8 (17)	2 (9)	6 (24)
Asthma	4 (9)	3 (14)	1 (4)
Bronchiectasis	1 (2)	1 (5)	0 (0)
Smoker			
Yes	17 (40%)	7 (32%)	10 (40%)
Missing	4	3(14%)	1(4%)
APACHE II score (mean ±SD)	19 (7)	19.1 (6.2)	19.7 (7.1)
Missing	8	-	-
Time from hospital admission to intubation (days) (median[IQR])	0 [0-1]	0 [0-1]	0 [0-1]
Reason for intubation			
COPD exacerbation	3 (6)	1 (5)	2 (8)
Post-operative respiratory failure	11 (23)	7 (32)	4 (16)
Acute lung injury	1 (2)	1 (5)	0 (0)
Thoracic trauma	1 (2)	1 (5)	0 (0)
Sepsis	4 (9)	2 (9)	2 (8)
Cardiac arrest	18 (38)	9 (41)	9 (36)
Other	9 (19)	1 (5)	8 (32)
Other (n=9):			
Bronchiectasis exacerbation	1 (2)	1 (5)	0 (0)
Overdose-intubated for safety	2 (4)	0 (0)	2 (8)
Acute pancreatitis with delirium/confusion	1 (2)	0 (0)	1 (4)
Post seizure neuroprotection/airway management	2 (4)	0 (0)	2 (8)
Reduced GCS (unknown cause)	3 (6)	0 (0)	3 (12)
Ventilator settings (split by mode of ventilation)			
CPAP/PS	24 (51%)	12 (55%)	12 (48%)
CPAP (cmH_2O) (median[IQR])	9.1 [8-10]	9.1 [8-10]	9 [8-10]
PS (cmH_2O) (n=23)	0 [0-5]	4 [0-5]	0 [0-2.5]
FiO_2	0.3 [0.25-0.35]	0.3 [0.25-0.35]	0.3 [0.25-0.35]

Characteristic	Overall (n=47)	Intervention (n=22)	Control (n=25)
SIMV	20 (43%)	12 (55%)	12 (48%)
Set volume (ml) (median[IQR])	425 [400-450]	430 [400-450]	420 [360-460]
Achieved volume (ml)	441.5 [408.5-490.5]	453 [420-480]	428 [360-567]
PEEP (cmH_2O)	8 [5.5-10]	8 [6-10]	8 [5-10]
FiO_2	0.3 [0.21-0.35]	0.3 [0.25-0.35]	0.3 [0.21-0.4]
ASB/PS (cmH_2O)	0 [0-0]	0 [0-0]	0 [0-0]
APRV	3 (6%)	1 (5%)	2 (8%)
Phigh (cmH_2O) (median[IQR])	20 [16-25]	25 [25-25]	18 [16-20]
Plow (cmH_2O)	0 [0-10]	0 [0-0]	5 [0-10]
Thigh (seconds)	6 [5-7]	6 [6-6]	6 [5-7]
Tlow (seconds)	0 [0-0.5]	0 [0-0]	0.25 [0-0.5]
FiO_2	0.35 [0.3-0.35]	0.35 [0.35-0.35]	0.3 [0.3-0.35]

n=47 unless otherwise missing data points stated. Data presented as n (%) unless otherwise indicated

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation Score; APRV, Airway Pressure Release Ventilation; COPD, Chronic Obstructive Pulmonary Disease; CPAP, Continuous Positive Airway Pressure; ETT, endotracheal tube; FiO_2, fraction of inspired oxygen; IQR, interquartile range; P, pressure; PEEP, positive end expiratory pressure; PS, pressure support; SD, standard deviation; SIMV, Synchronised Intermittent Mandatory Ventilation; T, time; TT, tracheostomy tube.

5.1.2 Intervention arm-device set up

There were 138 MI-E treatment sessions recorded in the MI-E intervention arm. MI-E device set up is described in Table 5.3. Settings are described as an overall cohort, when intubated and once extubated.

The MI-E device was most frequently used in manual mode (83%), with a median [IQR] insufflation pressure of 28 [25 to 30]cmH_2O and median [IQR] exsufflation pressure of -35 [-40 to -30]cmH_2O. Oxygen was entrained through the MI-E device in less than half of cases (46/135, 34%), with a median [IQR] FiO_2 of 0.36 [0.3-0.45] prescribed. Across all MI-E treatment sessions, a median [IQR] of 3 [2-5] MI-E cycles were completed and repeated

across 2 [1-5] sets within one treatment session. MI-E settings were titrated during treatment sessions in 29 (22%) of treatment sessions.

When pre-programmed modes ('basic auto' and 'programmed auto') were used the median [IQR] insufflation and exsufflation times were recorded as 1.8 [1.7-2.0] and 1.8 [1.5-2.0] seconds respectively, with a median [IQR] pause time of 8 [6-8] seconds. Stepped insufflations and re-recruitment breaths were not used by clinicians within the pre-programmed MI-E device prescriptions (Table 5.3).

Physiotherapy treatments occurring alongside the MI-E intervention are presented in Table 5.4. Patient positioning, suctioning (with and without saline), manual techniques and mobilisation were the most frequently reported. Mobilisation activities specified by clinicians included physical mobilisation, transfers from bed to chair, sit to stand practice and sitting on the edge of the bed. When separating treatment sessions by those completed when patients were intubated versus extubated, positioning, suctioning with and without saline and manual techniques were mostly used in the intubated group in conjunction with MI-E. A greater number of mobilisation sessions were used alongside MI-E in the extubated group.

5.1.3 Standard care

There were 134 physiotherapy treatment sessions within the standard care arm across the 25 participants. The most frequent physiotherapy treatments used in the standard care arm

were positioning, suctioning (with and without saline), manual techniques and mobilisation (Table 5.4). Types of mobilisation reported by clinicians (via the CRF) was similar to the intervention group and included physical mobilisation, transfers from bed to chair and sit to stand practice with the addition of orientation work, passive range of movement and dressing practice.

In the intubated standard care group, manual hyperinflation and ventilator hyperinflation were used more frequently in comparison to the MI-E treatment arm. Mobilisation frequency was similar across the intubated and extubated groups within standard care. There was one episode of MI-E being used against protocol in the standard care arm.

Table 5.3 MI-E device set up and prescription (intervention arm)

Device setting	**MI-E prescription** (overall cohort)	**Missing data points***	**MI-E prescription** (intubated)	**MI-E prescription** (extubated)
MI-E interface				
ETT	72 (53)	3	NA	NA
TT	29 (21)			
Face mask	30 (22)			
Mouthpiece	4 (3)			
MI-E mode				
Manual	111 (83)	4	93 (92)	18 (55)
Basic auto	4 (3)		1 (1)	3 (9)
Programmed auto	19 (14)		7 (7)	12 (36)
Insufflation pressure (cmH_2O)	28 [25-30]	4	28 [25-30]	25 [25-30]
Insufflation rise	5 [3-5]	27	5 [3-5]	5 [5-5]
Oscillation				
Yes	1 (1)	4	1 (1)	0
No	133 (99)		100 (99)	33 (100)
O_2 entrainment				
Yes	46 (34)	3	39 (39)	7 (21)
No	89 (66)		62 (61)	27 (79)
FiO_2	0.36 [0.30-0.45]	1	0.38 [0.3-0.45]	0.28 [0-0.5]
Exsufflation pressure (cmH_2O)	-35 [-40, -30]	4	-35 [-40, -30]	-35 [-40, -30]
Insufflation time (seconds) **	1.8 [1.7-2.0]	0	1.9 [1.8-2.1]	1.8 [1.5-2.0]
Stepped insufflation ***				
Yes	0	0	0	0
No	19 (100)		7 (100)	12 (100)
Insufflation repeat ***	4 [4-5]	0	4 [4-5]	5 [4-6]
Exsufflation time **	1.8 [1.5-2.0]	0	1.8 [1.2-1.9]	1.5 [1.5-2.0]

Device setting	MI-E prescription (overall cohort)	Missing data points	MI-E prescription (intubated)	MI-E prescription (extubated)
Pause **	8 [6-8]	0	7 [3-8]	8 [6-8]
Flow **	4 [3-5]	0	5 [4-5]	4 [3-5]
Trigger **	3 [2-5]	0	3 [3-4]	3 [2-5]
Recruitment breaths **	0 [0-3]	0	2 [0-4]	0 [0-0]
Number of cycles	3 [2-5]	3	4 [2-6]	2 [1-5]
Number of sets	2 [1-5]	3	2 [1-5]	2 [1-4]
Titration of MI-E setting during session *Yes*	29 (22)	6	21 (22)	7 (23)

*from 138 MI-E treatment sessions. **setting relevant to automatic modes only. *** setting relevant to 'programmed auto' mode only. Data is captured from 138 MI-E sessions. N values depict response size for each setting variable.

Abbreviations: ETT, endotracheal tube; FiO_2, fraction of inspired oxygen; IQR, interquartile range; MI-E, mechanical insufflation-exsufflation; N, number; NA, not applicable; TT, tracheostomy tube

Table 5.4 Physiotherapy treatment techniques used by treating physiotherapists in intervention and control arms of study

Treatment Techniques	Intervention arm (n=22)			Control arm (n=25)			
	All (138 treatment sessions)	**Intubated**	**Extubated**	**All** (134 treatment sessions)	**Intubated**	**Extubated**	**Point estimate (CI)**
Positioning	85 (62%)	63	22	75(56%)	51	24	1.1 (0.9-1.3)
Suctioning+/-saline	31(22%)	28	3	54(40%)	50	4	0.6 (0.4-0.8)
Manual techniques	25 (18%)	23	2	39(29%)	35	4	0.6 (0.4-1.0)
Mobilisation	20(14%)	9	11	31(23%)	13	18	0.6 (0.4-1.0)
MHI	2 (1%)	2	0	11(8%)	11	0	0.2 (0.04-0.8)
VHI	3 (2%)	3	0	10(7%)	10	0	0.3 (0.1-1.0))
Recruitment manoeuvre	7 (5%)	7	0	0	0	0	14.6 (0.8-252.6)
IPPB	0 (0%)	0	0	1(1%)	0	1	0.3 (0.01-7.9)
Other	13(10%)	11	2	21(16%)	2	19	0.6 (0.3-1.2)
ACBT	*2 (1%)*	0	2	*3(2%)*	0	3	
Coughing	*0(0%)*	0	0	*8(6%)*	0	8	
Deep breathing exercises	*0(0%)*	0	0	*4(3%)*	1	3	
*Use of non-invasive support**	*0(0%)*	0	0	*3(2%)*	NA	3	
O_2 titration	*1(1%)*	1	0	*2(1%)*	0	2	
PEEP increase	*1(1%)*	1	NA	*0(0%)*	0	0	
MAC	*1(1%)*	1	0	*0(0%)*	0	0	
TT weaning	*0(0%)*	0	0	*1(1%)*	1	0	
ETT shortening	*1(1%)*	1	0	*0(0%)*	0	0	
Nil other treatment specified	*5(4%)*	5	0	*0(0%)*	0	0	
Unable to use MI-E	*2(1%)*	2	0	*NA*	NA	NA	
MI-E	*NA*	NA	NA	*1(1%)*	0	1**	

Results are presented as frequency of occurrence n (%) for each treatment technique across treatment sessions in either the intervention arm (138 treatment sessions) or standard care arm (134 treatment sessions). Clinicians were able to record multiple treatment technique for each session; therefore, the total percentage exceeds 100%.

*to include use of CPAP and NIV **MI-E used against protocol

Abbreviations: ACBT, active cycle of breathing technique; CI, confidence interval; ETT, endotracheal tube; IPPB, intermittent positive pressure ventilation; MAC, manual assisted cough; MI-E, mechanical insufflation-exsufflation; MHI, manual hyperinflation; NA, not applicable; O_2, oxygen; PEEP, positive end expiratory pressure; TT, tracheostomy tube; VHI, ventilator hyperinflation

5.1.4 Physiological parameters

Physiological parameters for cardiovascular, respiratory and pain responses to physiotherapy treatment sessions for both the intervention and control arm are reported in Tables 5.5, 5.6 and 5.7 respectively.

Complete data were obtained for all cardiovascular parameters, heart rate (HR), systolic and diastolic blood pressure (SBP and DBP) (Table 5.5). There were minimal changes reported from baseline to 5 minutes post intervention for all cardiovascular measurements.

Respiratory parameters included respiratory rate (RR), peripheral oxygen saturations (SpO_2), compliance, resistance and the LUS (Table 5.6). Only RR and SpO_2 had complete data. Both compliance and resistance had 30% missing data points. The LUS was poorly completed with only nine complete datasets recorded across both treatment arms, equating to over 75% missing data points.

The CPOT was the most commonly used pain score with complete data for all participants included in the analysis. Only 12 and 15 complete pain NRS datasets were recorded for the intervention and control arms respectively. Pain scores were generally recorded as being absent or mild (Table 5.7). Results suggest that pain was not impacted by physiotherapy intervention across either treatment arms when using both the CPOT and a pain NRS (point estimate (CI) 0.1(-0.23,0.43) and 0.2(-0.31,0.71) respectively.

Table 5.5: Cardiovascular parameter changes during and after physiotherapy interventions (intervention and control arm)

	Intervention (n=22)			**Control** (n=25)			
Clinical outcome	**Baseline**	**5 mins post**	**Change from baseline**	**Baseline**	**5 mins post**	**Change from baseline**	**Point estimate (CI)**
HR (bpm)	82.7 (11.9)	82.9 (11.8)	0.26 (3.68)	83.8 (14.6)	86.3 (15.1)	2.34 (4.10)	-2.09 (-4.39-0.22)
Systolic BP (mmHg)	128.5 (16.2)	130.8 (16.4)	2.22 (5.8)	125.7 (16.4)	127.0 (15.7)	1.01 (7.16)	1.20 (-2.66-5.07)
Diastolic BP (mmHg)	60.6 (8.4)	65.3 (11.3)	4.67 (7.28)	66.4 (28.7)	63.92 (8.4)	-2.20 (4.79)	6.87 (3.29-10.45)

Data is expressed as mean(±SD).

Abbreviations: bpm, beats per minute; BP, blood pressure; CI, confidence interval; HR, heart rate.

Table 5.6: Respiratory parameter changes during physiotherapy interventions (intervention and control arm)

	Intervention (n=22)			**Control** (n=25)			
Clinical outcome	**Baseline**	**5 mins post**	**Change from baseline**	**Baseline**	**5 mins post**	**Change from baseline**	**Point estimate (CI)**
Respiratory rate (breaths/min)	22.1 (4.7)	22.4 (3.9)	0.23 (2.24)	22.3 (4.5)	23.7 (4.9)	1.33 (2.47)	-1.10 (-2.49, 0.29)
SpO_2 (%)	91.5 (5.94)	94.3 (3.33)	2.94 (5.54)	93.2 (4.68)	93.9 (4.57)	0.69 (1.59)	2.25 (-0.08, 4.58)
Compliance*	28.5 (29.3) (n=18)	23.4 (25.6) (n=18)	-3.6 (8.5) (n=16)	18.7 (25.7) (n=16)	17.8 (23.8) (n=16)	0.04 (9.9) (n=14)	-3.64 (-9.10, 1.82)
Resistance*	8.5 (17.7) (n=18)	4.0 (4.4) (n=18)	-4.3 (16.1) (n=16)	11.0 (18.4) (n=17)	5.7 (9.7) (n=15)	-0.1 (0.9) (n=15)	-4.2 (-12.7, 4.3)
LUS	17.1 (6.56) (n=7)	15.1 (7.05) (n=6)	-1.6 (2.6) (n=5)	15.2 (5.26) (n=5)	14.0 (5.72) (n=5)	-0.5 (1.0) (n=4)	-1.1 (-4.4, 2.2)

*Data is expressed as mean(±SD). Dataset complete (n=22 intervention arm; n=25 control arm) unless otherwise stated. *intubated cohort only*

Abbreviations: CI, confidence interval; LUS, lung ultrasound score; SpO_2, peripheral oxygen saturations

Table 5.7 Pain parameter changes during physiotherapy interventions (intervention and control arm)

	Intervention (n=22)			**Control** (n=25)			
Clinical outcome	**Baseline**	**5 mins post**	**Change from baseline**	**Baseline**	**5 mins post**	**Change from baseline**	**Point estimate (CI)**
CPOT overall cohort	0.90 (0.84)	0.81 (0.87)	-0.10 (0.61)	1.07 (0.94)	0.83 (0.84)	-0.20 (0.51)	0.10 (-0.23, 0.43)
CPOT intubated cohort	0.74 (0.88)	0.74 (0.92)	-0.002 (0.60)	1.12 (1.20)	0.76 (0.94)	-0.32 (0.94)	0.32 (-0.15, 0.79)
CPOT extubated cohort	1.21 (1.73)	0.89 (1.09)	-0.34 (1.58)	0.83 (1.07)	0.68 (0.99)	-0.14 (0.60)	-0.20 (-0.89, 0.49)
NRS	1.69 (2.90) (n=13)	1.28 (2.60) (n=16)	-0.17 (0.33) (n=12)	1.90 (2.25) (n=15)	1.40 (1.77) (n=16)	-0.37 (0.83) (n=15)	0.20 (-0.31, 0.71)

Data is expressed as mean(SD). Dataset complete (n=22 intervention arm; n=25 control arm) unless otherwise stated.

Abbreviations: CI, confidence interval; CPOT, critical care pain assessment tool; NRS, numeric rating scale of pain.

5.1.5 Adverse events

There was a total of 27 adverse events (20 in the intervention arm) recorded during the study period as illustrated in Table 5.8. The most common adverse event was a change in blood pressure (hypertension), with a greater frequency of occurrence in the intervention arm in comparison to the control arm (13 v 4 respectively). In all cases clinicians paused physiotherapy treatment to allow blood pressure to reduce before re-commencing treatment. In no case was medical intervention required. As a result, none of these adverse events were subsequently reported as SAEs as per study protocol. There were no events in terms of arrythmias, pneumothorax, accidental extubation or cardiopulmonary arrest during physiotherapy treatment sessions in either treatment arm.

There was one SAE (pneumothorax) reported to the study sponsor involving a patient in the intervention arm. This occurred outside of a physiotherapy treatment session. Following review, the SAE was considered possibly related. Other potentially related factors included the use of positive pressure ventilation, the use of manual hyperinflation during a physiotherapy treatment session and the patient coughing spontaneously on the ventilator during a sedation hold.

Table 5.8 Frequency of adverse events recorded during physiotherapy treatment sessions for the intervention and control treatment arms

Adverse events	**Intervention**	Intervention (Intubated)	Intervention (Extubated)	**Control***
HR/SBP/DBP increase/decrease >20% from baseline	13	12	1	4
Arrhythmia (requiring intervention)	0	0	0	0
pneumothorax	0	0	0	0
acute desaturation to < 85% or >10% below baseline	3	3	0	1
accidental extubation	0	0	0	0
cardiopulmonary arrest	0	0	0	0
Other	4	2	2	2
"Increased RR and restlessness"	*1*	*1*	*0*	*1*
"Patient bit and occluded ETT"	*1*	*1*	*0*	*0*
"Vomited post MI-E use"	*1*	*0*	*1*	*0*
"agitation"	*1*	*0*	*1*	*0*
"Vomit and attempted self-extubation"	*0*	*0*	*0*	*1*

*all adverse events in control arm occurred in the intubated population.

Abbreviations: DBP, diastolic blood pressure; ETT, endotracheal tube; SBP, systolic blood pressure; HR, heart rate; MI-E, mechanical insufflation-exsufflation; RR, respiratory rate

5.1.6 Resource Use

Resource use is illustrated in Table 5.9. For the resources of physiotherapy session duration, number and grade of clinicians, use of new circuit and/or interface antibiotic (respiratory) use there were three missing data points per measure. Suction frequency and use of on-call physiotherapy each had one missing data point. A complete dataset was documented for use of NIV, tracheostomy and high flow nasal cannula (HFNC) (n=47).

The median duration (minutes) of physiotherapy treatment sessions was longer in the MI-E intervention arm in comparison to the control arm (30 [20-40] v 20 [15-30], (median [IQR]),

point estimate (CI) 10(7-13). The median [IQR] number of clinicians involved in the physiotherapy sessions was the same across treatment arms, 1 [1-2] with a variety of staff bandings involved. A greater proportion of new device circuits and device interfaces were used in the MI-E treatment arm in comparison to the standard care arm, equating to 16 (12%) of the 136 MI-E treatment sessions. Antibiotics use (respiratory) was similar across treatment arms (relative risk (CI) 1.0(0.8-1.3)) being administered to over half of the participants in both arms. Suction frequency over each 24-hour period was similar across the study arms with a median [IQR] of 22 [10-30] suctions in the intervention arm and 22 [12-31] suctions completed per 24 hours in the control arm. There was a greater proportion of patients given NIV and HFNC in the control arm in comparison to the intervention arm. Generally, there were a low number of patients requiring tracheostomy in the intervention and control arm (4/22 (18%) and 3/25 (12%) respectively). Across all participants there was only one reported use of on-call physiotherapy, this was in the control arm.

5.1.7 Patient outcomes

Patient outcomes are illustrated in Table 5.10. Complete data were recorded for duration of IMV, re-intubation rates and mortality. Five missing data points were present for ICU LOS and ICU re-admission. The duration of IMV and ICU LOS was longer in the intervention arm reported as a mean (±SD) of 16 (15.9) days v 13 (7.6) days in the control arm (point estimate (CI) 2(-1,5) and 3(-4,10) respectively). Re-intubation rates were low but occurred with greater frequency in the control arm (3 (12%)) versus the intervention arm (1 (5%)) (relative risk (CI) 0.4(0.04-3.38). There was one ICU re-admission reported which occurred in the

control arm (relative risk (CI) 0.33 (0.01-7.76). The 60-day mortality rate was 27% and 20% in the intervention and control arms respectively (Table 5.10).

Table 5.9: Resource use during physiotherapy sessions and for each 24-hour period of data collection (per participant)

Resource	Intervention arm (22 participants/138 treatment sessions)	Control arm (25 participants/134 treatment sessions)	Point estimate (CI)
Physiotherapy session duration (mins) (median[IQR])	30 [20-40]	20 [15-30]	10 (7-13)
Number of clinicians involved in physiotherapy session (median[IQR])	1 [1-2]	1 [1-2]	0 (0-0)
Grade of physiotherapist (count (%))			
5	6 (4)	4 (3)	0.8 (0.5-1.3)*
6	65 (47)	53 (40)	
7	42 (30)	50 (37)	
8a	22 (16)	20 (15)	
Missing	3 sessions	7 sessions	
New equipment circuit used during physiotherapy session (count (%))			
Yes	16 (12)	1 (1)	1.0(0.2-6.3)**
NA	20 (14)	120 (90)	
Missing	3 sessions	7 sessions	
New equipment interface used during physiotherapy session (count (%))			
Yes	21 (15)	0	40.5 (2.5-661.2)**
Missing	3 sessions	7sessions	
Antibiotics (respiratory) in use per 24-hour period of data collection (count (%))			
Yes	78 (57)	74 (55)	1.0 (0.8-1.3) **
Missing	3 24-hour periods	11 24-hour period	

Resource	Intervention arm (22 participants/138 treatment sessions)	Control arm (25 participants/134 treatment sessions)	Points estimate (CI)
Endotracheal Suction frequency per 24-hour period of data collection (median[IQR])	22 [10-30]	22 [12-31]	0 (-4.4, 4.4)
Use of on-call physiotherapy (count (%)) *No* *Planned* *Unplanned* Missing	 137 (99) 0 0 1(1) sessions	 127 (95) 1 (1) 0 7 (5) sessions	 0.3 (0.01, 7.6)
NIV use: Number of patients using NIV (count (%)) Hours of use per 24-hour period (for NIV users) (mean± (SD)	2/22(9) 1.4 (1.3)	5/25(20) 3 (3.6)	0.45 (0.1-2.1) -1.6 (-3.2, 0.03)
Tracheostomy use: Number of patients requiring tracheostomy (count (%))	4/22(18)	3/25(12)	1.5 (0.4-6.0)
HFNC use: Number of patients using HFNC (count (%)) Hours of use per 24-hour period (for HFNC users) (mean±SD)	15/22(68) 5.3(3.5)	18/25(72) 5.8(4.7)	0.95 (0.7, 1.4) -0.5 (-3.0, 2.0)

*Complete datasets obtained unless stated. Data presented as n(%) unless stated otherwise. *values presented as odds ratio(CI) or **relative risk based on yes/no answer (CI).*

Abbreviations: CI, confidence interval; HFNC, high flow nasal cannula; IQR, interquartile range; mins, minutes; NIV, non-invasive ventilation; SD, standard deviation

Table 5.10: Patient outcomes

Outcome	Intervention	Control	Missing data points	Points estimate (CI)
Duration of IMV (days) (n=47) (median[IQR])	7[5-9]	5[4-7]	0	2 (-1, 5)
ICU length of stay (days) (n=45) (mean ±SD)	16 (15.9)	13 (7.6)	2	3 (-4, 10)
ICU re-admission (n=44) Yes	0	1 (5)	3	0.33 (0.01-7.76)*
Died (n=47): Yes	6 (27)	5 (20)	0	1.4 (0.5-3.9)*
Re-intubation within 48hrs(n=47) Yes	1 (5)	3 (12)	0	0.4 (0.04-3.38)*

*Data presented as frequency count (proportion %) unless otherwise stated. *values presented as relative risk based on yes/no answer (CI).*

Abbreviations: CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range

5.1.8 Acceptability

Detailed results from the AIM, IAM and FIM are illustrated in Table 5.11. A near complete dataset was generated with less than 10% missing data points.

The majority of clinicians rated these measures as four or above illustrating positive acceptability, appropriateness and feasibility. MI-E was rated as acceptable by clinicians (scored as 4 or 5) in 93% of MI-E treatment sessions and deemed feasible in 91% of completed sessions. The IAM had a greater spread of results in comparison to the AIM and FIM, with 71% of MI-E sessions rated as appropriate by clinicians. Acceptability is considered further within the presentation of interview findings (section 5.2).

Table 5.11: Clinician rated MI-E acceptability

Outcome	Frequency (%) of responses	Missing datapoints*
Acceptability of Intervention Measure		
MI-E meets my approval (n=129):		9
Completely disagree	2 (2%)	
Disagree	6 (5%)	
Neither agree nor disagree	3 (2%)	
Agree	33 (26%)	
Completely agree	85 (66%)	
MI-E is appealing to me (n=129):		9
Completely disagree	1 (1%)	
Disagree	2 (2%)	
Neither agree nor disagree	5 (4%)	
Agree	34 (26%)	
Completely agree	87 (67%)	
I like MI-E (n=128):		10
Completely disagree	1 (1%)	
Disagree	0	
Neither agree nor disagree	7 (6%)	
Agree	34 (27%)	
Completely agree	86 (67%)	
I welcome MI-E (n=127):		11
Completely disagree	2 (2%)	
Disagree	0	
Neither agree nor disagree	6 (5%)	
Agree	31 (24%)	
Completely agree	88 (69%)	
Intervention of Appropriateness Measure		
MI-E seems fitting (n=130):		8
Completely disagree	14 (11%)	
Disagree	14 (11%)	
Neither agree nor disagree	9 (7%)	
Agree	30 (23%)	
Completely agree	63 (48%)	
MI-E seems suitable (n=129):		9
Completely disagree	15 (12%)	
Disagree	13 (10%)	
Neither agree nor disagree	10 (8%)	
Agree	30 (23%)	
Completely agree	61 (47%)	
MI-E seems applicable (n=130):		8
Completely disagree	14 (11%)	
Disagree	11 (8%)	
Neither agree nor disagree	10 (8%)	
Agree	31 (24%)	
Completely agree	64 (49%)	

Outcome	Frequency (%) of responses	Missing datapoints*
MI-E seems like a good match (n=130):		8
Completely disagree	16 (12%)	
Disagree	13 (10%)	
Neither agree nor disagree	11 (8%)	
Agree	27 (21%)	
Completely agree	63 (48%)	
Feasibility of Intervention Measure		
MI-E seems implementable (n=128):		10
Completely disagree	4 (3%)	
Disagree	3 (2%)	
Neither agree nor disagree	3 (2%)	
Agree	42 (33%)	
Completely agree	76 (59%)	
MI-E seems possible (n=129):		9
Completely disagree	4 (3%)	
Disagree	2 (2%)	
Neither agree nor disagree	4 (3%)	
Agree	41 (32%)	
Completely agree	78 (60%)	
MI-E seems doable (n=130):		8
Completely disagree	4 (3%)	
Disagree	2 (2%)	
Neither agree nor disagree	7 (5%)	
Agree	38 (29%)	
Completely agree	79 (61%)	
MI-E seems easy to use (n=130):		8
Completely disagree	4 (3%)	
Disagree	2 (2%)	
Neither agree nor disagree	7 (5%)	
Agree	35 (27%)	
Completely agree	82 (63%)	

*data from 138 MI-E treatment sessions

Abbreviations: MI-E, mechanical insufflation-exsufflation

5.1.9 Quality of life

Eleven participants (11/47 23%) completed and returned EQ-5D-5L questionnaires across both the intervention and control arms. All eleven questionnaires were returned via post. EQ-5D-5L results are illustrated in Table 5.12, with similar values across treatment arms.

Table 5.12: Quality of life results

Measure	**Intervention** (n=7) Median[IQR]	**Control** (n=4) Median[IQR]	**Point estimate (CI)**
EQ5D VAS	75 [40-90]	77.5 [62.5-87.5]	-2.5 (-59.6, 50.0)
EQ5D Index Value	0.81 [0.37-0.94]	0.91 [0.40-0.97]	-0.1 (-0.8, 0.6)

Abbreviations: VAS, visual analogue scale

5.1.10 Protocol fidelity

There was one episode of MI-E use in the control arm. On two occasions MI-E was not used in the intervention arm as it was deemed unsafe by the treating clinician. In the intervention arm, there were six episodes where the minimum number of treatment contacts was not completed. This was due to participants being transferred to a different hospital causing cessation of data collection (n= 4) or clinician error (n=2). Two patients in the intervention arm had data collected over a longer period of time than per protocol (11 and 13 days), both had tracheostomy tubes in situ.

Data collection and associated data completeness was poor for QOL (23% complete) and LUS (23% complete). For QOL specifically, no EQ-5D-5L responses were returned electronically.

5.2 Qualitative investigation results

5.2.1 Recruitment and Participant demographics

Where possible, all patients in the intervention arm were approached for interview (Figure 5.1). Six patients had died at the time of interview recruitment; four patients were uncontactable and five other patients were excluded due to no recall of MI-E use (n=4) or not being able to speak English (n=1). In total seven patients initially consented to

participate in the interviews but only four interviews took place as the remaining three participants could not be contacted following discharge from hospital.

Five family members were approached for consent for interview participation. Their roles during the feasibility trial included acting as a personal consultee for consent and being present during a physiotherapy treatment session that involved MI-E. Three of the five were excluded as they had no specific memory of MI-E and the remaining two family members did not consent due to ongoing carer burden (hands on caring commitments to the patient including attendance at multiple appointments).

All consultants who acted as a professional consultee were approached for inclusion into the interview study (n=7). One was not contactable during the recruitment timeframe due to a career break. Four consultants did not provide consent because they did not feel they had played a significant role in the study beyond the consent process. The remaining consultants (n=2) verbally consented to participation but it was not possible to arrange specific interview times due to clinical commitments. Five nurses were approached; four did not consent to interview participation as they did not feel they had sufficient knowledge to participate. There were twelve physiotherapists involved in the study all of whom were eligible for interview participation. Two physiotherapist clinicians were excluded as the recruitment window had passed and five did not consent to participate because they had only treated one or two patients in the trial.

A total of ten online interviews were conducted (4 patients; 1 nurse and 5 physiotherapists). For all patient participants this had been their first ICU admission with LOS ranging from 7 days through to 5 weeks in duration. Clinicians (Agenda for Change Band 6-8a) held static ICU, rotational or other senior respiratory posts with a median [IQR] of 10 [1-40] years of ICU experience (Table 5.13). Online interviews were 23.5 [16-48] median [IQR] minutes in duration, with no differences in duration between patients and healthcare professionals.

5.2.2 Codes

There were 242 codes generated from the interview transcripts covering all constructs of the TFA (Table 5.13).

Table 5.13 Frequency of interview codes assigned to TFA constructs

Theoretical Framework of Acceptability Construct	**Frequency**
Affective attitude	52
Burden	44
Perceived effectiveness	35
Ethicality	34
Intervention Coherence	32
Self-efficacy	24
Opportunity Costs	21

Findings are presented according to TFA constructs and frequency of their representation. For the purpose of this study and presentation of results, the term '*intervention*' within TFA construct definitions was viewed as synonymous with the terms '*study protocol'* and '*study training'* as the key factors being explored. Where appropriate, presentation of results was sub-divided to differentiate between acceptability of MI-E and acceptability of the trial and associated processes.

5.2.2.a Affective attitude

TFA Construct definition: '*how an individual feels about the intervention/protocol/training'*

This construct provided general information about participants opinion of the intervention, protocol and associated processes and as a result overlaps with other constructs.

MI-E acceptability

Patient participants described a range of opinions relating to MI-E which were influenced by previous experiences. Whilst they acknowledged that MI-E was beneficial, their experience of the actual treatment was often negative.

"I can remember, I think I said to them at the time I said oh yeah that was really weird, but I do remember feeling almost a bit better somehow" (Participant 1, patient).

Generally, MI-E was perceived as safe within the ICU population despite adverse events being recorded throughout the study. Adverse events involving episodes of cardiovascular instability were described. Clinicians did not appear concerned about these, viewing them as transient changes requiring a pause to treatment rather than treatment cessation. Clinicians also described situations where they needed to consider risks to staff and patient safety alongside potential clinical benefit from MI-E. Common examples included patients with delirium who may not respond to instructions to optimise an effective treatment session or where behaviour may be unpredictable potentially resulting in staff safety concerns. Physiotherapy participants expressed concerns about patients with rib fractures and the use of positive pressure, which may place the patient at risk of further injury or clinical deterioration. In these more complex cases, where risk-benefits needed additional

consideration, multi-disciplinary discussions would take place rather than MI-E use being an autonomous physiotherapist led decision.

"we should or shouldn't include some patients based on safety and feasibility if you're talking about your, erm, sort of highly delirious patients that may or may not actually tolerate it…..for me it's the safety of could I use cough assist with them, essentially…. safety for staff and safety for the patient would be your two different elements then, yeah" (Participant 10, Physiotherapist).

Trial acceptability

Clinician participants shared opinions on the study protocol including the timing of intervention, outcome measures used and the study training. They identified challenges regarding MI-E indications, precautions and contraindications. This included the definition of 'retained secretions' which was highlighted as being subjective and therefore open to interpretation by different clinicians.

"the challenge often with respiratory physiotherapy is, erm, how much secretions is, is, er, an issue, like how much is, is there a problem enough to warrant, er, an additional intervention and I think some, some, erm, therapists would argue that that person had significant secretion retention when another therapist might say that's fine, the nurses are managing it" (Participant 10, Physiotherapist).

Physiotherapy participants had mixed opinion regarding the timing of MI-E. Some physiotherapy clinicians did not think that the protocol reflected how they used MI-E in clinical practice. Generally, physiotherapists understood the rationale for MI-E use pre and

post extubation. However, some felt the timing of MI-E use as pre-post extubation should occur earlier in the clinical course. Some physiotherapy participants highlighted other key timepoints of MI-E use being prior to, or very early in the weaning period and it was felt that the protocol did not reflect this potential use of MI-E. Furthermore, some clinicians did not always feel that a patient required MI-E post extubation. This was linked to patients being more awake due to less sedation at the point of extubation, facilitating spontaneous cough.

"I'm using it as an intervention, early in their recovery rather than pre-extubation. So, yes, I think it's appropriate to use it at that early point in their care to get them to a point where they're safe to wake up and extubate, but I don't, I'm not using it as like, right this person's going to get the tube out, I need to optimise their chest, because, you know, I wouldn't be taking the tube out on many people where I'm like their, their secretions are so bad I need to use MI-E, I just wouldn't be extubating them. They'd be going for trachys" (Participant 5, Physiotherapist).

The ability to specify and adjust MI-E treatment prescriptions was viewed positively by physiotherapy clinicians. In some cases, the ability to adjust MI-E settings helped to overcome the identified limitations in the prescribed timing of intervention in the protocol. This mostly related to MI-E use following extubation when the patient was self-ventilating.

"it made it much more feasible that I could feel comfortable to go and apply the intervention in a way that I felt was going to at least be partially effective or at least be comfortable for the patient, so no it was nice to be able to adjust things to the individual patient" (Participant 5, Physiotherapist)

Clinician participants described benefits of being involved in the study which included access to hands on practice with MI-E and the opportunity to discuss MI-E use with colleagues. Study involvement was reported to have a positive change in relation to MI-E use in the ICU setting.

"I think it's, the whole study has been really beneficial, in that it's really encouraged me to use MI-E a lot, lot more….. So, actually I think my, my opinion was becoming positive once I discovered a) you could have remote controls and manual settings. But actually, yes, I think sheer familiarity with use and our discussions, yeah. And it's, the brilliant thing about the study, it's really opened up lots of discussions about MI-E and how we use it and who we use it with" (Participant 6, Physiotherapist).

"I don't think it would kind of change what I am doing with intubated patients but potentially with some of the extubated ones it has made me think maybe this has got a little bit more of a place post-extubation than maybe I originally would have thought when it's being used prophylactically" (Participant 8, Physiotherapist).

5.2.2.b Burden

TFA construct definition: *'the perceived amount of effort that is required to participate in the intervention'*

This construct describes the personal impact of participation in the feasibility study.

MI-E acceptability

From a patient perspective, the experience of receiving MI-E was described negatively due to discomfort. Additionally, patients described ongoing burden from MI-E use.

"I remember the, I think I can remember the smell of it more than anything else….it definitely was weird. And having your cheeks almost blown out….coughing, moving, anything was just horrific so yeah anything that was sort of like causing that, that sort of sensation was horrific…… You know I've got no idea how heavily sedated or sort of how unconscious you are in that final bit but yeah there's definitely, it almost feels like there's memories you know" (Participant 7, Patient).

The patients did put this into the context of the overall impact of an ICU stay. The overwhelming nature of this experience influenced the individual's ability to engage in clinician interactions and treatment.

"There was probably a lot of other things going on. It wasn't necessarily that device in particular. It was probably just a bit; the whole situation was a bit overwhelming" (Participant 4, Patient).

One patient specifically highlighted emotional burden from the perspective of a relative. In this situation the relative was from a medical background. Therefore, the relative had a clear understanding of what was happening clinically and this resulted in additional emotional burden. This was related to the ICU stay in general rather than specifically to trial participation but remains an important consideration.

Trial acceptability

A positive finding expressed by a nurse participant was how the study had fitted well into their normal working day and was within their normal scope of practice. The participant reported the study protocol had not increased the bedside nurses' workload.

"from our point of view I think the nurses accepted it, they know that the physio is going to do the treatment so it is not like a big bother for the bedside nurses" (Participant 3, Nurse).

The nurse participant also considered future burden for forthcoming trials. This discussion highlighted the need for ongoing collaboration across the ICU MDT to ensure future trials were feasible from a co-enrolment perspective.

Physiotherapist participants described both positive and negative impacts of the protocol. Clinicians reported that delivery of MI-E was not time consuming in comparison to standard care, which was viewed as a positive consideration. Both clinician groups (nurse and physiotherapist) acknowledged the workload of the consent process. The method of consenting and use of professional and personal consultees was not viewed as challenging and was accepted as a standard process across the ICU caseload. However, the time burden associated with re-consenting patients once they had left ICU and were ward based was raised by a nurse participant. Fluctuating cognitive states post ICU, varying medical stability and multiple patient locations across the hospital often resulted in the re-consent process taking a considerable amount of time.

"it is very time consuming and if you did it properly…. that can go on for days, so re-consenting is time consuming" (Participant 3, Nurse)

Physiotherapy clinicians also made comments about the outcomes used within the study, describing the LUS as challenging due to the time that it took for completion. One physiotherapy participant highlighted that they preferred to use lung ultrasound as an

outcome with a more focussed approach, for example concentrating on the affected area rather than completing a measure of the overall lungs.

Overall, the opportunity to participate in a research study was viewed as a positive experience from the clinician's perspective.

"Well I think the thing is, we're all, we are all interested in research. We read research. So, to be involved is, was really great and it's a great privilege to be involved" (Participant 6, Physiotherapist).

5.2.2.c Ethicality

TFA construct definition: *'the extent to which the intervention has good fit with an individual's value system'*

The construct of ethicality focused on the topics of trust provided by the patient in clinicians and the conflict of equipoise linked to the randomisation process.

Trial acceptability

When discussing the consent process patients reported no concerns about a healthcare professional providing consent on their behalf. Responses showed that patients felt clinicians were constantly making decisions in their best interests for which they were grateful. Furthermore, there were multiple episodes where patients referred to their participation and focussed on potentially helping future patients.

"I never felt that I had to worry about it in the sense that gosh am I going to end up in a worse situation than I am now. Because I knew they were there and I knew just at the drop of a hat it [MI-E] could just stop like that. So no it was no big worry in that sense" (Participant 1, Patient).

"If I know that it's going to help in the future you know I am quite happy that you find out whatever you want to and try different things out. You know I don't want to be a guinea pig but I think it's you know the more it does to help people" (Participant 7, patient).

"No I think everybody in the hospital knows their job and they obviously see what is best for the patient then fine with that" (Participant 9, patient).

The outcome of randomisation was at times viewed as challenging, causing internal conflict for physiotherapy participants particularly when the randomisation allocation went against the clinicians independent clinical reasoning and associated treatment selection.

"If a patient is to be, er, put in one of the arms that we wouldn't have done, er, we wouldn't have chosen that treatment choice then that feels challenging, erm, because you always try and deliver the best, or what you consider to be the best intervention to that patient, if that hasn't met your clinical reasoning, erm, it feels slightly uncomfortable" (Participant 10, Physiotherapist).

This conflict particularly occurred when a patient was randomised into the standard care arm when a clinician felt they would have benefitted from the use of MI-E.

"I think one of the, almost one of the challenges was for people in the control arm was you know potentially would, well for us MI-E has become quite a name stay within ITU, it's something people are really familiar with and I think it was almost felt a bit odd to people that that had been taken away from them as at treatment option" (Participant 8, Physiotherapist).

However, one clinician participant did reflect that despite this initial challenge, the treatment outcomes of MI-E had not been detrimental to the patient.

"I've got to be honest in normal circumstances I would not have done MI-E with her at all. That being said though, actually after I'd done it I thought well actually, and she did after we'd done it she did, she'd got good expansion, she did have a little bit of a cough afterwards, it was non-productive and actually it did make me think well although I wouldn't routinely have done it I don't think this has been detrimental to her and actually maybe it is beneficial" (Participant 8, Physiotherapist).

5.2.2.d Intervention coherence

TFA construct definition*: 'the extent to which the participant understands the intervention and how it works'*

Discussion within this construct focused predominantly on the clinician training component for the trial which impacted intervention coherence. Generally, the impact of the study training package and resources was viewed as positive. Participants commented on the benefits of the multiple components of the training package and found it useful to receive training both in a face to face format and as a take-away resource.

"I quite liked it was like face to face, that we were able to do it that way, so I could ask any questions quite freely, erm, about any of, erm, kind of the training side of things, erm, and that you gave a resource with it as well to refer back to" (Participant 2, Physiotherapist).

However, some physiotherapist participants stated they would have liked to have practiced data collection in real time with the data collection form rather than through simulation. A further point referred to the study training provided for weekend and on-call staff. Physiotherapy participants described experiences where these staff were less confident in their knowledge of the study and understanding of each treatment arm. It was acknowledged that these staff had less frequent exposure to the ICU setting so the one-off training may not have been sufficient.

"I think it might have been useful to do something with the remainder of the on-call staff as well because I think certainly on some weekends it's not always, just from speaking to people it's not always been the team leads that have done data collection" (Participant 8, Physiotherapist).

Patient participants found the participant information sheet useful, acknowledging that there was a lot of information on initial viewing. However, participants went on to acknowledge that the detail was needed to ensure comprehension of the MI-E treatment. The importance of effective communication between the clinician and patient during intervention delivery was also stressed by patient participants as important, impacting resultant treatment effectiveness. When clinicians had spent time explaining the treatment to the patient in real-time, the patients felt this was of benefit in making it more effective.

"I mean I think possibly at first when they first told me about it I think I probably was just thinking well yes what's all the fuss about, it's just a machine that I breathe into. I can't understand what you're going on about. But obviously once I started doing it I could see exactly where they were coming from. So yeah but the fact is they did prepare me for it" (Participant 1, Patient).

"You've explained everything that you were doing, yeah absolutely fine you know. As I say I am very much of a mindset that the more you know, the more things you do to help people it's you know and it really doesn't worry me. As long as I am not a guinea pig and you are saying oh we are going to try and you know, try something that seems totally bizarre then I am you know I am quite happy. So the err, the information was plenty enough to explain" (Participant 7, Patient).

5.2.2.e Opportunity costs

TFA construct definition: *'The extent to which benefits, profits or values must be given up to engage in the intervention'*

MI-E acceptability

Patients did describe a positive view of resultant MI-E outcomes, reporting that often they felt better following use. These positive outcomes would then overcome the discomfort experienced during MI-E delivery and negate the negatives regarding a lack of control and input into the decision-making process (see below).

"As I say it wasn't something that I don't think you would necessarily look forward to it but at the same time I think it was something that yes possibly will do some good so yes I am prepared to give it a go. That was my take on it" (Participant 1, Patient).

Trial acceptability

Trust was key within the construct of 'opportunity costs'. Patient interviews demonstrated how much patients had to forfeit in terms of a lack of choice and input into the decision-making process due to their critical condition. The consent process was discussed with patients, with a clear consensus that they understood and accepted the processes in place, acknowledging that there was not a way for patients to input in real time during the initial consent stage due to their critical illness.

"And when you think about it, it's the only way round it isn't it? I mean obviously if I am zonked out I am not going to be in a position to err, to debate the topic am I?" (Participant 1, Patient).

Conflict for clinicians occurred again regarding the outcome of randomisation allocation. This was relevant specifically when a patient had been randomised into standard care, eliminating MI-E from available treatment options and when a patient was randomised into the treatment intervention arm.

"There were people that I was cough assisting that it felt wholly inappropriate for, erm, because either their sputum load wasn't a problem, wasn't compromising them or their cough had improved …. then vice versa, sometimes people are being randomised into the Cough

Assist arm and I'm like, I mean they've got sticky secretions, they're a bit difficult to clear, but in a couple of days when we've got their sedation off, I don't think that's going to be a problem and sure enough it wasn't and then you feel really uncomfortable because you're using a device that, that day to day you wouldn't clinically reason and use" (Participant 5, Physiotherapist).

5.2.2.f Perceived effectiveness

TFA construct definition: *'the extent to which the intervention is perceived as likely to achieve its purpose'*

MI-E acceptability

Patients described a positive opinion of treatment outcomes following the use of MI-E.

*"I just felt that having done it could, I remember thinking yes I can see why they are doing this…You know because it has improved something whatever it's done. Whether it's moved the phlegm or whether it's done anything. Yes it did do something" (*Participant 7, patient*).*

Clinicians generally had a positive view on the potential effectiveness and experienced effectiveness of MI-E in the intubated population. Physiotherapy clinicians also described the mechanism of action of MI-E related to effectiveness. Specifically, clinicians described enhancing expiratory flow bias to optimise the clearance of secretions. Other treatment options were discussed including the use of manual hyperinflation and endotracheal suctioning. In some cases, participants described use of other techniques, which if failing

would then make them use MI-E. Other clinicians stated that in some patient scenarios other treatment techniques would be potentially contraindicated, for example following abdominal or cardiac surgeries, which made MI-E an ideal treatment option in this situation.

"…much greater expiratory flow by a cough assist that you generally can't achieve with other, er, devices or intervention and I said that the only way you can come close to it, to use something like an assisted cough the majority of patients won't tolerate it when they're awake" (Participant 10, Physiotherapist).

The safety of the technique was also discussed within the construct of perceived effectiveness. There was general consensus across participants that MI-E was safe for ICU patients. Physiotherapy participants acknowledged adverse events occurring during the feasibility study but did not view these as clinically significant as they had not required a change in clinical prescription.

"No, I mean the occasional patient that say dropped blood pressure. But that's temporary and you can mitigate that just by stopping" (Participant 6, Physiotherapist).

"Other than the agitation that I alluded to in a patient but no actually harmful events, no" (Participant 5, Physiotherapist).

Trial acceptability

Specific to the feasibility study, the clinician determined MI-E prescription was viewed as a positive aspect of the protocol as clinicians felt they could manipulate MI-E settings more specifically to optimise effectiveness on an individual patient basis.

"because I prefer to be able to change, change the pressures but more so I prefer to be able to change the, erm, number of insufflation bias to the exsufflations, er, depending on whether I think that I want to recruit them more, initially prior to clearance or whether this is all about clearance so therefore, potentially more insufflations to re-, like to recruit or biasing plenty of exsufflations of the secretions I just want to clear" (Participant 10, Physiotherapist).

5.2.2.g Self-efficacy

TFA construct definition: 'the participants confidence that they can perform the behaviour(s) required to participate in the intervention'

This construct focused on the impact of study training and resultant clinician confidence in using MI-E. Generally, the training was well received. Some physiotherapy participants commented on the opportunity to further practice data collection with the database for familiarisation prior to the study going live.

"Whether running a couple more, because the database, as with any research database tends to take a little bit of time to get used to" (Participant 10, Physiotherapist).

"I would have probably done better with a case study and an actual like work through on Red Cap as a thought" (Participant 5, Physiotherapist).

Confidence levels across physiotherapy participants varied. Some physiotherapists

described their pre-study confidence in using MI-E in this patient group, which in turn enabled them to consider additional information and clinical detail, further optimising the likely effectiveness and safety. Communication across the physiotherapy team for support in setting up MI-E was also highlighted.

"I think some of them have come to me and said, oh what settings would you use to me, but, erm, because I'm a confident so and so, I just toddle along on my own and, and, er, set it up how I'm happy with. I guess I'm just happy with my, my knowledge and background of cough assist" (Participant 5, Physiotherapist).

In some cases, a transition in confidence was illustrated, whereby physiotherapy clinicians described how participation in the trial had empowered them to be more independent when using MI-E. Prior to the study, one clinician described how they knew how to use the device but did not feel confident in changing the settings so would just use the setting that had been previously applied. However, due to hands on practice with the device within the study their confidence had grown. The positive impact of a supportive network of clinicians was also stressed by clinician participants. Physiotherapy participants described how unplanned patient discussions would occur which helped study engagement and provided a shared learning opportunity.

"I think I have become much more happy with using it…. It's the actual patients under my belt using it, confidence with using it, but actually I found it really useful doing things like the Ventilator Study day. But also, when we all as a group sat and chatted about MI-E" (Participant 6, Physiotherapist).

5.2.3 Determining Feasibility

Outcomes used to determine feasibility are listed in Table 5.14. These are rated in accordance with pre-defined progression criterion as described in Chapter 4 (Table 4.2).

In summary, this study met feasibility outcomes specifically relating to recruitment, protocol fidelity and acceptability of MI-E and study processes. The recruitment target for the feasibility intervention study was 50 participants. At the end of the recruitment period, 47 participants had been consented and randomised into the study which equated to 84% of all eligible patients (Table 5.14). There were only two occasions (over 136 treatment sessions) when MI-E was not used in the MI-E intervention arm. Outcome measures were generally well completed, with the exception of reduced data sets for LUS and respiratory resistance and compliance. Physiotherapy participants raised barriers to using LUS as an outcome in clinical practice due to its time-consuming nature. Results demonstrated that it was feasible to collect patient reported pain, an outcome deemed important through the patient interviews. Experience and findings gained from this feasibility study could be of value for future design of a larger scale trial which will be discussed in subsequent sections.

Table 5.14: Completed feasibility outcomes

Feasibility outcome	**Detail**	**Progression rating** (red/amber/green)
Proportion of eligible patients: -Approached -Consented -Randomised	 89% (50/56) 84% (47/56) 84% (47/56)	
Proportion of MI-E treatment sessions completed	99%	
Proportion of recruited patients with all outcome measures recorded	(see section 5.1.4)	
Attrition (participant withdrawal and loss to follow up)	No withdrawals 12 deaths 23% return of EQ-5D-5L	
Acceptability (quantitative) of trial processes to participants and clinicians	AIM 93% FIM 91% IAM 71% (see section 5.1.8)	
Acceptability of outcome measures to participants and clinicians	(see section 5.2)	

Abbreviations: AIM, acceptability of intervention measure; EQ-5D-5L, FIM, feasibility of intervention measure; IAM, intervention appropriateness measure; MI-E, mechanical insufflation-exsufflation

5.3 Discussion

This study aimed to determine the feasibility of conducting a RCT of MI-E use to promote extubation success in critically ill, intubated adults on ICU. Despite previous investigations of MI-E in this specific patient group, the scoping review (Chapter 2) highlighted a number of limitations of the evidence base including poor reporting of MI-E treatment prescription, lack of consistency in outcome measures used across studies and an absence of the patient voice. Furthermore, findings from clinician interviews (Chapter 3) reinforced previous work, illustrating ongoing clinician concern and questions regarding safety criteria for MI-E in an intubated critically ill population (Swingwood et al., 2020). Prior to undertaking a definitive RCT, a feasibility study was warranted to explore clinician determined MI-E treatment

prescriptions, define study outcome measures and endpoints, and detailed safety reporting. A qualitative element provided further evidence concerning the feasibility and acceptability of MI-E and the associated protocol. To the doctoral fellows' knowledge, this is the first study to explore both clinician and patient experiences of MI-E use in the ICU through semi-structured interviews.

In the first instance, this discussion section considers results in order to determine feasibility of a definitive trial of MI-E use in an ICU setting. In doing so, discussions are positioned in context with the evidence base, including studies published following completion of the scoping review (Chapter 2). Additional themes from the results are also discussed. The chapter concludes with considerations for clinical practice and recommendations for future research activities.

5.3.1 Recruitment

Results illustrate that it was possible to recruit participants for the feasibility trial. The proportion of patients deemed eligible, consented and randomised were within pre-defined feasibility targets. A total of 47 (94%) participants were randomised which was three participants short of the recruitment target. However, there were three potential participants who were eligible but not approached for consent as they were already enrolled in a different trial and the relevant co-enrolment documentation had not been finalised. This was only a barrier in month one of study recruitment after which the relevant co-enrolment paperwork was in place. An additional six participants missed the consent window prior to extubation. Again, these missed opportunities occurred early on in the

study where potentially clinicians were less familiar with the study processes. It was possible to manage these issues in a timely manner due to the presence of the doctoral fellow on the study site. For any future studies, such issues would need to be considered prior to a study opening with detail included within study training and opportunities to liaise with the study team to facilitate recruitment.

Most participants were initially consented into the study using a professional consultee. The use of a personal consultee was much less frequent mainly due to infrequent interactions between potential personal consultees and research staff on the ICU. Ongoing restrictions to patient visiting due to COVID-19 may have impacted this. Ongoing consent to participate was gained in a small number of patients. This was a challenging process due to fluctuating levels of patient capacity, internal ward moves and access to the patient. The challenges of re-consenting patients following the use of a professional consultee was raised by both nurse and physiotherapy participants during interviews. Patient participant interviews raised no concerns about the processes linked to consent, acknowledging the challenges but stressing their desire to be part of research.

The exploration of recruitment processes in ICU trials has been identified as important (Raven-Gregg et al., 2021). Since initiation of the current feasibility study the 'INCLUDE Impaired Capacity to Consent Framework' has been published (Sheppherd et al., 2024). This framework aims to guide trial design to ensure recruited participants represent the anticipated population who would receive the intervention being investigated. Despite

recruiting a high proportion of eligible participants into the study, reference to this framework would be beneficial to optimise consent processes in future.

Participants recruited into the study were similar to those in previous studies of MI-E in relation to age, gender mix and reason for intubation. One difference was the exclusion of patients with a known NMD from the current study; this was felt to be an important exclusion as the benefits of MI-E in this cohort were already well documented (Chatwin et al., 2018). Participants were retained throughout the study with no withdrawals reported. The 60-day mortality rate in the current study was 27% and 20% in the intervention and control arms respectively, which is comparable to the expected mortality rate of a critically ill population.

5.3.2 Randomisation

Participants were randomised to either standard care or the MI-E intervention arm using 'sealed envelopes', a blinded process. Demographics across the two treatment arms were similar. Clinician interviews raised some concerns with the randomisation process including an 'internal conflict' when a participant had been randomised to standard care and the clinician wanted to use MI-E, thus challenging clinician equipoise. This is an important finding and demonstrates how the use of MI-E in the ICU is potentially evolving. At the time of the study, the use of MI-E did not form part of standard practice on ICU at the study site. This may differ across centres and should be considered for future studies because the cessation of an active treatment is not ethically viable. This issue has been given further consideration in section 5.3.8.

5.3.3 Protocol fidelity

Good protocol fidelity was demonstrated throughout the feasibility study. There were two episodes (out of 138 MI-E treatment sessions) where MI-E was not used for participants in the intervention arm. Information provided indicated that the patient was not suitably stable for the intervention due to a raised blood pressure (greater 200mmHg systolic). The protocol enabled the clinician to make this clinical judgement and therefore not place the patient at an increased risk of clinical deterioration. An extended time period of data collection (up to 13 days) also occurred in two patients, both of whom had a tracheostomy. Although there are multiple reasons for tracheostomies to be inserted, it should be considered whether this is an end point to data collection and viewed as a category of prolonged weaning or as a failed extubation in a future trial.

Despite study training being completed prior to study initiation, there are improvements that could be made to improve protocol adherence. Clinician interviews demonstrated positive feedback about the pre-study training and associated resources. However, a gap in knowledge and awareness for physiotherapists working either at the weekend or in an on call (out of hours) capacity was also highlighted. It was initially presumed that there would be an ICU trained clinician working at weekends but this was not the case. For a future trial, the method of informing non-ICU specific staff should be re-considered. This includes consideration of which staff are offered training, training content and associated resource availability. The timing and frequency of the training should also be considered as training needs may differ depending on frequency of exposure to the study. Therefore, ensuring there are study information resources such as pre-recorded presentations, and frequently

asked questions documents available is a key recommendation for a future training package. A recent abstract publication described the use of an online training package resulting in increased clinician confidence in both the prescription and application of MI-E to adult patients (Lambrinos et al., 2023). Full details of the content of online training is not yet available but this method of education delivery is worthy of further consideration.

5.3.4 Data completeness

Data completeness of outcomes during physiotherapy interventions generally achieved the pre-set feasibility threshold except for EQ-5D-5L, LUS, lung compliance and airway resistance which had poor completion. The poor return of EQ-5D-5L can likely be attributed to a computer system error. Many emails being sent to patient participants either failed to send or went straight to a junk folder and were therefore missed by patients. If longer term follow-up of patients is important following the use of MI-E, the method of data collection for the EQ-5D-5L needs to be re-considered.

The LUS had a 23% completion rate. The ability of lung ultrasound to identify change in lung aeration has been documented (Bouhemad et al., 2015; Hayward and Janssen, 2017; Gustafson et al., 2021; LeNeindre et al., 2023) and could be useful when using MI-E for real-time analysis of treatment effectiveness. However, in clinician interviews, physiotherapy participants reported that the use of this measure was too time consuming to complete on a day to day basis and on multiple occasions during one treatment session. Due to the impracticalities raised it would be deemed impractical for use in a definitive study.

It is not possible to ascertain why poor completion of compliance and resistance occurred as no additional detail was obtained through clinician interviews. These outcomes have been used previously (Coutinho et al., 2018; Ferreira de Camillis et al., 2018) and a complete data set would allow comparison across studies. Additionally, when considering ongoing safety concerns for the use of MI-E in the ICU population, these measures can provide useful physiological detail regarding the stress and strain potential during lung inflation (Gattinoni et al., 2016). Inclusion of such measures including the physiological impact of MI-E warrants further exploration. Such detail would be useful in providing direction for device set up recommendations which do not currently exist.

Some physiotherapy participants suggested that the outcomes were limited, particularly regarding the lack of measure for sputum clearance. Previous studies have used measures of wet sputum weight or volume (Farina et al., 2017; Coutinho et al., 2018; Ferreira de Camillis et al., 2018; Sanchez-Garcia et al., 2018; Vokes et al., 2019; Martinez et al., 2021) despite the fact that it does not provide an accurate indication of disease severity (Fahy and Dickey, 2010). However, the effectiveness of MI-E for sputum clearance is an important part of the justification of using the technique to promote extubation success. Acknowledgement and quantification of whether sputum was cleared or not during physiotherapy sessions in the current study may have been beneficial. This conflict of opinion further supports the need for a standardised core outcome set for measuring effectiveness of airway clearance techniques in the critically ill intubated population.

5.3.5 Acceptability

Acceptability was assessed using objectives measures (FIM, IAM, AIM), and through interviews with patients and clinicians. MI-E was rated as acceptable by clinicians in 93% of MI-E treatment sessions and deemed feasible in 91% of completed sessions. The IAM had a greater spread of results in comparison to the AIM and FIM, with 71% of MI-E sessions rated as appropriate by clinicians. This could be linked with findings from the qualitative study component which indicated challenges regarding the timing of study intervention in some patients. Physiotherapy clinicians described how the protocol did not reflect their current use of MI-E across the disease process and ventilation continuum, stating they would sometimes use it at an earlier timepoint.

There is no evidence resulting in recommendations on the most effective time to use MI-E in the intubated population, something also raised by a multi-disciplinary cohort during a focus group study exploring MI-E use in ICU (Stilma et al., 2022). MI-E effectiveness has been investigated at different stages of the ventilation continuum. This includes a study of COVID-19 patient receiving MI-E during acute pneumonitis in prone position (Apps et al., 2021); an earlier study exploring MI-E pre and post extubation (Gonçalves et al., 2012); and further research exploring MI-E delivered post extubation to prevent the development of acute hypoxaemic respiratory failure and the need for re-intubation (Nishida et al., 2023; Wibart et al., 2023). Investigating MI-E delivered at different stages of the ventilation continuum in a single RCT would not be realistic due to the number of treatment arms and the subsequent required sample size. An alternative approach could include an epidemiological approach whereby standardised data collection of MI-E use occurs with relevant outcomes employed. Such an approach would be more practical given the

challenges of equipoise and increased use of MI-E in standard care previously discussed. For example, an observational cohort study would enable a group of participants to be followed in order to ascertain the relationship between exposure to MI-E and relevant health related outcomes. This type of study can be completed retrospectively or prospectively. Chapter 2 illustrated a lack of consistency in outcomes and associated measures employed across studies examining MI-E. Prospective data collection would therefore enable more consistency in outcomes. This is a versatile methodology but can be costly depending on factors such as the duration of follow up. Findings may also be impacted by confounding factors which impact the relationship between MI-E exposure and outcomes measured. However, overall such an approach would enable multiple exposures (for example use of the treatment technique at different time points) to be considered.

Standardised data collection has been employed in a recent ICU study (WEAN SAFE) aiming to describe the epidemiology, management and timing, and outcomes of patients weaning from IMV (Pham et al., 2023). WEAN SAFE was a multi-centre, prospective, observational cohort study across 481 ICUs in 50 countries, enrolling a total of 5869 patients. A key finding showed that of all patients who received IMV for greater than two days, only 65% were weaned at the 90day timepoint. These findings have informed recommendations for future weaning studies which included the need to understand factors that delay weaning. Such an approach could lead to a better understanding of how MI-E is used across different centres and countries and to explore associations between MI-E application and clinical outcomes.

Patient acceptability was explored through semi-structured interviews. To the doctoral fellows knowledge, this is the first study to gain patient perspective of MI-E in the ICU setting through semi-structured virtual interviews. Valuable insights were provided by patient participants and key findings included acceptance of MI-E due to positive outcomes following use. This was despite experiencing some discomfort during treatment. When considering the patient and clinician role, there was a huge amount of trust placed in clinicians. This was relevant to inclusion in the study, the consent process, and treatment. The value of trust has been emphasised in other ICU based studies. One study exploring patient experiences of early mobilisation, rehabilitation and recovery after critical illness, completed 15 semi structured patient interviews (Corner et al., 2019). Trust was dependent on rapport between the clinician and their patient and had subsequent impact on patient engagement. This is a useful consideration for future MI-E use and clinician education for a definitive study.

Findings from the clinician interviews suggested that acceptance of MI-E was influenced by positive experiences when using the technique in ICU. The strong influence of knowledge and skills of MI-E across the MDT, the importance of ongoing education, and development of the evidence base were also highlighted. These mirror findings by Stilma et al., (2022) who completed a series of four focus groups with 35 healthcare professionals exploring factors influencing decision making for the use of MI-E in invasively ventilated patients.

5.3.6 Clinical outcomes

In order to attend to the pre-set feasibility outcomes, a number of clinical outcomes were collected. These data raised some interesting findings that warrant further discussion including how clinicians have prescribed MI-E in this critically ill population, detail of standard care and the safety of MI-E.

5.3.6a Device set up

No previous research was identified that had explored MI-E use whereby clinicians could individualise the MI-E prescription to the patient. Compulsory data entry points around all MI-E device set up prescriptions provided useful insight into how the clinicians were using MI-E in the ICU setting. This will be useful to consider for future education content. Clinicians used insufflation pressures +28[25-30] (median [IQR]) and median exsufflation pressures -35[-40, -30]). This is potentially lower than in previous studies reported in the scoping review (Chapter 2), where average pressure settings of +40:-40cmH_2O had been used. It should be considered whether the variation in settings would influence the therapeutic effectiveness of MI-E. Additionally, reasons why clinicians were implementing lower pressure settings than recommended in the evidence base should be considered. Clinician interviews replicated concerns previously discussed regarding the safety of MI-E specifically for pneumothorax risk with higher positive pressure settings and possible cardiovascular instability (Chapter 2; Swingwood et al., 2020; Stilma et al., 2022). Interestingly, all MI-E pressure prescriptions in the current study had an asymmetrical set up. This has been demonstrated and recommended previously in the NMD population to generate an expiratory flow bias (Chatwin et al., 2020; Chatwin and Wakeman, 2023).

Clinicians in the current study employed similar MI-E insufflation pressure settings in intubated and extubated participants (+28[25-30] v +25[25-30] median [IQR]) respectively. Previous studies have made recommendations to increase insufflation pressure when using MI-E via an artificial airway (Guerin et al., 2011) and demonstrated lower generated expiratory flow rates with the same MI-E pressure settings in narrower tubes. This was thought to be due to an increased resistance to airflow. More recently the impact of differing interfaces for MI-E delivery has been examined (Hyun et al., 2021). Slower generated flow rates were found when MI-E was delivered via an ETT in comparison to a face mask with the same MI-E settings. It was concluded that higher pressure settings up to +/-50cmH_2O could be used in intubated patients with no safety concerns. Clinicians in the current study rarely adjusted the MI-E treatment prescription once a patient had been extubated. This was not specifically explored in the clinician interviews. Insight and further understanding of clinical reasoning linked to the use of MI-E warrants further exploration.

5.3.6b Standard care

No agreed definition of 'standard physiotherapy care' exists, so it was important to collect this information to inform a definitive trial. Future implementation of MI-E would also need to occur within the context of existing standard care (O'Cathain et al., 2015; Swingwood et al., 2020, Chapter 3). Data collection of physiotherapy interventions prescribed by physiotherapy clinicians took place over 272 separate physiotherapy sessions (standard care and MI-E intervention arm). Components of standard care were similar across groups with positioning, manual techniques, suctioning and mobilisation being used most frequently. There was less use of MHI and VHI in the MI-E intervention arm in comparison to the standard care arm. More frequent suctioning was used in the standard care arm. Recent

guidance recommends the use of suction only when indicated rather than as a routine procedure (Blakeman et al., 2022). The increased use in the standard care arm could therefore be due to improved secretion clearance effectiveness in the MI-E arm. As outcomes such as wet sputum weight and volume were not collected, it is not possible to determine the reason for this pattern of practice. There is conflicting evidence regarding the effectiveness of MI-E in clearing sputum as follows. MI-E was reported to be superior in clearing sputum volume in comparison to respiratory physiotherapy alone which comprised of positioning, manual techniques and suctioning (Ferreira de Camillis et al., 2018). Additionally, Martinez et al., (2021) demonstrated increased sputum volume clearance with MI-E in comparison to respiratory physiotherapy in 26 mechanically ventilated patients. Conversely Coutinho et al., (2018) found no significant difference in sputum clearance with MI-E when compared to conventional endotracheal suctioning. Differences in study findings are likely due to heterogeneity of study protocols.

All treatments used in the current study are reflected in a publication by Twose et al., (2019) which documents minimum standards of clinical practice for physiotherapists working in critical care settings in the UK. Through a modified Delphi technique, they listed 107 items of knowledge and skills which were essential. They stated that clinicians should be able to "*provide the following techniques, including an understanding of indications, contraindications, evidence for the technique and progressions*". Clinician interviews demonstrated ongoing challenges with confidence in using MI-E, again stressing the importance of hands on practice with the device and linking back to knowledge and

awareness of the evidence base. A perceived lack of knowledge and skills has been highlighted previously and emphasises the importance of relevant training for clinicians.

5.3.6c Safety reporting

The scoping review demonstrated a lack of detail regarding safety reporting. Additionally, previous work (Chapter 3) has illustrated clinician concerns regarding the use of MI-E specifically in the ICU intubated population. As a result, a number of data points were included in the current feasibility study to address this. Previous research reporting on the safety of MI-E in ICU have also included these outcomes (Ferreira de Camillis et al., 2018; Martinez et al., 2021). In the current study, MI-E interventions caused minimal changes to measures including RR, SpO_2, SBP and DBP (measured pre and post intervention). Any changes observed were not clinically significant. Despite 13 adverse events being reported in the intervention arm of the study, these did not require medical intervention either during or following the use of MI-E. Ten episodes of brief desaturation or haemodynamic variations were also documented during ERCC and MI-E in the recent study comparing ERCC with and without MI-E (Martinez et al., 2021). For a definitive trial it should be considered whether these outcomes need to be routinely measured; particularly as pre-defined adverse events would be reported. Earlier recommendations for the development of a core outcome set for airway clearance strategies in the intubated population would further determine a definitive dataset and help develop consistency in future research.

5.3.6d Measures of pain

This study has demonstrated that it is feasible to collect clinician reported and patient reported measures of pain. There was a complete dataset for CPOT scores. The NRS was

able to be completed by approximately 50% of participants, reasons for non-completion stated by physiotherapy clinicians included sedation levels and presence of delirium. The inclusion of a patient reported measure was raised as being important by PAG members during protocol development so despite a lower completion rate its inclusion in a future trial is recommended. A recent study has demonstrated that the CPOT and NRS cannot be used inter-changeably (correlation coefficient 0.56) with factors such as delirium and reduced arousal levels impacting the relationship between the measures (Stollings et al., 2024). This strengthens the justification to include both a clinician reported and patient reported measure of pain. Patient interviews described discomfort during the use of MI-E, with one patient participant querying the terminology of 'pain' as they did not feel it was the right word with 'discomfort' being more appropriate. This should be considered, particularly for the use of the NRS-V going forward.

5.3.7 Economic scoping

This study provided scoping for future economic evaluation which has not been completed to date for MI-E in the ICU setting. This is an important consideration as earlier work highlighted resource availability and associated device costs as a barrier to use (Swingwood et al., 2020). Additionally, with non-infinite resource supply, it is important to consider value of interventions regarding health consequences and actual monetary costs to help determine longer term resource allocation (Kahn et al., 2021). Results from the current study have demonstrated that it is feasible to collect data regarding resource use which included staffing and equipment resources linked to monetary costs and associated time. However, a poor completion rate of the EQ-5D-5L was experienced as previously discussed. Preference towards cost-utility analysis in the ICU setting has been stated (Kyeremanteng et al., 2016; Kahn, 2021) but the lack of EQ-5D-5L data from the current study would limit this.

The EQ-5D-5L was intended for completion at six months post ICU discharge to provide longer term QOL data.

It should be considered whether a descriptive comparison of resource use across the intervention and standard care arms would be beneficial as a starting point. Another consideration could be the completion of a descriptive cost analysis to determine potential cost savings linked to a primary outcome of extubation success, for example time to extubation and associated length of stay costs in the ICU. A cost analysis would provide a useful commentary as to whether MI-E is cost effective and provides either a cost saving on a patient by patient basis or on a longer-term basis, for example the number of patients needed to be treated with MI-E in order to initially become cost neutral. The outlay for one MI-E device (as used in the current trial) is circa £4000, with ongoing consumable costs for patient device circuits (single patient use). Costs associated with clinician training time should also be considered. The importance of training has been highlighted across studies within this thesis (Chapter 2 and Chapter 5, section 5.2) linked to clinician knowledge and skills of MI-E application.

A micro-costing exercise was considered based on the current results. However, the generalisability of these findings would be limited as results were generated from a single centre. Previous work has demonstrated variance in MI-E use across and within countries (Rose et al., 2016; Swingwood et al., 2020; Stilma et al., 2022) and therefore implementation is likely to differ across centres in comparison to the current study protocol. Findings of a micro-costing exercise would therefore not be directly translatable.

5.3.8 Limitations of the feasibility methods

Evaluation of the current feasibility trial provides insight into methodological considerations important for future investigation planning. It is important to consider the strengths and weaknesses of the study protocol. Additionally, and in accordance with the MRC Guidance for complex interventions, such review is often completed through process evaluation (Skivington et al., 2021). Although elements of process evaluation have been completed it has been done so retrospectively within the feasibility discussion. Ideally process evaluation is designed prospectively and completed systematically as a key component of an RCT (Oakley et al., 2006). The aim of process evaluation is to consider more than the effectiveness of an intervention. It also provides consideration of the multifaceted nature of trials of complex interventions with multiple overlapping and interacting components (Oakley et al., 2006; Skivington et al., 2021). The current feasibility has provided valuable insight through both quantitative and qualitative approaches, which can then be placed in further context of preceding work as presented in the thesis.

The current study protocol was based on thorough background work as presented in Chapters 2 and 3 and with extensive patient involvement to design a study that was relevant and would contribute to progressing the evidence base. The protocol introduced new elements to the investigation of MI-E in the ICU population, including clinician determined MI-E prescriptions. The inclusion of both quantitative and qualitative assessment of feasibility is an additional strength of the study (O'Cathain et al., 2015; Skivington et al., 2021).

The critically ill population is a challenging group to investigate due to the complexity and diversity of disease and presentation. The current study had a pre-specified eligibility criterion which had been pre-trialled during protocol development. A total of 1017 patients were screened during the recruitment period. There were 115 participants assessed for eligibility, with 56 (49%) deemed eligible to participate. The proportion of non-eligible patients was slightly higher than in previous studies (Gonçalves et al., 2012) which was based in a specialised weaning centre and not necessarily comparable to a general ICU setting. The indications for MI-E use, and reasons for exclusion, which were built into the eligibility criteria were consistent with other studies and further supported by findings in Chapters 2 and 3. Recent publications (Stilma et al., 2022) have also corroborated these indications.

Data from the feasibility study demonstrated good protocol fidelity and associated MI-E delivery. Acceptability of MI-E was good as highlighted through qualitative work with both clinicians and patients. Challenges arose regarding the dose of MI-E, and specifically that relating to the timing of the intervention. Clinicians commented that the protocol did not always reflect how they used MI-E in this patient group as they would often use it earlier in the intubated period. Concurrently, clinicians raised conflict regarding the use in some patients who had been extubated as they questioned whether indications for MI-E use remained. There is an element of equipoise to be considered but the optimal timing of MI-E remains unknown and has not been investigated to date. Studies instead have focused on the extubation timepoints or applied MI-E during the intubation period but the use of different outcomes makes comparisons between studies challenging. The use of clinician determined MI-E prescriptions was seen as a positive in the current study as it allowed clinicians to adapt the MI-E device set up and prescription when they felt challenged. This

adds a layer of complexity in future evaluation as additional variables are then introduced including the timepoint of MI-E use, treatment prescription and outcomes used to measure effectiveness.

The comparator in the current feasibility study is that of 'standard care'. From the scoping review (Chapter 2) there were a variety of descriptions of standard care employed across studies. A strength of the current study was an initial definition and description of what standard care included. An additional strength was the collection of data during the study to provide an accurate description of standard care for future studies. A breadth of interventions were used in the standard care arm. For a future trial this would have to be further considered as direct replication from this single site study may not be representative of standard care in other centres. Turner et al., (2024) stressed the importance of considering the cause of variability in practice. They described multiple influencing factors including the needs of the patient, resource availability and clinician preferences. Work by the doctoral fellow to date has demonstrated factors such as resource availability (to include the actual device, ongoing availability of consumables, and storage space) and clinician preferences, particularly when further influenced by team culture as key influencers of MI-E use. Chapter 3 (figure 3.5) demonstrated the complexity of interactions, all influencing clinician preferences. It is therefore apparent that the ability to accurately define standard care would be challenging for a definitive trial. ICU patients are a highly vulnerable population so clinicians need to be able to prescribe treatment interventions that meet their specific needs. Mischaracterisation of standard care may lead to inaccurate analysis and interpretation (Parker et al., 2013; Applefeld et al., 2020). With MI-E being an

emerging intervention in the ICU setting, defining standard care that does not include MI-E is likely to be challenging (Silverman and Miller, 2004). This would require careful consideration for future MI-E studies.

The description and definition of standard care is important but there is currently no guidance on how it should be achieved (Turner et al., 2024). A definition could be quite open to accept the heterogeneity across centres but this would be challenging when interpreting results. Another important consideration is whether standard care changes to include MI-E as a result of study exposure (Applefeld et al., 2020). Interviews with clinicians suggested an increased confidence in using MI-E because of using it more frequently within the feasibility study. If MI-E is adopted as part of standard care as a result of this exposure, it would be problematic for a future trial as ethically a treatment cannot be withdrawn from a patient.

This study used the Clearway 2 MI-E device (Breas Medical LTD, Stratford-Upon-Avon, Warwickshire, UK). It should be acknowledged that there are other MI-E devices available globally and therefore results presented here are not necessarily generalisable. Feasibility findings, particularly related to 'acceptability of MI-E' should be considered carefully prior to extrapolation. Different clinicians may have found different devices more or less acceptable within the protocol being tested. The study was based in a single centre which may also limit generalisability of findings. The doctoral fellow did engage a SAG throughout study development and during analysis which helped provide a wider perspective on some points raised in the discussion. In the current intervention study, it was not possible to blind

clinicians to treatment arm allocation following randomisation. This may have caused over-estimation of individual assessments or treatment effects, however much of the data collected was objective which reduces the risk of bias. Clinician interviews were completed by the doctoral fellow so a working relationship between the interviewer and interviewee should be acknowledged as this may have influenced participant responses. A general introduction to the interviews was included to reinforce the roles specific to the study and reiterate confidentiality of responses to help overcome the potential influence of any previous working relationship. The qualitative sample was small but this allowed deep exploration of interview transcripts from a physiotherapist and patient perspective. The qualitative investigation was limited by challenges with the recruitment of participants. No doctors or personal consultees participated in the interviews, these groups may have provided additional insight into the study processes. Analysis of the interviews was based on the TFA with interview quotes being assigned deductively. It should be acknowledged that this may have limited valuable themes being generated if they did not fit directly into the pre-defined framework. Despite these limitations, the inclusion of the qualitative element to the feasibility study is viewed as a strength (O'Cathain et al., 2015; Skivington et al., 2021). Findings have provided valuable insight and detail into the acceptability of MI-E and the associated study protocol at an individual level which have shaped future recommendations.

5.4 Researcher reflections

If there was the opportunity to repeat the feasibility study, there are things that I would do differently, particularly relating to the progression criteria rated amber (Table 5.14). With regard to outcomes, I would not include the LUS. There was both poor completion and poor clinician acceptability associated with this outcome. The EQ-5D-5L also had a poor completion rate. This measure is important as it links to the wider consideration of QOL and also has the potential to contribute towards economic evaluation. Rather than eliminate the measure entirely, I would change the way in which the data are collected. Rather than using the electronic return system through the study database, I would explore the option of completing follow up phone calls for example to ascertain if this improves the dataset for this measure.

From the clinician interviews some valuable changes to the study education package were identified. These would include extending the training to staff on the weekend working and oncall rota. These staff would be involved in the study on a less frequent basis and so the frequency of training should be considered and/or availability of the electronic study information. Clinicians also raised the suggestion of practicing data collection with the database in real time. I would also add detail to the description of some data collection timepoints to ensure data collection ceases in a timely manner, to prevent ongoing data collection that is not required. Such a change would optimise protocol fidelity.

The semi-structured interviews did not include any personal consultees or doctors. If the feasibility were to be repeated it would be important to maximise opportunities to recruit individuals from these groups and understand their experiences. Consideration of how, when and where study information is advertised would be an important consideration. This will ensure potential participants have awareness of the study but more importantly, understand why their participation is important. Further engagement with the PAG would also be beneficial to help with interview recruitment of these participant groups.

My beliefs prior to commencing this work have been previously described (Chapter 1). It is important to consider and acknowledge my passion and enthusiasm for the use of MI-E to ensure the presentation of findings and recommendations are not misplaced. Throughout the presentation of results and discussion of the feasibility trial, I have aimed to focus on the determination of feasibility rather than the detail of the clinical findings, from which I cannot make inferences because the study was not designed or powered to do so. However, there are still important trends to observe, which showed no clear benefits for MI-E and in some cases worse outcomes with MI-E. These trends must be considered when determining the next research approach.

One of the key concerns raised by the clinicians related to the timing of the intervention and how the protocol did not reflect their use of MI-E as a treatment technique in the clinical setting. I acknowledge and agree with this concern as I also tend to use this technique at much earlier timepoints. From this perspective, I do not believe that even with amendments to the protocol that a RCT is warranted. At this stage the completion of another RCT may

actually be too simplistic an approach as it would not allow exploration of aspects such as individual patient variance, sub-group effects, and the analysis of more complex causal mechanisms related to MI-E. I believe that an observational or realist approach would provide more detail and allow for the differing practices across the UK and different MI-E devices used, alongside further exploration to understand the specific conditions under which MI-E will and will not work.

5.5 Conclusion

In conclusion, this study has demonstrated feasibility of a RCT examining the technique of MI-E to promote extubation success in critically ill adults, based on ICU. However, through retrospective process evaluation, several methodological factors have been highlighted that require additional consideration. A key factor influencing next steps relates to the emerging use of MI-E which may make it difficult to exclude it from the standard care arm in a future RCT. Alternatively, an observational study designed to describe MI-E use and associated outcomes across multiple sites has been proposed. This could provide further insight into MI-E use and support progression of the evidence base relating to its' use in the ICU setting. Furthermore, consensus of a core outcome set for airway clearance interventions would assist future evaluation of MI-E.

Chapter 6

A nested exploratory physiology study examining lung recruitment and de-recruitment during Mechanical Insufflation-Exsufflation

6.1 Background and rationale

In patients with moderate to severe respiratory failure there is often ventilation heterogeneity, particular in cases of Acute Respiratory Distress Syndrome. The concept of a 'baby lung' (Gattinoni et al., 2016; Gattinoni et al., 2018) describes this heterogeneity whereby the overall lung consists of regions of normal to near normal aeration, and regions totally deprived of air (due to consolidation or collapse for example), thus impairing gas exchange and impacting resultant oxygenation. The 'baby lung' has near normal mechanical properties and so still has the ability to achieve tidal volumes. This small region becomes responsible for managing the physiological needs (clearance of carbon dioxide and oxygenation) of the patient.

In intubated and mechanically ventilated patients, lung recruitment and de-recruitment are important considerations (Brower et al., 2000; Park et al., 2013; Chen et al., 2020; Jonkman et al., 2023). Clinically, mechanical ventilation has focused on lung protective strategies, for example the use of lower tidal volumes, lower driving pressures and the use of positive end expiratory pressure. The Acute Respiratory Distress Syndrome Network study (Brower et al., 2000) was key to examining the impact of low (6mL/kg) versus high (12mL/kg) tidal

volumes. A significant reduction in mortality was seen in the lower tidal volume group and this has since become an accepted ventilation strategy in the ICU.

During IMV, a positive pressure breath is delivered by the ventilator followed by a passive expiration. In contrast, MI-E delivers positive (insufflation) and negative (exsufflation) pressure breaths. The use of negative pressure during exsufflation breaths is hypothesised to lead to de-recruitment which may have negative consequences for critically ill patients including an adverse impact on oxygenation, ineffective ventilation and the attenuation of lung injury (Costa et al., 2009; Park et al., 2013; Chen et al., 2020). A greater volume expired during exsufflation may result in de-recruitment and atelectrauma due to cyclic opening and closing of lung units, thereby predisposing a patient to subsequent clinical deterioration.

Furthermore, re-recruitment of atelectatic lung units may be challenging. Consideration is also given to the pattern of recruitment, with the aim of not over-distending lung units that are already recruited (Terragni et al., 2007). With the 'baby lung' in mind, the pressure required to re-expand areas of atelectasis or collapse may results in other lung units becoming over-distended (Costa et al., 2009; Gattinoni et al., 2018) which may have further negative impact. The manner in which MI-E is delivered in invasively ventilated patients therefore may also have consequences on alveolar recruitment and over distention. For example, as illustrated in the scoping review (Chapter 2), the most frequently used pressure settings in MI-E were +/-40cmH_2O. However, a bench study (Guerin et al., 2011) examined the impact of MI-E delivery via an artificial airway (ETT and tracheostomy tube) on generated PEF. Presence of an artificial airway significantly reduced PEF, likely due to increased resistance to airflow. Based on these findings, the Guerin et al (2011)

recommended pressures of +/-40-50cmH_2O when using the device with an artificial airway in situ to ensure optimal generation of expiratory flow rates. Bench studies have demonstrated an increase in generated expiratory volume with increasing MI-E pressures (Gomez-Merino et al., 2002; Sancho et al., 2004). Indeed, volumes greater than those during a normal (non-augmented) cough have been reported. This is challenging because the impact of using such pressures setting recommendations and the impact on recruitment is not known.

The effect of MI-E on recruitment, de-recruitment and overexpansion of lung units in critically ill patients with heterogeneous ventilation receiving invasive mechanical ventilation are therefore important considerations to explore further in vivo. Understanding the impact of MI-E on ventilation distribution is beneficial to ensure the provision of effective and safe treatment prescriptions.

6.2 Quantification of recruitment and de-recruitment

There are a number of methods in which alveolar recruitment and de-recruitment can be quantified. These include indirect strategies, for example through oxygenation status and lung compliance values. Alternatively, direct methods include computed tomography (CT) scans, pressure-volume loops, electrical impedance tomography (EIT) and lung ultrasound (Jonkman et al., 2022).

6.2.1 Electrical Impedance Tomography

EIT is a non-invasive, radiation free technique used at the bedside to provide pulmonary ventilation data in real-time (Hinz et al., 2003; Walsh and Smallwood, 2016; Frerichs et al., 2017; Vasques et al., 2019). A series of between 8 and 32 skin electrodes (device dependent) are placed around the chest wall, through which small electrical currents are passed to measure impedance, conductivity, permittivity. The EIT device delivers a known alternating current to a pair of electrodes (injecting electrode pair) and measures the resultant surface potential across the remaining 13 electrode pairs (measuring electrode pair). This process rotates around the entire thorax, with one complete circuit resulting in profiles. Scan rates can generate approximately 50 images per second (Frerichs et al., 2017). These measurements provide a two-dimensional image made up of a 32X32 matrix of pixels of impedance-the resistance/opposition to alternating currents presented by the combined effect of resistance and reactance across the circuit.

The impedance map of the thoracic cross section has the same orientation as a CT scan whereby the left-hand side of the chest is represented on the right-hand side of the image. The EIT impedance map can be divided into 4 regions of interest (ROI), either as quadrants or layers (Frerichs et al., 2017; Vasques et al., 2019). The impedance map is colour coded along an arbitrary colour scale which again varies depending on device. A real-time waveform illustrates changes in impedance over a respiratory cycle. These waveforms are displayed as a global waveform, relating to overall impedance changes across the whole area of analysis and regional waveforms which correspond to the ROI. Additionally, numerical descriptors represent the global impedance (100%) and corresponding

impedance for each ROI providing an estimation of homogeneity of ventilation across lung units (Frerichs et al., 2017; Vasques et al., 2019).

EIT has been compared to CT which is often viewed as the gold standard technique for the visualisation of thoracic aeration and pathology. However, in contrast to EIT, CT can only be used intermittently as the technique requires a patient to be moved away from the bedspace and be exposed to radiation. Additionally, the size of the machine and cost should be considered (Kobylianskii et al., 2016). EIT has been shown to have good agreement with CT in the visualisation of ventilation distribution (Costa et al., 2009; Kobylianskii et al., 2016).

6.2.2 Application of EIT in the ICU setting

A 2016 systematic review summarised the evidence base on the validity and clinical application of EIT in adults receiving IMV (Kobylianski et al., 2016). The review included 67 studies; 35 on EIT validation and the remaining 32 evaluating the clinical application of EIT. Results demonstrated EIT to have good validity in comparison to CT scans, for the assessment of ventilation distribution and changes in lung volumes. The review highlighted the ability of EIT to illustrate respiratory system changes during interventions but highlighted that more data are required. Interventions explored across studies were most commonly PEEP titration or PEEP recruitment manoeuvres, with only three studies examining the effects of airway suctioning. There were no studies identified that explored physiotherapeutic airway clearance strategies.

A number of studies have since been published building on the evidence base for use of EIT during PEEP trials (Eronia et al., 2017; Zhao et al., 2019) and demonstrating the versatility of EIT in quantifying changes in lung aeration during spontaneous breathing trials (SBT) and following extubation (Bickenbach et al., 2017; Longhini et al., 2019), suctioning or identifying adverse events such as pneumothorax (Frerichs et al., 2017).

6.2.3 The use of EIT to evaluate respiratory physiotherapy interventions

There are a small number of studies in non-critically ill patients that have used EIT to evaluate changes in lung ventilation distribution due to physiotherapeutic airway clearance interventions. These studies evaluate interventions such as deep breathing exercises, incentive spirometry, positive pressure devices, and MI-E, both in paediatric and adult populations (Gilgado et al., 2021; Pigatto et al., 2021; Casaulta et al., 2022).

There remains a sparsity of data using EIT to examine the effects of airway clearance strategies in critically ill patients. One pilot randomised physiology study ascertained the effects of high frequency chest wall oscillation and recruitment manoeuvres on lung aeration and ventilation distribution in 60 critically ill adult patients using EIT (Longhini et al., 2020). Results demonstrated aeration of dorsal lung units following high frequency chest wall oscillation, without impacting gas exchange. The addition of recruitment manoeuvres to high frequency chest wall oscillation was also found to have no additional benefit from an aeration perspective. This study illustrates the utility of EIT in analysing the effects of airway clearance strategies.

A published series of clinical scenarios, based in a paediatric ICU population illustrated the use of EIT which included one case of targeted MI-E physiotherapy intervention (Davies et al., 2019). The MI-E physiotherapy case described a nine-year-old patient with right total lung collapse for which MI-E was used alongside manual techniques as part of a regular airway clearance regime. The treatment effectively cleared secretions but the inclusion of EIT monitoring enabled early identification of further de-recruitment following the corresponding exsufflation negative pressure breath of MI-E. This was not improved following the delivery of the pre-set re-insufflation breaths available on the MI-E device. Clinicians were therefore able to adapt their treatment prescription for effective re-recruitment of the right side, preventing clinical deterioration. Davies et al (2019) also reported ongoing use of EIT during the clinical course, negating the need for any chest x-rays during this time.

6.2.4 Lung Ultrasound

Lung Ultrasound is an emerging, readily available, bedside imaging tool that is non-invasive and has the ability to assess and visualise pleura, lung and diaphragm. It can be used to diagnose and assess pneumothoraces, consolidation, pleural effusion and interstitial syndrome (Via et al., 2012; Leech et al., 2015; LeNeindre et al., 2016; Hayward and Janssen, 2017; Mojoli et al., 2018; Hansell et al., 2021). There is evidence of increasing use of LUS by physiotherapists in the respiratory setting (LeNeindre et al., 2016).

One case report illustrates the use of LUS using lung recruitment techniques in a patient with post-operative atelectasis resolution. LUS was used to ascertain if the images

generated enabled treatment modification of two techniques in real time. LUS was used pre/post manual hyperinflation versus ventilator hyperinflation to assess re-expansion of collapsed lung units (Cavaliere et al., 2011). More recently, Le Neindre and colleagues (2023) completed a prospective, observational, multi-centre study which evaluated experienced physiotherapist diagnoses with and without the use of a LUS report.

The emerging evidence of the diagnostic utility of LUS and EIT in the ICU setting and the ability of the technique to impact clinical treatment decisions appears positive. These techniques may be considered as diagnostic tools evaluating the effect of MI-E in the ICU setting. To date, no studies have examined the extent of recruitment and de-recruitment or possible adverse events in relation to alternating positive (insufflation) and negative pressure (exsufflation) breaths applied during MI-E in the adult ICU population. This is an important consideration as there are currently no evidence-based recommendations to guide clinical practice and the application of MI-E specifically in this population.

6.3 Sub-study aim

To examine lung recruitment and de-recruitment during MI-E using EIT and LUS to consider:

- patterns of recruitment during insufflation
- patterns of de-recruitment following exsufflation
- any associated adverse effects of MI-E use

6.4 Sub-study design

This nested exploratory physiology study is presented as a case series. Each patient is presented separately and includes a brief case presentation with ventilator settings at the time of data collection, any relevant past medical history and a description of physiotherapy treatment (including MI-E settings and prescription).

6.4.1 Participants

The recruitment of trial participants has been described previously (Chapter 4). All patients randomised into the MI-E treatment arm were initially eligible for inclusion in the nested study. Patients were excluded from the nested study if they had any contraindications to EIT use including a pacemaker; implantable cardioverter defibrillator; implantable pump; or were pregnant. Additionally, patients were excluded if they had any damage to the skin or fractures/lesions in the area of electrode belt placement. These are listed contraindications of the EIT device use as per manufacturers guidelines.

The target sample for the sub-study case series was between 5 and 10 patients over a six-month period. The duration of this nested study was reliant on device availability.

6.4.2 Consent

Consent for inclusion in this nested study was gained within the scope of the overarching feasibility study. Where the participant did not have capacity to provide informed consent a consultee was approached (personal/professional) as per the main trial protocol (Chapter 4, section 4.4.4).

6.4.3 Data collection and reporting

Electrical Impedance Tomography

The PulmoVista 500 (Drager, Lubech, Germany) was used within the nested study. A silicone belt containing 16 electrodes was placed between the 4-6th intercostal space (Karstan et al., 2016; Vasques et al., 2019) (Figure 6.1). Below this level may impact generated results due to interference from the diaphragm moving into the measurement plane (Freichs et al., 2017). On the belt, electrodes 1 and 16 were placed symmetrically and equidistant from the sternum, with electrodes 8 and 9 positioned posteriorly equidistant from the spine. Additionally, a reference electrode was attached to the central abdomen.

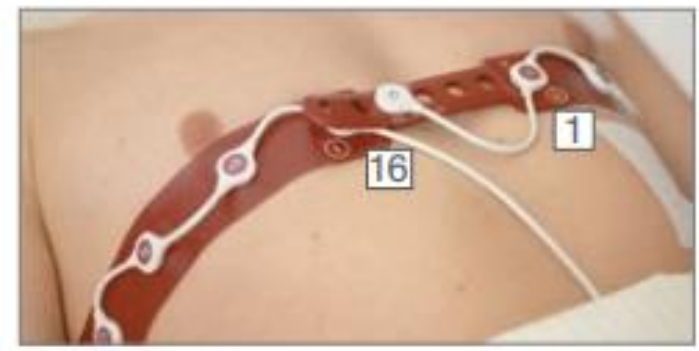

Figure 6.1 EIT electrode belt placement.

Numbers 1 and 16 refer to electrodes to be placed equidistant to the sternum at approximately the 4-6th intercostal space. Reproduced with permission from Draeger Dräger PulmoVista® 500 | Draeger).

Abbreviations: EIT, electrical impedance tomography

The EIT screen set up included ROI as 'layers' thus enabling comparison of left and right, and dorsal and ventral. Screenshots and event markers were used throughout to highlight any additional information that may aid subsequent analysis, for example disconnection from

the ventilator, insufflation and exsufflation breaths, spontaneous coughs, suction and patient agitation.

The device was set to record once the electrode belt was in situ with data visualised on screen. The study procedure was recorded throughout and started with 5 minutes of quiet breathing on the ventilator to act as a baseline reference. The patient was then disconnected from the ventilator and physiotherapy treatment including MI-E was completed. On completion of the physiotherapy treatment, the patient was returned to the ventilator and a second 5 minute period of ventilator quiet breathing was recorded. EIT data recording was then stopped.

EIT data analysis

Distribution of regional ventilation was recorded before, during and after MI-E, using baseline values as a reference to describe changes during MI-E. End inspiratory lung volumes (EILV) were used to describe changes in recruitment and de-recruitment during and following the MI-E intervention using baseline values as a reference. Screenshots were taken for illustrative purposes to aid description of results (Figures 6.2 and 6.3). Any adverse effects occurring during data collection were recorded as per the feasibility study protocol (see section 4.8).

Lung Ultrasound

The ultrasound device, Venue Go (GEHealthcare, Buckinghamshire, UK) was used within the nested study. The LUS was calculated before the MI-E intervention (during the 5 minutes quiet ventilator breathing) and after the MI-E intervention (once the patient was

reconnected to the ventilator). The use of the LUS has been previously discussed in Chapter 4 (section 4.6).

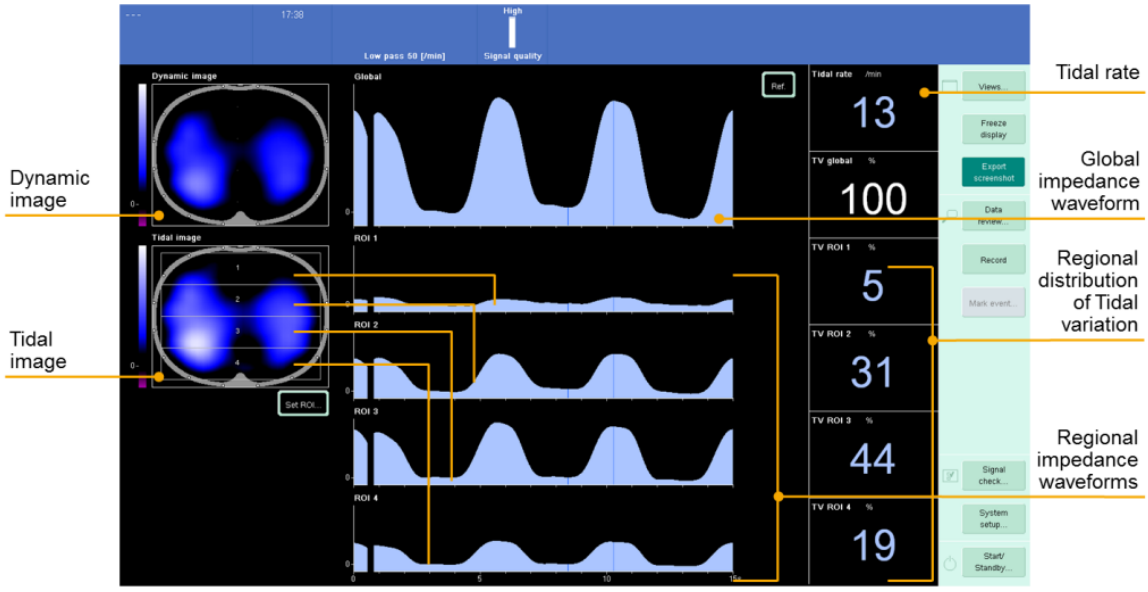

Figure 6.2 EIT Main screen view. Illustrating regional distribution of tidal volume. (The dynamic image displays in real-time the distribution of regional volume changes during inspiration and expiration.)

Reproduced with permission from Draeger [Dräger PulmoVista® 500 | Draeger]).

Abbreviations: EIT, electrical impedance tomography

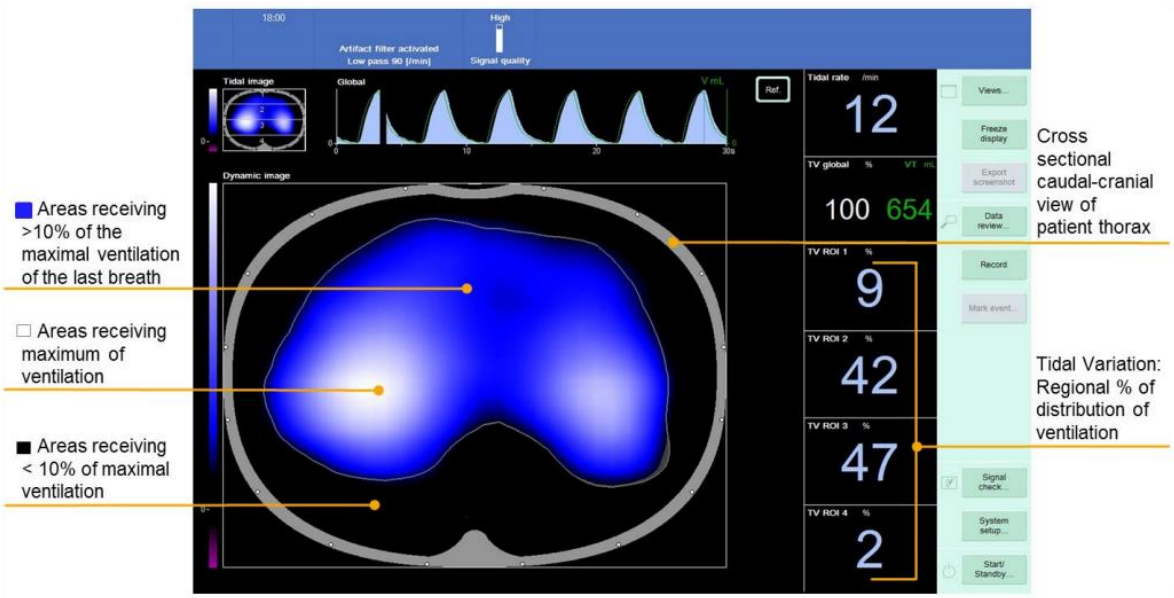

Figure 6.3: EIT full screen view. Illustrating ventilation distribution via a heatmap (blue, white and black). Reproduced with permission from Draeger [Dräger PulmoVista® 500 | Draeger]).

Abbreviations: EIT, electrical impedance tomography

6.5 Findings

Data were collected from five individual patients over a 6-month period (1st January 2023-30th June 2023). Detail regarding patient baseline ventilation settings and MI-E set up are described in tables 6.1 and 6.2 respectively.

6.5.1 Case presentation 1: Patient A

Patient A was admitted to ICU with a left sided empyema with bilateral consolidation on a background of bronchiectasis. He was intubated due to worsening respiratory failure, increased work of breathing (WOB) and persistently high oxygen requirements ($FiO_2$0.7). At the time of study recruitment, patient A had failed extubation once.

On ICU admission, the family reported that patient A had experienced worsening cough and multiple infective exacerbations during the previous year. Exercise tolerance remained reasonable; with ability to complete activities such as gardening but at a slower pace than normal. Past medical history (PMH) included severe lung disease (bronchiectasis and asthma) and previous pseudomonas infection in the last year treated with nebulised colomycin.

From an airway clearance perspective physiotherapy and nursing documentation stated that Patient A had retained secretions that were challenging to clear with endotracheal suction alone. Physiotherapy in the previous 24 hours had included manual techniques (expiratory vibrations), saline and suction with minimal successful secretion clearance. Prior to data collection the patient had been re-positioned. At the time of EIT data collection, Patient A was ventilated using Synchronised Intermittent Mandatory Ventilation (SIMV) (Table 6.1 for detailed ventilation settings at the time of data collection).

Physiotherapy treatment description

Physiotherapy treatment (Table 6.2) consisted of a positioning change from side lying into supine with a head up tilt, MI-E and suction with the instillation of saline. One cycle of repeated insufflations (up- to five) were completed prior to each exsufflation. A cycle was then repeated five times before the patient was reconnected to the ventilator. Suctioning was completed during the exsufflation breath (parallel suction), timed to start in synchrony

with the start of the exsufflation breath, with secretions being cleared. A desaturation to 84% occurred on returning to the ventilator but this resolved without further intervention.

Subsequent MI-E cycles (repeated five times) were completed with oxygen entrained. On the final MI-E cycle minimal sputum was cleared therefore the patient was returned to the ventilator and the treatment session ended.

Findings

The LUS was only recorded pre-treatment (Table 6.3). During MI-E, recruitment was apparent on the first insufflation breath illustrated through a change in impedance (brighter white pixels) and a positive change to EILV as measured by EIT (Figure 6.4A and table 6.4). Recruitment was initially preferential to lung units already recruited (ROI 1 and 2) resulting in ventilation heterogeneity. The distribution of ventilation across the ROI remained fairly static but with repeated insufflation breaths the posterior segments started to gain recruitment (Figure 6.4B). The exsufflation breath caused mass de-recruitment illustrated through reduced impedance and a negative change to EILV (Figure 6.4C). Despite five repeated insufflation re-recruitment breaths occurring at the end of MI-E treatment, changes to global EILV remained negative in comparison to pre-treatment (Table 6.4).

Table 6.1 Patient ventilation settings

Patient case	Mode of ventilation	Interface	Ventilator settings	FiO_2
A	SIMV	ETT	Set volume 400ml; PEEP 8cmH_2O, set rate 26bpm, spontaneous breaths 2bpm	.30
B	CPAP	ETT	PEEP+5 cmH_2O, PS 0	.25
C	CPAP	ETT	PEEP +8cmH_2O, PS 0	.30
D	APRV	ETT	Phigh 21cmH_2O, Plow 0cmH_2O, T high 6seconds	.40
E	SIMV	ETT	PEEP 10cmH_2O, set volume 400mls	.35

Abbreviations: APRV, airway pressure release ventilation; bpm, breaths per minute; cmH_2O, centimetres of water; CPAP, continuous positive airway pressure; ETT, endotracheal tube; FiO_2, fraction of inspired oxygen; ml, millilitres; PEEP, positive end expiratory pressure; Phigh, pressure high; Plow, pressure low; PS, pressure support; SIMV, synchronised intermittent mandatory ventilation

Table 6.2 Physiotherapy treatment prescription during EIT data collection

Patient case	MI-E prescription						Other physiotherapy interventions used during treatment session*
	MI-E mode	Insufflation pressure (cmH_2O)	Exsufflation pressure (cmH_2O)	Repeated insufflation	No of cycles	Entrained O_2	
A	manual	35	-45	5	10	10L	positioning, saline and suction
B	manual	30	-40	3	10	NA	suction
C	Manual	30	-30	1	4	5L	Positioning, suction
D	Manual	24	-35	6	3	NA	Saline and suction
E	Manual	30	-40	5	5	NA	Manual techniques, suction

*Treatments in addition to MI-E

Abbreviations: cmH_2O, centimetres of water; L, litres; MI-E, mechanical insufflation-exsufflation; NA, not applicable; *O_2, oxygen*

Table 6.3 Lung ultrasound score and variation of ventilation distribution during MI-E

Patient case	Lung Ultrasound Score		Variation of ventilation distribution (%) across EIT regions of interest			
	Pre-treatment	Post treatment	1	2	3	4
1	20	Not recorded	16-54	21-51	11-27	7-24
2	Not recorded	Not recorded	34-52	34-43	4-16	1-9
3	Not recorded	Not recorded	18-36	11-46	21-36	4-19
4	Not recorded	Not recorded	21-40	22-31	25-37	3-11
5	Not recorded	Not recorded	28-51	20-46	5-21	1-8

Abbreviations: EIT, electrical impedance tomography; MI-E, mechanical insufflation-exsufflation

Table 6.4 Changes to EILV during MI-E treatment: Patient A

Patient case	EIT Region of interest	Timepoints of comparison		
		Pre-treatment v Insufflation breaths	Insufflation v post exsufflation	Pre-treatment v post treatment
A	Global			
	1			
	2			
	3			
	4			

Key: blue denotes a positive change in EILV (suggesting an increase in ventilation); orange denotes a negative change in EILV (suggesting a loss in ventilation)

Abbreviations: EILI, end inspiratory lung volume; EIT, electrical impedance tomography

Image A: Insufflation breath 1

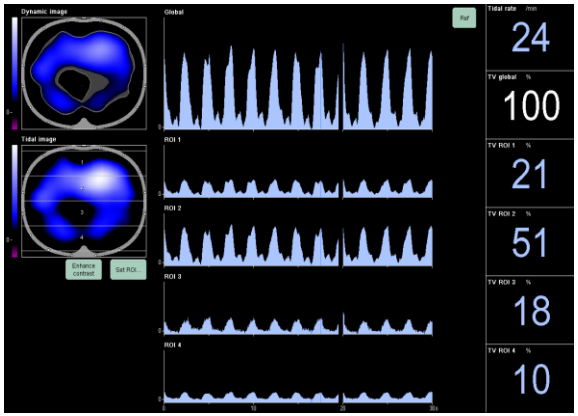

Image B: Insufflation breath 5

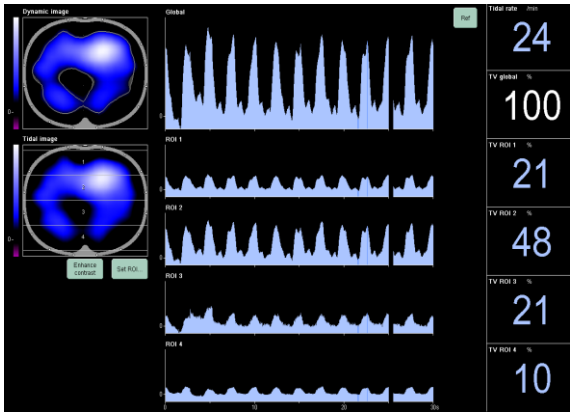

Image C: Exsufflation breath

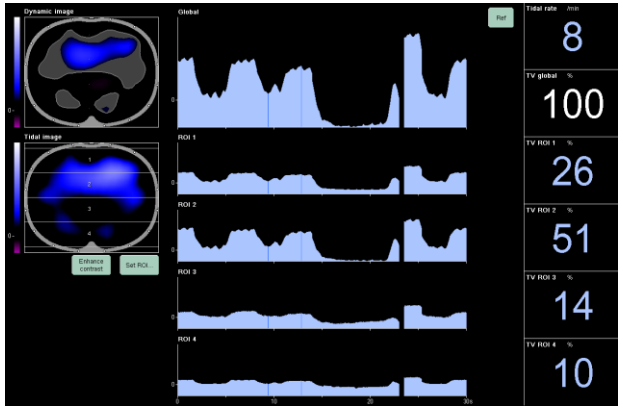

Figure 6.4: EIT screenshots for Patient A. Demonstrating impedance change in each ROI with brighter (white) pixels denoting a greater impedance change (image A and B), equivalent to increased ventilation/recruitment. Image C shows darker pixels due to a reduction in impedance, equivalent to reduced ventilation and a lack of recruitment particularly in posterior segments.

Abbreviations: EIT, electrical impedance tomography; ROI, region of interest

6.5.2 Case presentation 2: Patient B

Patient B was admitted to ICU and intubated following an elective whipples procedure for ampulla adenocarcinoma after presenting initially to hospital with jaundice.

PMH for this patient included asthma, hypertension and a high alcohol intake (approximately 5 pints/day with the patient reducing this intake prior to surgery).

At the time of data collection, the patient was receiving IMV (CPAP) (see table 6.1). They remained sedated with propofol and alfentanil and were on noradrenaline to support their cardiovascular system. Auscultation revealed quiet breath sounds bi-basally with course creps apically and tactile fremitus apically. Previous airway clearance treatment sessions included positioning and manual techniques but these had not been successful in clearing the sputum load.

Physiotherapy treatment description

MI-E settings are described in Table 6.2. Five cycles of MI-E were completed in both left and right side lying, and in supine with parallel suction timed to each exsufflation breath. Secretions were successfully cleared but on repeat auscultation, evidence of retained secretions remained, with reduced air entry on the right base. MI-E pressure settings were subsequently increased to +35:-45cmH_2O and five further MI-E cycles were repeated. There were no adverse events to report during this treatment session.

Findings

The LUS was not recorded for this patient. During insufflation breaths, recruitment was illustrated through a positive change to EILV (Table 6.5). Preferential recruitment occurred to ROI 1 and 2 throughout MI-E delivery (Table 6.3). Repeated insufflations resulted in a positive change to EILV across ROI 1, 2 and 4. From insufflation to exsufflation breaths a negative change to EILV occurred (Table 6.5) demonstrating decruitment to lung units across all ROI. Following repeated insufflation re-recruitment breaths, there remained a positive change to EILV globally and specifically in ROI 1 on returning to the ventilator in comparison to pre-treatment values, demonstrating heterogeneity of ventilation distribution post treatment.

Table 6.5 Changes to EILV during MI-E treatment: Patient B

Patient case	EIT Region of interest	Timepoints of comparison		
		Pre-treatment v Insufflation breaths	Insufflation v post exsufflation	Pre-treatment v post treatment
B	Global			
	1			
	2			
	3			
	4			

Key: blue denotes a positive change in EILV (suggesting an increase in ventilation); orange denotes a negative change in EILV (suggesting a loss in ventilation)

Abbreviations: EILI, end inspiratory lung volume; EIT, electrical impedance tomography

6.5.3 Case presentation 3: Patient C

Patient C was admitted following an out of hospital cardiac arrest having collapsed whilst playing basketball with friends. Bystander CPR was completed whilst waiting for an ambulance. The patient was intubated in the emergency department. A CT scan following intubation demonstrated significant pan-lobar aspiration with a right lower lobe lung collapse. There was no evidence of rib fractures from either the CT or chest x-ray. Since intubation the patient had an ongoing secretion load which had been challenging to clear for both nurses and physiotherapists.

Relevant PMH for this patient included mild asthma (salbutamol inhaler prescribed PRN), otherwise they were fit and well with no previous hospital admissions. There was no family history of heart conditions. At the time of data collection, the patient was invasively ventilated with airway pressure release ventilation (Table 6.1). On auscultation there were quiet breath sounds throughout, which were slightly quieter on the right side.

Physiotherapy treatment description

The patient was re-positioned from supine into a tilt to the left side. MI-E was commenced using pressure settings of 30:-30cmH_2O (Table 6.2) with oxygen entrained. Parallel suction was completed on each exsufflation which cleared secretions and old blood. The treatment session was otherwise uneventful.

Findings

The LUS was not completed for this patient during this treatment session. As illustrated on EIT images (Figure 6.5), insufflation breaths resulted in an impedance change (whiter pixels) suggesting increased recruitment of lung units (Figure 6.5 Image A and C). This was also demonstrated by a positive change in EILV from pre-treatment to post insufflation breaths across ROI 1-3 (Table 6.6). A negative change to EILV in ROI 4 demonstrates a lack of recruitment particularly in the posterior segments. In contrast, following the exsufflation breath, a reduction in impedance (darker pixels) suggestive of lung unit de-recruitment was noted (Figure 6.5 Image B and D). This was supported by a negative change in EILV (Table 6.6). This pattern repeated with each MI-E cycle. Throughout MI-E the ventilation distribution was predominantly across ROI 1-3, with ROI 4 having the least percentages of ventilation distribution (Table 6.3) suggestive of poor recruitment to the posterior lung segments. On returning to the ventilator, a positive change in global EILV in comparison to pre-treatment values was recorded, this was pre-dominantly seen across ROI 1 and 2 (Table 6.6).

Table 6.6 Changes to EILI during MI-E treatment: Patient C

Patient case	EIT Region of interest	Timepoints of comparison		
		Pre-treatment v Insufflation breaths	Insufflation v post exsufflation	Pre-treatment v post treatment
C	Global			
	1			
	2			
	3			
	4			

Key: blue denotes a positive change in EILV (suggesting an increase in ventilation); orange denotes a negative change in EILV (suggesting a loss in ventilation)

Abbreviations: EILI, end inspiratory lung volume; EIT, electrical impedance tomography

Image A: Insufflation breath (cycle 2)

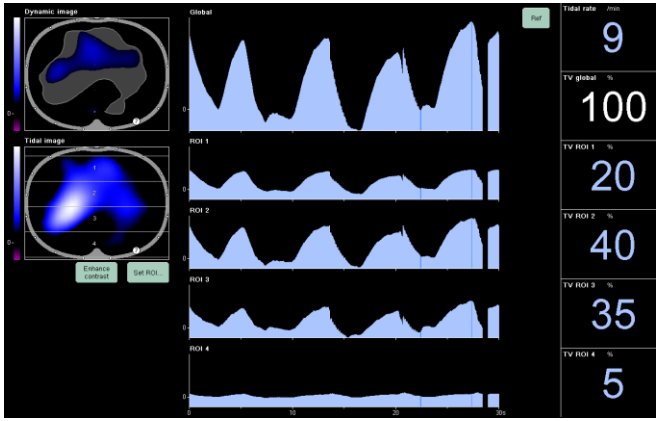

Image B: Exsufflation breath (cycle 2)

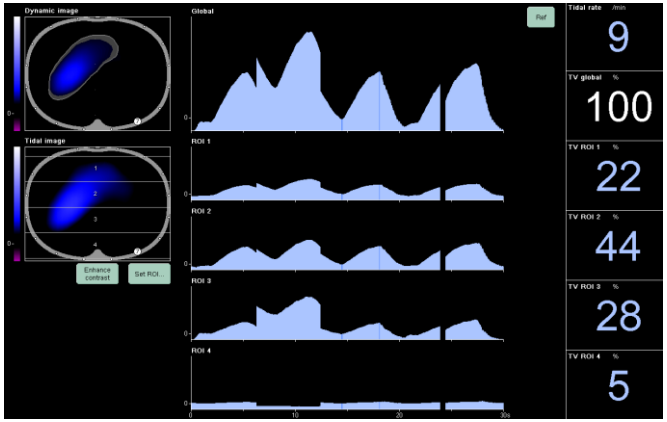

Image C: Insufflation breath (cycle 4)

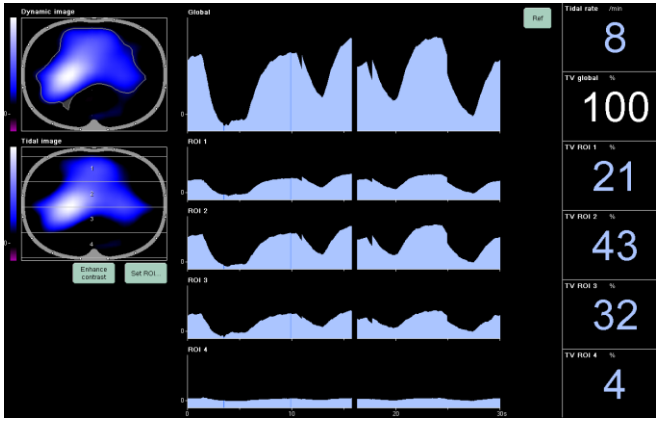

Image D: Exsufflation breath (cycle 4)

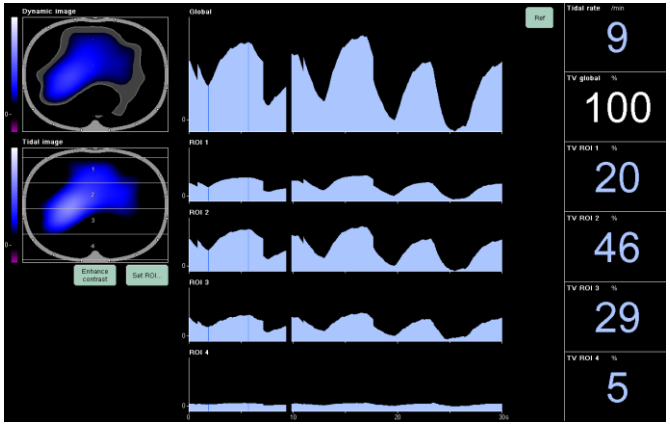

Figure 6.5: EIT screenshots for Patient C. Demonstrating impedance change in each ROI with brighter (white) pixels denoting a greater impedance change following insufflation (Image A and C). Images B and D show darker pixels due to a reduction in impedance, equivalent to reduced ventilation.

Abbreviations: EIT, electrical impedance tomography; ROI, region of interest

6.5.4 Case presentation 4: Patient D

Patient D was admitted with right upper quadrant pain and worsening breathlessness. A CT demonstrated loculated pleural fluid therefore a video assisted thoracic surgery procedure was completed for removal of what was found to be pus (approximately 1.2Litres). Two days later the patient experienced a further clinical deterioration illustrated through rising FiO_2 requirements and worsening arterial blood gases. A CT showed a left sided empyema and anterior mediastinal collection. The patient returned to theatre for a left sided decortication.

PMH for patient D included active illicit drug use (including intravenous) of crack cocaine and heroin. There was nil other history to note and no previous hospital admissions. The patient had no fixed abode but occasionally lived with his Grandfather.

Post operatively the patient remined intubated. By day 18 the nursing staff reported clearing copious amounts of secretions with suction, particularly during recent sedation holds. However, an ongoing secretion load was apparent on auscultation which was limiting his weaning ready for extubation. At the time of data collection, the patient was ventilated on APRV (Table 6.1). The patient was cardiovascular stable (unsupported) with a blood pressure of 102/44mmHg, mean arterial pressure of 62 and a heart rate of 78bpm. Auscultation completed pre-MI-E showed reduced breath sounds bibasally with creps audible throughout the right side.

Physiotherapy treatment description

MI-E was initially used with pressure settings of +24:-35cmH_2O and a rise of 2 (Table 6.2). Six repeated insufflations were completed with parallel suction on each exsufflation breath which cleared copious amounts of thick secretions. This was repeated for three cycles before returning to the ventilator. Despite clearing secretions, an audible secretion load remained on auscultation. An increase to the pressure settings occurred to 30:-40cmH_2O, all other settings remined the same. Six repeated insufflations were delivered prior to an exsufflation which was then repeated for three cycles. Parallel suction timed with each exsufflation breath continued to clear secretions.

Findings

The LUS was not recorded for this patient. Throughout MI-E delivery, distribution of ventilation was predominantly across ROI 1-3, with sparing of ROI 4 (Table 6.3). When comparing insufflation breaths to pre-treatment a negative change to EILV was recorded both globally and across ROI 3-4 illustrating heterogeneity of ventilation distribution during insufflation breaths (Table 6.7). A negative change in EILV, suggesting a loss in volume occurred across all ROI following exsufflation. On returning back to the ventilator a global reduction in EILV remained despite re-recruitment occurring at the end of the MI-E treatment (Table 6.7).

Table 6.7 Changes to EILV during MI-E treatment: Patient D

Patient case	EIT Region of interest	Timepoints of comparison		
		Pre-treatment v Insufflation breaths	Insufflation v post exsufflation	Pre-treatment v post treatment
D	Global			
	1			
	2			
	3			
	4			

Key: blue denotes a positive change in EILV (suggesting an increase in ventilation); orange denotes a negative change in EILV (suggesting a loss in ventilation)

Abbreviations: EILV, end inspiratory lung volume; EIT, electrical impedance tomography

6.5.5 Case presentation 5: Patient E

Patient E was admitted with sepsis secondary to pneumonia and a secondary diagnosis of acute kidney injury on the background of dialysis dependent end stage renal failure. The patient had had a 'chesty cough' with sputum production for a week prior to admission with a progressive worsening of symptoms. The patient was admitted to ICU on day 3 of hospital admission due to hypotension, tachycardia and respiratory distress. He was intubated secondary to worsening respiratory failure.

Relevant PMH included opioid dependence with a history of heroin inhalation, ulcerative colitis with a total colectomy and ileostomy (March 2023), and thrice weekly haemodialysis at a neighbouring Trust.

Physiotherapy treatment up to the point of data collection included positioning, manual techniques and suction. Initially physiotherapists and nurses had managed to clear secretions but a worsening sputum load had been reported by nurses over the last 24 hours.

Physiotherapy treatment description

MI-E was used in manual mode with repeated insufflations followed by an exsufflation breath making up one cycle. During passive expiration (in between each repeated insufflation) vibrations were used. Parallel suction timed to the exsufflation breath was completed at the end of each cycle. A total of five cycles were completed.

Findings

Preferential distribution of ventilation was seen across ROI 1 and 2 (ventral regions) with sparing of ROI 3 and 4 (dorsal regions) throughout MI-E (Table 6.3). EIT images mirror the heterogeneity of ventilation distribution. Additionally, there was an apparent difference across left and right regions, with the left posterior segment illustrating reduced ventilation (Figure 6.6). Insufflation breaths resulted in a global increase in EILV, associated to ROI 1 (Table 6.8). Following exsufflation breaths a global reduction in EILV occurred, suggestive of de-recruitment. Post treatment, a positive change to EILV was recorded globally, again associated to ROI 1 and 2.

Table 6.8 Changes to EILV during MI-E treatment: Patient E

Patient case	EIT Region of interest	Timepoints of comparison		
		Pre-treatment v Insufflation breaths	Insufflation v post exsufflation	Pre-treatment v post treatment
E	Global			
	1			
	2			
	3			
	4			

Key: blue denotes a positive change in EILV (suggesting an increase in ventilation); orange denotes a negative change in EILV (suggesting a loss in ventilation)

Abbreviations: EILI, end inspiratory lung volume; EIT, electrical impedance tomography

Image A: Insufflation breath

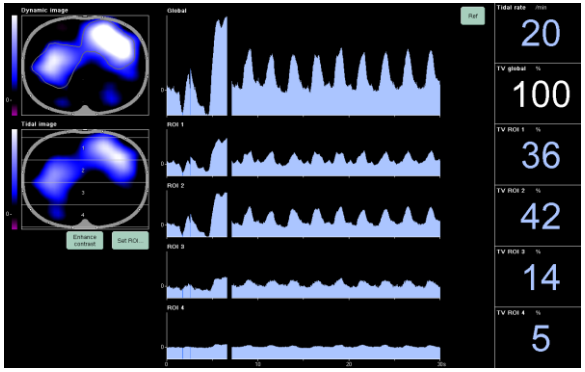

Image B: Exsufflation breath

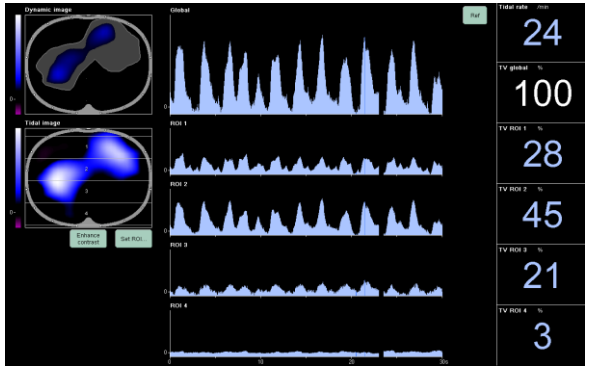

Image C: Insufflation re-recruitment breath

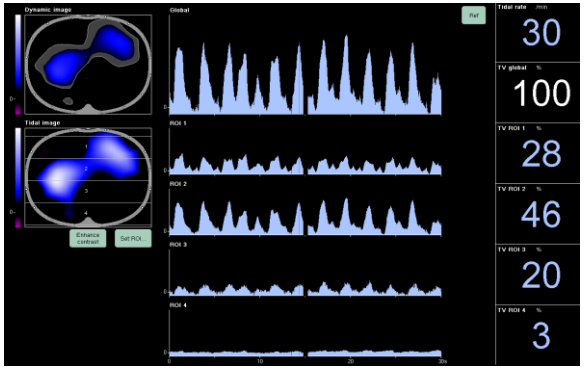

Figure 6.6: EIT screenshots for Patient E. Demonstrating impedance change in each ROI with brighter (white) pixels denoting a greater impedance change following insufflation (Image A). Images B shows darker pixels due to a reduction in impedance, equivalent to reduced ventilation and a lack of recruitment particularly in the posterior segments following exsufflation. Image C demonstrates re-recruitment breaths

Abbreviations: EIT, electrical impedance tomography; ROI, region of interest

6.6 Discussion

To the authors knowledge this was the first study to explore recruitment and de-recruitment during MI-E using EIT in critically ill intubated adults. The clinical impact of lung overdistention and de-recruitment is well documented (Brower et al., 2000; Park et al., 2013; Gattinoni et al., 2018; Chen et al., 2020; Goligher et al., 2020) alongside a paucity of data pertaining specifically to MI-E in the ICU population. The study is reported as a case series of a small sample size; as a result, no inferences could be made. However, patterns across the case series are apparent which are further discussed in relation to the current literature and with consideration for clinical practice implications and future research recommendations.

Across the five clinical cases likely lung recruitment occurred during the application of insufflation breaths, however, patterns of recruitment resulted in heterogenous ventilation distribution. In all cases, posterior/distal regions were spared and, in some cases, required multiple insufflation breaths to demonstrate any change in impedance and subsequent ventilation. With the heterogenous ventilation distribution and an apparent delayed inflation of more dorsal lung units, it is possible that lung units already recruited and 'open' have the potential to become overdistended predisposing a patient to lung injury. The concept of a 'baby lung' is well documented (Gattinoni et al., 2016; Gattinoni et al., 2018) and the pressure required to re-expand atelectatic or collapsed lung may result in the over-distension of this 'baby-lung' (Terragni et al., 2007). Additionally, it should be considered that the 'time constants' of each lung unit are likely to vary across the lung further contributing to a heterogenous ventilation pattern. Clinicians have the ability to adapt the

MI-E prescription to include changing the flow rate of the insufflation breath. A slower, longer duration insufflation breath may help to overcome some of these physiological challenges. The case series was not set up to consider such inferences but this would be a useful area for future investigation in order to understand the physiological impact of using MI-E in the ICU population.

With bench studies examining MI-E set up to optimise expiratory flow generation and recommending insufflation pressures of approximately +50cmH_2O, the concept of potential overdistension and subsequent clinical safety implications must be considered (Guerin et al., 2011; Hyan et al., 2021). Pressures to these recommended levels were not applied in the current study, but the heterogenous pattern of ventilation was still apparent. With higher pressures, patients may have been at an even greater risk over distention and lung injury. Previous authors (Tremblay and Slutsky, 2006) have described the resultant lung injury and release of inflammatory mediators following the application of ventilation strategies including increased tidal volumes with reduced PEEP. These findings cannot however be directly translated when considering use of MI-E. MI-E is used transiently throughout IMV in comparison to the continuous use and effects of IMV, therefore the degree of impact from MI-E is unknown.

Clinical studies of MI-E to date, as described in Chapter 2 have commonly used protocolised MI-E prescription with pressure settings of +40:-40cmH_2O. These settings are higher than used in the current exploratory sub-study and lower than recommended pressure settings from previous bench studies (Guerin et al., 2011; Hyan et al., 2021). Despite no adverse events being reported during MI-E application and EIT measurements in the current case

series, the clinical consequences of these changes are unknown and worthy of future consideration.

Following exsufflation breaths, global de-recruitment was apparent across all clinical cases. This could leave a patient at risk of clinical deterioration. Impedance changes and associated de-recruitment with MI-E use has been reported previously in a case series including a paediatric patient on IMV (Davies et al., 2019). Authors described temporary collapse of the right lung in association with MI-E use. At the bedside, clinicians reported the clearance of secretions which could be viewed as a positive treatment outcome, however the negative impact was apparent via EIT images. These findings, illustrating both positive and negative sequalae of exsufflation breaths are important to consider as they illustrate the importance of individual assessment and balance between clinical risk and patient benefit. In order to mitigate or reduce clinical risk, adaptations to MI-E treatment prescriptions could be considered.

It is important to acknowledge that despite global de-recruitment being apparent across all clinical cases following an exsufflation breath, MI-E was used in conjunction with other treatment techniques so changes described cannot be solely attributed to MI-E. Previous studies have demonstrated a reduction in end inspiratory and expiratory lung volumes with EIT following suctioning via an ETT (Lindgren et al., 2007). Also, the simple process of disconnecting a patient from the ventilator to use the MI-E device will have resulted in a loss of PEEP (as delivered by the ventilator). This will have also had an impact on resultant lung volumes.

Re-recruitment breaths (repeated insufflation breaths using MI-E) prior to returning the patient to the ventilator were used by clinicians in all described cases. Anecdotally, it is thought that using repeated insufflation breaths will help to re-recruit lung units prior to returning a patient to the ventilator. This is an interesting finding as there is currently no evidence for or against this prescription. The data suggests an improvement in ventilation with these repeated insufflations but again a heterogenous ventilation distribution is apparent. It is possible that following significant de-recruitment, these early re-insufflation breaths cause atelectrauma through cyclic opening and closing of the distal airways and alveolar units (dos Santos and Slutsky, 2006; Gattinoni et al., 2018). This may be due to the lack of PEEP when using the MI-E device.

In all cases there remained regions where impedance and therefore ventilation were sub-optimal in comparison to pre-MI-E treatment (when patient was on the ventilator). This is an important consideration for clinical practice because patients may be returning to the ventilator in a 'less recruited' state than pre-treatment, thus predisposing them to an increased risk of deterioration. The clinical implications and optimal number of re-recruitment breaths post MI-E treatment is not known. There are also other physiotherapy interventions which could be employed once a patient has returned to the ventilator including VHI. This technique, as described in Chapter 1, aims to re-inflate collapsed lung units in order to increase lung volumes (Paulus et al., 2012; Tronstad et al., 2022). Another point for consideration is the positive impact of secretion clearance due to airway clearance techniques employed by clinicians (Cork et al., 2022; Tronstad et al., 2022). With more secretions being cleared, there should be a positive impact on airway resistance, opening

channels of ventilation and potentially improving recruitment once normal ventilation is restored. Again, it is not known whether re-recruitment should or needs to occur using the MI-E device or with other treatment strategies when the patient has returned to the ventilator. It is unlikely that there is a 'one size fits all' recommendation. However, gaining a greater understanding of the physiological impact of MI-E application on recruitment and de-recruitment would be a truly valuable addition to the evidence base and potentially support practice recommendations.

There are limitations to this study that should be acknowledged. As a case series of five patients no inferences can be made from the generated data. Additionally, clinical conditions and patient diagnoses varied. This protocol used one MI-E device (Clearway 2) and so outcomes may have been different if other devices had been used. The protocol under investigation allowed clinician determined MI-E prescription and so each patient received a different MI-E set up and delivery which may also have impacted outcomes. EIT measurements were completed pre-MI-E treatment, during MI-E and for 5 minutes after MI-E treatment. There is the potential that with a greater period of time using MI-E post treatment, for example 30 minutes post treatment, there may be changes in ventilation that are overall positive and improve homogeneity in those with a previously more heterogenous lung.

Despite there being a number of studies demonstrating the ability of EIT to accurately measure recruitment and de-recruitment of lung units, there are sources of error when using EIT including repeatability of belt placement, and patient movement impacting device

readings (Karsten et al., 2016; Vasques et al., 2019). No such occurrences were recorded during data collection however these sources of error are still important to consider. Furthermore, EIT imaging does not provide information about the whole lung, and is instead reported to be closer to approximately a 50% coverage with the belt being central to that image (Spadaro et al., 2018). Finally, there was poor completion of LUS throughout the study which resulted in a lack of data to include in the discussion of this case series. Poor utility of the LUS and barriers to use have been previously reported (Hansell et al., 2022) and has been discussed in context of the current body of work in Chapter 5.

6.7 Researcher position

Despite this chapter representing a sub-study within a larger feasibility RCT, it is these findings that have made me pause and think about how the technique of MI-E is working and what is happening from a physiological perspective, particularly regarding safety. I acknowledge the limitations to the current sub-study and the inability to draw any firm conclusions from presented results. However, the patterns of recruitment suggest overdistension of lung units. Equally the extent of derecruitment following a negative pressure exsufflation breath has made me question whether I finish treatment sessions leaving the patient to rest or recover. I believe I am now more considered when using MI-E in this specific population. Current bench studies recommend using an increased pressure set up to overcome resistance of the artificial airway. The current study used lower settings but there was still change related to recruitment and derecruitment. These findings have made me appreciate how much there still is to learn about the use of MI-E as a technique in the ICU cohort.

6.8 Conclusions

This nested exploratory physiology study explored the impact of MI-E application on lung recruitment and de-recruitment, demonstrating potential perpetuation of heterogenous ventilation patterns and resultant overdistension, alongside likely global de-recruitment following an exsufflation breath. Due to the small sample size additional research is recommended to determine the physiological effects of MI-E on recruitment and de-recruitment in the intubated population and the impact on clinically important patient outcomes. Such information will be a valuable contribution to evidence-based guidance for MI-E use in this vulnerable population.

Chapter 7 Summary and conclusions

This chapter provides an overview of the thesis to include novel aspects to the work completed, alongside strengths and limitations. To conclude, learning points and future research opportunities and recommendations to continue development of the evidence base are made.

7.1 Novel aspects to this thesis

Based upon available literature the work included in this thesis presents the first studies to investigate:

- The feasibility of a clinician determined mechanical insufflation-exsufflation (MI-E) protocol
- Clinician and patient experiences of using MI-E in the intensive care unit (ICU) setting
- The physiological impact of MI-E using electrical impedance tomography (EIT)

7.2 Summary

Extubation failure is often linked to retained secretions and poor cough effectiveness and is associated with an increase in duration of IMV, ICU LOS and mortality rates. MI-E is a non-invasive cough augmentation technique which has been successfully implemented in the NMD population and has some early evidence for its use in the ICU setting. The primary aim

of this thesis was to investigate the emerging use of MI-E as an airway clearance intervention to promote extubation success in the adult ICU setting. The studies reported in the thesis have employed a variety of methods addressing a number of specific research questions. Undertaking this research has facilitated my development as a clinician and researcher. During this time, I have also had the opportunity to develop collaborations with international experts in the field of ICU.

In order to gain an understanding and appreciation of how MI-E had been used in research to date, Chapter 2 of this thesis presented a scoping review which adhered to PRISMA-SR guidance for the design and conduct of the study (Tricco et al., 2018). The modified and updated literature search generated additional references to those included in the earlier Cochrane review (Rose et al., 2017) enabling the advancement of knowledge. Results included 28 studies which demonstrated little consistency in how MI-E was used and reported, thus limiting the ability to implement individual study conclusions and make general practice-based recommendations. A lack of qualitative data was also apparent. The variation in outcomes used across studies also had little consistency impacting the ability to compare and contrast findings as well as the overall quality of the evidence.

An exploration of clinician experiences of using MI-E in the ICU setting was presented in Chapter 3; the first study of this nature in the UK. The interviews aimed to investigate barriers and enablers to MI-E use in the ICU setting. Knowledge and skills were shown to be important determinants of MI-E application with clinician perceived evidence gaps relating to the safety of MI-E, optimal device set up and timing of intervention delivery in the ICU

setting. This study also emphasised the impact of the MDT and associated culture and hierarchy often limiting MI-E use.

The use of MI-E to promote extubation success was investigated in a feasibility RCT (Chapters 4 and 5). This study specifically had good ecological validity as it was conceived and developed from a real-world problem as seen by the doctoral fellow, a practising clinician in this field. The study was developed with input from patients. Findings are therefore relevant to the NHS setting but as a single centre feasibility study, it is acknowledged that wider transferability is limited. Again, this was the first study to explore clinician determined MI-E prescriptions and present patient and clinician experiences of MI-E use in the ICU setting. Feasibility outcomes were achieved with regard to recruitment numbers, data completeness and protocol fidelity. A strength of this study was the inclusion of semi-structured interviews with patients and clinicians which contributed to feasibility and acceptability determination. Qualitative findings provided an overall positive view of both MI-E and the study protocol from clinician and patient perspectives and offered new knowledge about the patient experience of MI-E in the ICU setting. This is a valuable addition, detailing what it is like to receive MI-E, but also how clinicians can improve the patient experience. This unique data will inform future MI-E education for clinicians, focusing on information regarding the value of positive patient-clinician interactions. Clinician interviews illustrated potential areas of individual clinician conflict which challenged study equipoise, mostly associated with the timing of MI-E use. A further important consideration highlighted is the need to fully understand and be able to describe physiotherapy standard care in an ICU setting. With the use of MI-E emerging, there remains

an ethical dilemma of with-holding treatment which includes MI-E. A number of factors were identified to enhance the design and conduct of a future trial including study training to a wider cohort of clinical staff and the choice of outcome measures used.

The feasibility study included a novel physiological based sub-study which presented a case series of MI-E treatment sessions with five patients, analysed using EIT to explore the impact of MI-E on lung recruitment and de-recruitment (Chapter 6). The heterogeneity of recruitment following insufflation and de-recruitment following exsufflation, alongside associated clinical implications is an area worthy of future exploration. Such findings would contribute to clinician understanding of how MI-E works, whilst potentially enabling some evidenced based clinical recommendations.

On reflection, what appeared obvious and an ideal approach at the start of this research project, has ended up far more complex. My hypothesis was that information and knowledge gained from the scoping review and clinician interviews would inform the feasibility trial design, findings of which would determine the protocol as feasible or not. Instead, studies within the thesis have revealed an interplay between sources of knowledge and therefore influencing factors impacting MI-E initiation, ongoing use and wider implementation. Furthermore, I have needed to consider my positionality throughout the thesis to remain as transparent as possible and to ensure recommendations are based solely on study findings. Although a new consideration within this thesis, the concept of 'mindlines' is not new and was first described in the literature by Gabbey and Le May (2004) and has since been supported by others (Gabbay and le May, 2011; Gabbay, 2016; Wieringa

and Greenhalgh, 2015). Mindlines is a useful concept to describe and summarise the findings from this thesis. The mindlines concept will now be further described.

Authors describe multiple facets of a mindlines model which include relevant research and guidelines; the role of social interactions; context and complexity; and tacit knowledge (that of personal wisdom, experience, insight and intuition) (Gabbay and Le May., 2004; Gabbay and Le May., 2011). Complex clinical decision-making uses all of these different knowledge forms (Locock et al., 2020). Relating back to the current body of work, it is apparent that there is a requirement for more research to be completed. However, the mindlines concept helps to understand why the completion of more research may not be sufficient to encourage the behaviour change that is required to see further implementation of MI-E into the ICU setting. Despite a body of evidence in existence (Chapter 2), clinician interviews (Chapter 3) illustrated multiple barriers to MI-E use which included anecdotal conversations, past clinical experiences, the MDT, culture and hierarchy. In the absence of published clinical guidance and an evidence base that is not robust, clinicians have to draw upon these other influences and sources of knowledge within their mindlines to support their decision making. The importance of research-based evidence and guidelines is highlighted, but they also stress that in many clinical situations guidelines needs to be adapted to the contextual complexity of practice. Rather than focusing solely on the implementation of evidence, it is proposed that 'knowledge-in-practice-in-context' is considered (Gabbay and le May, 2011).

Many of the barriers discussed and raised in Chapters 2, 3 and 5 relate back to education. Clinicians have raised specific areas that require further clarification including MI-E safety and gaining a better understanding of how it works. Additionally, clinicians highlighted the

importance of practical exposure to MI-E and the opportunity for hands-on experience with support from more experienced colleagues. Patient interviews raised the importance of the interaction and associated communication between the patient and clinician during an MI-E treatment session. This is an invaluable addition to future MI-E education which has the potential to optimise treatment outcomes.

7.3 Future work

It should be acknowledged that there is insufficient evidence regarding the use of MI-E in the ICU setting on which to base evidence-based guidelines. The development of a practice-based guideline which includes the evidence base alongside consensus from clinical experts would be a useful addition to clinical practice and the use of MI-E in the ICU setting. The work conducted and presented within this thesis has progressed understanding and highlighted areas that warrant further investigation.

Further research regarding the use of MI-E in the ICU setting is required. However, with MI-E being an emerging complex intervention in this setting, defining a standard care arm that does not include MI-E may be challenging. Further understanding of how MI-E is being used and the clinical outcomes associated with its use would be valuable. As a result, the consideration of different methodological approaches is important. Observing this across centres would allow for heterogenous MI-E implementation and prevent ethical dilemmas associated with a standard care treatment arm as previously discussed (Silverman et al., 2004). A further alternative to an observational study would be the adoption of a realist

evaluation approach. This methodology aims to understand why and how 'interventions' work with consideration of multiple contexts. Such an approach may enable further refinement of the MI-E intervention in the ICU setting prior to further evaluation of effectiveness. It will be essential to embed a thorough process evaluation within any future multi-centre trial to accurately identify differences across sites and potential confounding factors. The development of a core outcome set for airway clearance strategies in the ICU setting would also provide greater consistency across facilitating comparison.

7.4 Conclusion

In conclusion, the research within this thesis demonstrates the emerging use of MI-E in the critically ill, intubated adult patient. Additional awareness of the complex interplay between sources of knowledge and factors influencing MI-E initiation, ongoing use and wider implementation must be a key consideration when designing future trials examining the role of MI-E in the ICU setting. As a complex intervention, in a complex clinical area with a complex group of patients, the design of the 'next study' remains a significant challenge. However, the need to establish a robust evidence base through carefully designed trials with consideration of MI-E as a complex intervention will help determine whether MI-E has an effective role in promoting extubation success.

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Appendices

Appendix 1: Published scoping review protocol

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Systematic Reviews

PROTOCOL Open Access

The use of mechanical insufflation-exsufflation in invasively ventilated critically ill adults: a scoping review protocol

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Abstract

Background: Critically ill patients receiving invasive ventilation are at risk of sputum retention. Mechanical insufflation-exsufflation (MI-E) is a technique used to mobilise sputum and optimise airway clearance. Recently, interest has increased in the use of mechanical insufflation-exsufflation for invasively ventilated critically ill adults, but evidence for the feasibility, safety and efficacy of this treatment is sparse.
The aim of this scoping review is to map current and emerging evidence on the feasibility, safety and efficacy of MI-E for invasively ventilated adult patients with the aim of highlighting knowledge gaps and identifying areas for future research. Specific research questions aim to identify information informing indications and contraindications to the use of MI-E in the invasively ventilated adult, MI-E settings used, outcome measures reported within studies, adverse effects reported and perceived barriers and facilitators to using MI-E reported.

Methods: We will search electronic databases MEDLINE, EMBASE, CINAHL using the OVID platform, PROSPERO, The Cochrane Library, ISI Web of Science and the International Clinical Trials Registry Platform. Two authors will independently screen citations, extract data and evaluate risk of bias using the Mixed Methods Appraisal Tool. Studies included will present original data and describe MI-E in invasively ventilated adult patients from 1990 onwards. Our exclusion criteria are studies in a paediatric population, editorial pieces or letters and animal or bench studies. Search results will be presented in a PRISMA study flow diagram. Descriptive statistics will be used to summarise quantitative data. For qualitative data relating to barriers and facilitators, we will use content analysis and the Theoretical Domains Framework (TDF) as a conceptual framework. Additional tables and relevant figures will present data addressing our research questions.

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Discussion: Our findings will enable us to map current and emerging evidence on the feasibility, safety and efficacy of MI-E for invasively ventilated critically ill adult patients. These data will provide description of how the technique is currently used, support healthcare professionals in their clinical decision making and highlight areas for future research in this important clinical area.

Systematic review registration: Open Science Framework submitted on 9 July 2020. https://osf.io/mpksq/.

Keywords: Mechanical insufflation-exsufflation, Intensive care, Critically ill adult, Invasively ventilated adult

Background

Critically ill patients under invasive ventilation are at risk for sputum retention [1]. The relatively dry gases used during invasive ventilation cause airway mucosa to produce more mucus volume, potentially of increased viscosity [1]. Cough is an important defence mechanism to clear mucus from the upper and lower airways [1]. The presence of an endotracheal tube impairs the ability to cough as the vocal cords and glottis cannot be closed. This prevents the generation of high intrathoracic pressure and subsequent enhancement of cough velocity [2, 3]. Furthermore, critically ill patients frequently have an impaired or no cough reflex due to depressed levels of consciousness, sedation, muscle weakness or muscle paralysis. Sputum retention, resulting from an inability to cough effectively, is one cause of extubation failure which in turn is associated with increased mortality [4].

There are a number of techniques to mobilise sputum and optimise airway clearance for invasively ventilated patients. Endotracheal suctioning is the most common intervention used to remove retained airway secretions from within the endotracheal tube, trachea and upper airways [5]. Endotracheal suctioning though is not effective for clearing secretions from the lower airways [6].

Mechanical insufflation-exsufflation (MI-E) aids sputum clearance from upper and lower airways. This technique augments inspiratory and expiratory flows to improve sputum mobilisation, through the application of rapidly alternating positive and negative pressure, which approximates a normal cough [7].

MI-E was originally developed to prevent respiratory complications associated with sputum retention for patients with neuromuscular disease [8, 9]. Recently interest has increased in the use of MI-E for invasively ventilated critically ill adults in the intensive care unit (ICU) [10]. To date, evidence suggests limited and variable adoption of MI-E in this patient group. Our group has conducted practice surveys of cough augmentation techniques in ICUs in Canada [11, 12], the United Kingdom (UK) [13] and the Netherlands [14]. Results from all surveys illustrated that MI-E was predominantly used for sputum management in non-intubated patients to prevent intubation or reintubation [11–13]. Across all three countries, MI-E was not commonly used in invasively ventilated patients. Both Canadian and UK surveys cited lack of clinician expertise and knowledge as perceived barriers to MI-E use in intubated patients.

Evidence for the feasibility, safety and efficacy of MI-E in invasively ventilated critically ill adults is sparse [15]. To date, little is known about which patients would benefit most and in which stage of mechanical ventilation, i.e. before or during weaning or following extubation to prevent reintubation; the most appropriate technique or MI-E set up regarding pressure, flow and timing of insufflation and exsufflation; incidence of adverse events; reported outcomes; and the barriers and facilitators for using MI-E for invasively ventilated adults in an ICU setting.

The primary aim of this scoping review is to map current and emerging evidence on how to use MI-E for invasively ventilated adult patients with the aim of highlighting knowledge gaps and identifying areas for future research.

Methods

Study design

Scoping review following the methods outlined by Arksey and O'Malley and advanced by other authors [16–18].

Study questions

We will address the following study questions:

1. What primary clinical ICU diagnoses and/or reasons for mechanical ventilation are an indication to use/not use MI-E during invasive ventilation?
2. What are the clinical indications (i.e. sputum removal) and contraindications for commencing MI-E in invasively ventilated critically ill adults?
3. What MI-E settings are used for invasively ventilated critically ill adults? (i.e. interface type, flow, pressure and time settings)
4. What outcomes are reported in studies of MI-E for invasively ventilated critically ill adults and how are these outcomes measured?
5. What adverse events attributed to MI-E use are reported in the evidence base, and how are these defined/described?

6 What perceived barriers and facilitators to using MI-E for invasively ventilated critically ill adults are described in the evidence base, and how are these defined?

Identifying relevant studies

The search strategy will be developed in consultation with a medical information specialist and applied to the following bibliographic electronic databases: MEDLINE, EMBASE and CINAHL using the OVID platform. We will search PROSPERO and The Cochrane Library for relevant reviews, ISI Web of Science for conference abstracts and the International Clinical Trials Registry Platform (apps.who.int/trialsearch) for unpublished and ongoing trials. We will screen reference lists of included articles for additional studies meeting our inclusion criteria listed below.

A modified version of the published search strategy of the Cochrane systematic review of cough augmentation techniques will be used [15]. Modification was made to solely focus on MI-E in an adult population. Additionally, we will not exclude studies based on study design. The search strategy is provided in Additional file 1. We will not restrict article selection based on language. Inclusion and exclusion criteria are shown in Table 1.

Selection of studies

Two review authors (ES and WS) will independently screen titles and abstracts identified by our search methods. Full texts of studies considered by either author as potentially eligible will be obtained and reviewed to confirm selection against the inclusion/exclusion criteria. Any disagreements throughout the review process will be resolved by discussion or referred to a third reviewer for arbitration (LR/FP). Endnote x9 will be used to select articles independently.

Data charting process

The research team has developed the data charting form [17, 19] to collect information pertinent to our research questions. The data charting tool will be piloted by two authors (ES and WS) on five articles, with further refinement following discussion as required. Data will include article study demographics (author, year of publication, study location and population); study design and aim; primary clinical ICU diagnoses or reasons for mechanical ventilation of patients that use/do not use MI-E during invasive ventilation (RQ1); clinical indications and contraindications for using MI-E (RQ2); technical or practical application of MI-E (RQ3); study outcomes and measures (RQ4); adverse events/side effects (RQ5); and perceived barriers and facilitators to use of MI-E for invasively ventilated patients (RQ6).

Two reviewers (ES and WS) will independently chart these data using the data charting form. Data charting will be managed by two reviewers (WS and ES).

One reviewer will be responsible for contacting key author when clarification or additional data are needed. Contact efforts will be limited to a maximum of 3 emails.

Analysis of data

Three steps will be used to collate results [17]. Descriptive statistics will be used to summarise quantitative data. We will present counts and proportions of studies reporting each outcome that have been used by researchers. For qualitative data relating to barriers and facilitators, we will use content analysis and the Theoretical Domains Framework (TDF) as a conceptual framework [20, 21]. Finally, we will apply meaning to the results through the generation of recommendations for practice and future research based on our analyses.

Assessment of methodological quality of individual studies

Although the assessment of risk of bias is not essential for scoping reviews [18], we will use the Mixed Methods Appraisal Tool (MMAT) [22] to give an overview of the validity of current evidence. Previous studies have shown the MMAT to be an easy to use tool with moderate to perfect inter-rater reliability [22]. Two review authors (ES/WS) will independently complete quality

Table 1 Inclusion and exclusion criteria for studies

Inclusion	Exclusion
Mechanically ventilated adults via tracheostomy or endotracheal tube in a relevant clinical location (intensive care, weaning centres, respiratory high care/dependency areas)	Children (< 18 years)
Describes use of MI-E	Editorial pieces Letters to the Editor
Any study design (include randomised controlled trials (RCT), quasi and non-randomised clinical trials, before and after studies, interrupted time series cohort studies, qualitative designs, mixed methods, cross-sectional design, case reports/series, and research letters which present original data)	Bench and animal studies
Published from 1990 onwards	

assessment. We will not exclude studies from the review due to determined quality. Quality assessment instead will be used to facilitate description of rigour of included studies.

Presentation of findings

We will present our search results in a PRISMA study flow diagram [18] illustrating the total number of articles generated from the search strategy and following application of the inclusion/exclusion criteria, the number subsequently excluded and ultimately used for review.

A summary table will illustrate study characteristics from included articles, including population, study country, study design and methods. Additional tables and relevant figures will present data addressing our research questions. Where qualitative data is attained, tables will be produced to highlight key thematic content within each TDF domain.

Amendments

The protocol will be closely followed throughout with regular progress reports as a whole study team. If any amendments are made to the published study protocol, these will be reported in the final publication.

Dissemination of findings

We plan to disseminate results from this review in a peer-reviewed journal.

Discussion

There is growing interest in the role of MI-E for invasively ventilated critically ill adults but to date adoption and application of this technique is variable [11–13]. The primary aim of this scoping review is to map emerging and current evidence, on MI-E in an ICU setting, thus adding to previous Cochrane Review findings [15]. Our protocol also aims to apply the TDF framework to explore the perceived barriers and facilitators for MI-E use [20, 21]. Barriers and facilitators will be considered for the feasibility of this technique.

The results of this review will highlight gaps in the current evidence base to inform future research and will contribute to the clinical decision making processes of healthcare professionals who work with MI-E or are considering use of the technique within their ICU.

Strength and limitations

The protocol for this scoping review is transparent and in line with the PRISMA scoping review checklist [18] and the recent scoping review checklist [23]. Strengths include rigorous and systematic search, inclusion of studies in all languages, independent selection of studies and quality assessment using the MMAT [22].

A potential limitation is that we are focusing on a very specific patient group with an age restriction. This may restrict the amount of articles to be included.

Conclusion

This scoping review will provide a timely overview of emerging evidence of MI-E in invasively ventilated critically ill adults. We hope findings will facilitate clinician understanding the potential application of this technique for invasively ventilated critically ill adults and will direct future research.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-020-01547-8.

Additional file 1: Search strategy

Abbreviations

MI-E: Mechanical insufflation-exsufflation; ICU: Intensive care unit; RQ: Research question; TDF: Theoretical Domains Framework; MMAT: Mixed Methods Appraisal Tool; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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None.

Authors' contributions

ES and WS proposed and developed the scoping review topic. Ideas were developed further with academic supervisors LT, FC, LR, WSoR, MS and FP. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Appendix 2: Published scoping review

RESPIRATORY CARE Paper in Press. Published on May 24, 2022 as DOI: 10.4187/respcare.09704

The Use of Mechanical Insufflation-Exsufflation in Invasively Ventilated Critically Ill Adults

Ema L Swingwood, Willemke Stilma, Lyvonne N Tume, Fiona Cramp, Sarah Voss, Jeremy Bewley, George Ntoumenopoulos, Marcus J Schultz, Wilma Scholte Op Reimer, Frederique Paulus, and Louise Rose

Mechanical insufflation-exsufflation (MI-E) is traditionally used in the neuromuscular population. There is growing interest of MI-E use in invasively ventilated critically ill adults. We aimed to map current evidence on MI-E use in invasively ventilated critically ill adults. Two authors independently searched electronic databases MEDLINE, Embase, and CINAHL via the Ovid platform; PROSPERO; Cochrane Library; ISI Web of Science; and International Clinical Trials Registry Platform between January 1990–April 2021. Inclusion criteria were (1) adult critically ill invasively ventilated subjects, (2) use of MI-E, (3) study design with original data, and (4) published from 1990 onward. Data were extracted by 2 authors independently using a bespoke extraction form. We used Mixed Methods Appraisal Tool to appraise risk of bias. Theoretical Domains Framework was used to interpret qualitative data. Of 3,090 citations identified, 28 citations were taken forward for data extraction. Main indications for MI-E use during invasive ventilation were presence of secretions and mucus plugging (13/28, 46%). Perceived contraindications related to use of high levels of positive pressure (18/28, 68%). Protocolized MI-E settings with a pressure of ±40 cm H_2O were most commonly used, with detail on timing, flow, and frequency of prescription infrequently reported. Various outcomes were re-intubation rate, wet sputum weight, and pulmonary mechanics. Only 3 studies reported the occurrence of adverse events. From qualitative data, the main barrier to MI-E use in this subject group was lack of knowledge and skills. We concluded that there is little consistency in how MI-E is used and reported, and therefore, recommendations about best practices are not possible.

RESPIRATORY CARE Paper in Press. Published on May 24, 2022 as DOI: 10.4187/respcare.09704

Key words: mechanical insufflation-exsufflation; CoughAssist; ICU; extubation; airway clearance; physiotherapy; weaning. [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

Cough is an essential defense mechanism in clearing mucus from the airways. In invasively ventilated patients, cough is impaired due to an artificial airway as the vocal cords and glottis remain abducted.[1,2] Sedation further exacerbates sputum retention as it limits the cough reflex, mucociliary clearance, and muscle strength. As a result, sputum retention in patients with an advanced airway is a common problem that may have substantial impact on ability to wean and to be extubated in the longer term.[3]

Airway clearance techniques are used by clinicians to mobilize and clear retained secretions. Endotracheal suctioning is most commonly used to remove secretions from the endotracheal tube (ETT), tracheostomy, and the upper airway.[4] However, limitations to this technique include the inability to clear secretions from the lower airways and potential trauma to the upper airways.[2]

Mechanical insufflation-exsufflation (MI-E) is traditionally used in the neuromuscular population.[5-7] It is conventionally used as a noninvasive device that delivers a positive-pressure breath to optimize tidal volume (V_T) and lung recruitment and then quickly alternates to a negative-pressure breath. It is this rapid alternation between positive and negative-pressure breaths that augments gas flows, improves sputum mobilization, and ultimately stimulates a cough.[6] More recently, there has been growing interest of MI-E use for intubated critically ill adults.[7] Our research group has completed a number of practice surveys in Canada,[8,9] the Netherlands,[10] and the United Kingdom.[11] These surveys illustrate the variable adoption of MI-E both nationally and internationally. Barriers to use cited in these surveys include limited clinician experience and knowledge of MI-E. Additionally, results illustrated MI-E use predominantly in the non-intubated critically ill subject group.[8,9,11] The most frequently cited indication for MI-E use was the optimization of sputum clearance to prevent intubation or re-intubation.[8-11] A Cochrane systematic review concluded that further research is required to establish the feasibility, efficacy, and safety of MI-E in the intubated population given the dearth of efficacy studies.[12]

The aim of this scoping review was to map current and emerging evidence on how MI-E is used in invasively ventilated critically ill adults. We sought specific detail regarding the subject groups and stage of invasive ventilation for which MI-E as well as the practical application including pressures, times, and flows. We also sought to describe the outcomes and measures reported in MI-E studies as well as adverse events. This information will be used to inform research design in future MI-E studies.

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Mss Swingwood and Stilma are joint primary authors.

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Methods

Study Design

This scoping review followed the methods outlined by Arksey and O'Malley and advanced by other authors.[13-15] The scoping review protocol has been previously published.[16] There were no amendments made to the protocol during the conduct of the scoping review.

Study Identification

Our search strategy was a modified version of that previously used for the Cochrane systematic review of cough augmentation techniques in the critically ill.[12] Modification required removal of terms used for airway clearance strategies other than MI-E. Furthermore, we did not exclude studies based on study design and did not restrict article selection based on language.[16]

The search criteria were applied between January 1990–April 2021 using electronic databases MEDLINE, Embase, and CINAHL via the Ovid platform. PROSPERO and Cochrane Library were searched for relevant reviews, ISI Web of Science for conference abstracts, and the International Clinical Trials Registry Platform (trialsearch.who.int *Accessed April 12, 2022*) for unpublished and ongoing trials. The reference lists of relevant studies and reviews were examined to highlight any additional articles for inclusion.

Study Selection and Data Extraction

Criteria for inclusion of articles were (1) adult population with invasive ventilation via ETT or cuffed tracheostomy in an intensive care setting, (2) use of MI-E, (3) any study design with original data, and (4) published from 1990 onward. Citations were excluded if they included participants < 18 y or if they were editorial pieces, letters to the editor, and bench or animal-based studies.

Screening and data extraction were performed by 2 review authors (ES and WS) independently using a piloted data extraction form. Reviewers were responsible for contacting key authors for clarification of methods or additional data if required. Any disagreements during the review process were recorded and resolved by discussion or referred to a third reviewer (LR) for arbitration. EndNote X9 (Clarivate, Philadelphia, Pennsylvania) was used to manage citations.

Methodological Quality Assessment

The Mixed Methods Appraisal Tool[17] was used to provide an assessment of study quality of full-text papers. Quality scores were not used to exclude studies. Citations of full publications only were scored by assigning quality scores 0–100% (0%, no criteria met; 100%, all criteria met) with 20% assigned per methodological criteria of which there were 5 per study design. Score ratings > 80% were classified as high quality, 80% moderate quality, and < 80% low quality.[17] This process was completed independently by the reviewers (ES and WS) and then compared and discussed to generate consensus on ratings.

Data Analysis

Descriptive statistics were used to summarize quantitative data. The Theoretical Domains Framework[18,19] was used to interpret qualitative data relating to barriers and facilitators of MI-E use in invasively ventilated critically ill adults.

Results

The initial search generated 3,090 unique citations. The full-text papers of 133 citations were assessed for eligibility. Once inclusion and exclusion criteria were applied, 34 citations representing 28 studies were taken forward for data extraction. One conference abstract was additionally highlighted through direct contact with an author. The search results are presented using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses study flow diagram (Fig. 1).

Most studies (no. = 9) were randomized controlled trials (5 full-text publications,[20-24] 3 trial registrations,[25-27] and one abstract [28]) or descriptive studies (no. = 19) including observational cohort studies (no. = 7),[29-35] surveys (no. = 6),[8,10,11,36-38] and case study/series reports (no. = 5)[39-43] and crossover trials (no. = 2).[25,44] Studies were completed in 13 different countries. The Mixed Methods Appraisal Tool was completed for the 19 full-text publications. Only 5/19 (26%) studies scored 100% (high quality)[8,10,11,23,29] (Table 1 and appendix 1, see related supplementary materials at http://www.rc.rcjournal.com).

Population

Of the 28 studies, 20 studies provided information on the ICU population in which MI-E was studied (trial registrations no. = 3 and survey data no. = 5 excluded). Studies varied in terms of subject population with dissimilar reasons for intubation/invasive ventilation. The primary reason for intubation was recorded in 17/20 (85%) and was most commonly acute respiratory failure (no. = 12). Multiple underlying causes of acute respiratory failure were stated across studies including postoperative respiratory failure, pneumonia, cardiac arrest, acute spinal cord injury, and neuromuscular disease

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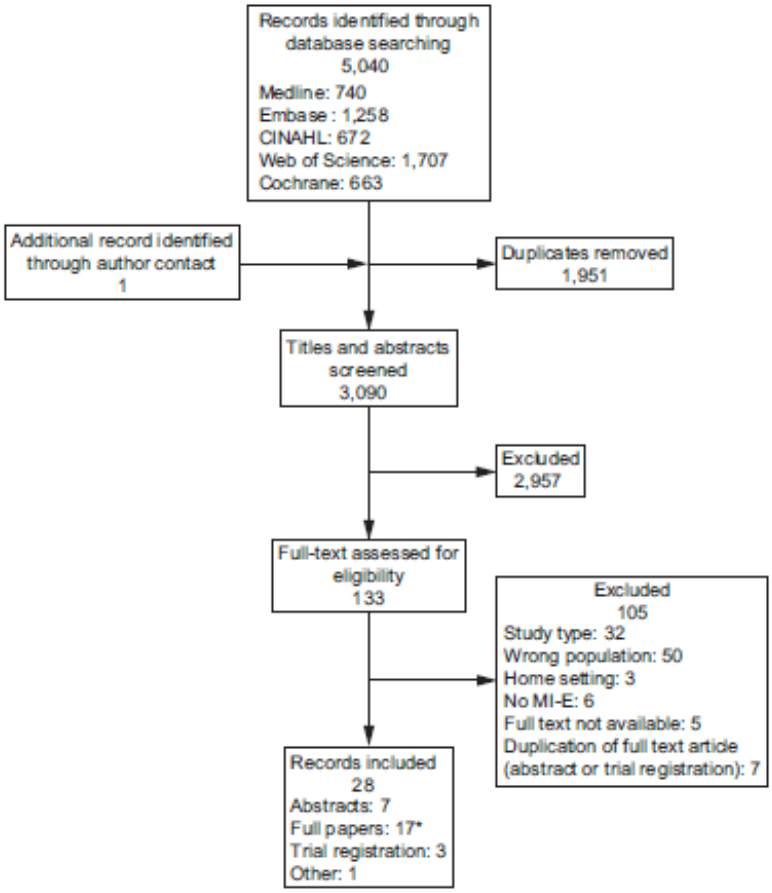

Fig. 1. PRISMA Flowchart. *Full paper identified of 2 abstracts after closing date search.

(NMD). Duration of invasive ventilation ranged from a minimum of 24 h to 10 d at the time of recruitment (Table 1).

Clinical Indications and Contraindications

We identified 10 different indications for use of MI-E. In clinical studies, the most commonly reported indication was presence of secretions and mucus plugging (9/28, 32%) followed by prophylactic airway clearance (7/28, 25%). Contraindications relating to concerns about using high levels of positive pressure (9/28, 32%) were most common. These findings were mirrored in survey reports of health care professionals (Table 2).

Clinical Studies

All 20 clinical studies reported on one or more elements of MI-E device settings. A range of devices were used; 11 (55%) reported using the E70 device and 2 (10%) the Emerson CoughAssist device. Eleven clinical studies did not specify device used. Twelve (60%) studies reported use via an ETT, 4 (20%) via tracheostomy, and 6 (40%) via a combination of ETT and tracheostomy.

A pressure setting combination of ± 40 cm H_2O was most commonly used across reporting studies (10/20, 50%).[21-24,26,28-30,39,44] Time settings were reported in 11/20 (55%) studies.[21-24,29,30,34,39-41,44] Most commonly used time settings were inspiratory time 3 s, expiratory time 2 s, and 1 s pause. A pause duration was reported in 8/20 (40%) studies.[20-24,30,34,44] Five studies (25%) reported use of one insufflation prior to an exsufflation breath (not reported in the remaining studies). Flow profile was specified in only 3 (15%) studies and was set at medium (no. = 2)[20,28] or high (no. = 1).[31] Use of oscillation was reported in 5/20 (25%) studies with 3/5[20,28,33] applying this option. One study applied an oscillation amplitude of 10 and frequency of 20 Hz,[20] whereas only oscillation frequency was reported in

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Table 1. Study Characteristics

Author, Year	Citation Format	Country	*N*	Population Description	Primary ICU Diagnoses/ Reason for Invasive Ventilation	Interface	Outcomes	MMAT (%)
Randomized Controlled Trials								
Goncalves, 2012[22]	Full paper	Portugal	75	General ICU	Acute hypoxemic and/or hypercapnic RF from a specific etiology	ETT	Re-intubation, mortality, total ICU LOS, postextubation LOS, NIV failure rates	80
Coutinho, 2018[21]	Full paper	Brazil	43	Invasive ventilation > 48 h	Traumatic brain injury, postoperative, polytrauma		Secretion clearance, hemodynamics (heart rate, systolic and diastolic blood pressure, $\bar{P}_{aw}$), respiratory mechanics (V_T, invasive ventilation, RR, C_{RS}, R_{RS}), S_{pO_2}	80
Ferreira de Camillis, 2018[23]	Full paper	Brazil	180	Invasive ventilation >24 h	Acute RF, decreased level of consciousness, hemodynamic stability, postoperative, cardiac arrest	ETT	Wet aspirated sputum weight, C_{RS}, R_{RS}, work of breathing, adverse ventilator or hemodynamic event	100
Campos, 2019[20]	Full paper	Brazil	22	Invasive ventilation > 10 d; no VAP	Postoperative RF (retained secretions)	ETT	VAP incidence, invasive ventilation duration, ICU LOS, mortality, bronchoscopy use, antibiotic use, bronchial obstruction	60
Jprn, 2018[26]	Trial registration	Japan		Invasive ventilation in ICU > 24 h and expected for 48 h			Ventilator days, ICU days, re-intubation, tracheostomy	
NCT04149873, 2019[27]	Trial registration	Taiwan	240[a]	Invasive ventilation on pressure support mode	Postoperative	ETT	Re-intubation rate, ICU mortality, postextubation LOS	
Sanchez Garcia, 2019[28]	Abstract	Spain	120	Critically ill subjects		ETT or TT	Safety, tolerance (pain and agitation scores, sedation/responsiveness score)	80
Martínez-Alejos, 2021[24]	Full paper	France, Spain	26	Invasive ventilation > 48 h		ETT	Sputum volume, effects on respiratory mechanics, hemodynamics and safety	100
Observational Cohort								
Bach, 2010[29]	Full paper	USA, Portugal	157	NMD, critical care myopathy	Acute RF due to pneumonia and/or surgery	ETT	Successful extubation, vital capacity, duration on NIV, CPF, pre-intubation NIV experience, total days intubated	100
Soares, 2014[35]	Abstract	Portugal	27	NMD	NMD with respiratory failure	TT	CPF	
Bach, 2015[32]	Full paper	USA	98	NMD with previous failed extubations	RF (pneumonia)	ETT	Successful extubation, S_{pO_2}, CPF, vital capacity	80
Farina, 2017[33]	Abstract	Spain	13			ETT and TT	Sputum clearance, ventilator/lab/respiratory parameters	

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Table 1. Continued

Author, Year	Citation Format	Country	*N*	Population Description	Primary ICU Diagnoses/ Reason for Invasive Ventilation	Interface	Outcomes	MMAT (%)
Sánchez García, 2018[91]	Full paper	Spain	13	Invasive ventilation subjects	Peritonitis, severe pancreatitis, nosocomial pneumonia, RF, coma, severe community acquired pneumonia, bronchospasm, cardiac arrest	ETT and TT	Ventilator modes and parameters, arterial blood gas, hemodynamic parameters, adverse events, secretion clearance, device tolerance	80
Kikuchi, 2019[90]	Full paper	Japan	10	NMD hospitalized with routine MI-E > 1 y	Acute RF	TT	CPF	80
Kuroiwa, 2021[34]	Full paper	India	30	Invasive ventilation subjects	RF-medical, postoperative, trauma	ETT and TT	VAP incidence, invasive ventilation duration, LOS ICU, mortality, number of VAP/invasive ventilation duration, bronchoscopy frequency, bronchoscopy/invasive ventilation duration, antibiotic use, antibiotic/invasive ventilation duration, bronchial obstructions	80
Crossover Study								
ISRCT-N25106564, 2013[25]	Trial registration	France		Invasive ventilation < 7 d and expected for > 48 h	Acute RF	ETT	Secretion drainage procedures 24 h and secretion volume, VAP incidence, extubation failure, hospital and ICU LOS, ICU and hospital mortality	
Sancho, 2003[64]	Full paper	Spain	6	ALS	Respiratory tract infections	TT	S_{pO_2}, peak inspiratory pressure, $\overline{P}_{aw}$, work of breathing, wet sputum weight and volume, patient preference for comfort and effectiveness	80
Case Study/Series Report								
Bialais, 2010[89]	Full paper	Belgium	1	Postoperative	RF-atelectasis	ETT	Atelectasis resolution	20
Khan, 2015[62]	Abstract	USA	5	ALS	Emergency intubation due to respiratory failure	ETT	Extubation success, interventions used, respiratory muscle strength, bulbar function, cough strength, ICU LOS, hospital LOS, survival, discharge location	
Tan, 2017[40]	Full paper	Malaysia	2	Acute SCI	Postoperative prolonged weaning and prolonged weaning post cervical SCI	ETT and TT	CPF	80
Vokes, 2019[61]	Abstract	United Kingdom	1	Previously fit and well	Aspiration pneumonia	ETT	Secretion clearance, F_{IO_2}, arterial blood gas	

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Table 1. Continued

Author, Year	Citation Format	Country	*N*	Population Description	Primary ICU Diagnoses/ Reason for Invasive Ventilation	Interface	Outcomes	MMAT (%)
Guarnieri, 2020[43]	Abstract	Italy	23	Cervical SCI	RF	ETT and TT	Extubation failure	
Surveys								
Schmitt, 2007[36]	Full paper	USA	86	SCI			Device use, patient satisfaction	60
Prevost, 2015[37]	Full paper	Canada	114	Respiratory therapists	NMD, SCI		Device use	80
Rose, 2016[8]	Full paper	Canada	157	ICU clinicians			Device use	100
Garstang, 2000[38]	Full paper	USA	18	Traumatic SCI	RF	TT	Patient's experience/preference (pain, preference, fatigue)	60
Stilma, 2019[10]	Full paper	Netherlands	78	ICU professional with expertise in airway care			Device use	100
Swingwood, 2019[11]	Full paper	United Kingdom	166	ICU physiotherapists			Device use	100

cyn = 30.
*Sample size mentioned in trial registration.
MMAT = mixed methods appraisal tool
RF = respiratory failure
ETT = endotracheal tube
LOS = length of stay
NIV = noninvasive ventilation
$\bar{P}_{aw}$ = mean airway pressure
V_T = tidal volume
RR = risk ratio
C_{RS} = lung compliance
R_{RS} = airway resistance
VAP = ventilator-acquired pneumonia
TT = tracheostomy tube
NMD = neuromuscular disease
CPF = cough peak flow
MI-E = mechanical insufflation-exsufflation
ALS = amyotrophic lateral sclerosis
SCI = spinal cord injury

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Table 2. Reported Indications and Contraindications Mechanical Insufflation-Exsufflation

Outcomes	Clinical Studies no. (%)	Survey Studies in Health Care Professionals no. (%)
Indications		
Secretions and mucus plugging	9 (32)	4 (13)
Prophylactic airway clearance	6 (21)	
Reduced cough peak flow or insufficient cough	4 (14)	2 (7)
Neuromuscular disease or spinal cord injury		13 (4)
Previous domiciliary use		7 (2)
Weaning failure	4 (14)	2 (7)
Atelectasis	3 (11)	2 (7)
Respiratory failure	2 (7)	2 (7)
ICU acquired weakness	-	1 (3)
Need for endotracheal suctioning	3 (11)	
Contraindications		
Contraindications to increased positive pressure†	9 (32)	9 (30)
Recent surgery (pulmonary/thoracic/abdominal/neuro)	3 (11)	4 (13)
Mechanical ventilation settings $F_{IO_2} > 0.60$ or PEEP > 10 mm Hg or Ppeak > 40 mm Hg	2 (7)	1 (3)
(Severe) bronchospasm, COPD, or asthma	1 (7)	
Hemodynamic instability	1 (7)	1 (3)
Active tuberculosis	1 (7)	
Increased intracranial pressures (> 25 mm Hg)		2 (7)
Severe COPD or asthma		2 (7)
Impaired consciousness (inability to respond to direct simple commands)		1 (3)
Trauma (facial, cranial, rib fractures)		1 (3)
Other‡	6 (21)	1 (3)

no. = 28*
*Multiple indications/contraindications per study.
†These included pneumothorax, hemothorax, hemoptysis, emphysema, subcutaneous emphysema, pulmonary bullae, barotrauma.
‡Other: palliative care, hemofiltration via jugular catheter, pregnancy, strict dorsal position, contractures, nausea and vomiting.
Ppeak = peak pressure

the remaining 2 studies as high[33] or 16 Hz. Treatment regimens varied across studies, with MI-E cycles being repeated up to every 20 min,[29] hourly,[32] 1–2 times per day,[34] 3 times a day,[22] 4 times a day,[43] and most commonly up to once per day.[20,21,23,24,30,31,33,39,44] Five studies (25%) reported the inclusion of other treatment adjuncts along-side MI-E including side positioning,[43] manual assisted cough,[34] and suction.[34,41,44] Table 3 provides an overview of described settings of MI-E use in invasively ventilated critically ill participants.

Seven (25%) studies described the individual applying MI-E. This was most commonly physiotherapists or respiratory therapists,[22,23,30,34,41] followed by ICU nurses,[22,29] caregivers/family,[29,32] and ICU physicians.[22]

Outcomes and Measures

Of the 28 studies, 23 were appropriate to extract outcomes and measures; the remaining 5 were survey-based studies reporting on organization of care.

We identified 21 different outcomes measured in included studies (Table 4). Only 7 studies (7/23, 30%) clearly specified a primary outcome; these included aspirated/wet sputum weight,[23,24] re-intubation rate,[22] suction frequency,[25] number of ventilator/ICU days,[26] incidence of ventilator-associated pneumonia (VAP),[34] and mortality rate in 1 year.[27]

Five (5/23, 22%) studies reported on one outcome only. These included cough peak flow (no. = 3),[30,35,40] re-intubation rate (no. = 1),[43] and atelectasis resolution (no. = 1).[39] Pulmonary mechanics was the most frequently reported outcome overall (no. = 9).[21,23,24,29,31-33,42,44] These measurements encompassed measures of V_T, minute ventilation, airway resistance, lung compliance, and vital capacity. Eight studies (8/23, 35%) reported on extubation failure/success;[22,25-27,29,32,42,43] 7 studies (7/23, 30%) reported on secretion clearance or wet sputum weight.[21,23-25,31,33,44] Methods of outcome measurement varied across studies. Secretion clearance was primarily measured by aspirated sputum or sputum weight, most commonly at 5 min post-

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Table 3. Detailed Overview of Mechanical Insufflation-Exsufflation Settings Across Studies

Author, Year	Mode	Insufflation Pressure (cm H_2O)	Exsufflation Pressure (cm H_2O)	Insufflation Time	Exsufflation Time	Pause	Flow Profile	Insufflation Repeat	Treatment Regimen
Randomized Controlled Trials									
Goncalves, 2012[22]		40	40	3	2	3		1	8 cycles* per session, 3 sessions per d; 1 d while intubated, 2 d postextubation
Coutinho, 2018[21]	Auto-timed	40	40	3	3	0		1	5 repetitions of 4 cycles
Ferreira de Camillis, 2018[23]		40	40	2	3	2			3 repetitions of 10 cycles
Campos, 2019[20]		30	15	2	2	0.5	Medium		30 s on, 30 s off until 5 min
Jpm, 2018[26]		40	40						10 cycles
Sanchez Garcia, 2019[28]		50	50						
Martínez-Alejos, 2021[24]	Automatic	40	40	3	2	1	Medium		4 repetitions of 5 cycles, with 1 min rest between repetitions
Observational Cohort									
Bach, 2010[29]	Manual	40	40						Up to every 20 min to maintain or return pulse oxygen saturation to > 95% in ambient air
Soares, 2014[35]		30–70	30–70						
Bach, 2015[32]	Manual	60–70	60–70						Hourly while awake
Farina, 2017[33]		50	45	3	4				2 cycles per session
Sánchez García, 2018[31]	Patient triggered	50	45	3	4		High	1	2 repetitions of 10–12 cycles
Kikuchi, 2019[30]	Automatic	40	40	1.5	1.5	2		0	2 repetitions per cycle
Kuroiwa, 2021[34]		15–40 (started low and gradually increased, through auscultation and changes in S_{pO_2})	15–40	2–3	2–3	2			2 repetitions of 5–10 cycles
Crossover									
ISRCTN25106564, 2013[25]									Daily intervention until day 14 or extubation 5 cycles

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Table 3. Continued

Author, Year	Mode	Insufflation Pressure ($cm H_2O$)	Exsufflation Pressure ($cm H_2O$)	Insufflation Time	Exsufflation Time	Pause	Flow Profile	Insufflation Repeat	Treatment Regimen
Sancho, 2003[44]		40	40	2	3	1			10 repetitions of 5 cycles
Case Study/Series Report									
Bialais, 2010[39]	Manual	40	40						10 repetitions of 5 cycles
Tan, 2017[40]		25 building up to 40 in increments of 50	26 building up to 40 in increments of 40						6–10 cycles with 20–60 s rest between each cycle
Vokes, 2019[41]		40	45						4 times a d
Guarnieri 2020[43]									

*Cycle refers to an insufflation breath rapidly followed by an exsufflation breath.

Table 4. Outcomes Measured*

Outcomes	Frequency
Physiologic Variables	
Pulmonary mechanics	9 (39)
Extubation failure/success	8 (35)
Secretion clearance/wet sputum weight	7 (30)
Cough peak flow	5 (22)
Pain/agitation score	5 (22)
Adverse event	5 (22)
Device use	3 (13)
Ventilator-acquired pneumonia incidence	3 (13)
Patient preference	3 (13)
S_{pO_2}	2 (9)
Bronchoscopy use	2 (9)
Antibiotic use	2 (9)
Frequency of bronchial obstructions	2 (9)
Hemodynamic parameters	2 (9)
Work of breathing	2 (9)
Atelectasis resolution	1 (5)
Clinical Outcome	
Mechanical ventilation duration	4 (17)
Noninvasive ventilation failure rate	3 (13)
ICU stay	7 (30)
Mortality	5 (22)
Discharge location	1 (4)

Data are shown as no. (%).
*Multiple outcomes reported per study at times.

study intervention.[23,44] When needed, 10 mL NaCl was used to rinse the suction catheter, and that weight was extracted from the result.[23] Alternatively, secretion clearance was measured by frequency of endotracheal suctioning over a 24-h period.[25] VAP incidence was measured throughout the period of intubation, with the frequency of assessment being unclear.[20,25,34] The definition of VAP provided was "pneumonia in a patient who was on invasive ventilation for > 48 h."[34] Re-intubation rate or extubation failure was used as an outcome measure in 8 (8/23, 35%) studies and defined in 3/8 studies. Definitions of extubation failure varied across studies including 48 h following extubation,[22] not needing a tracheostomy during hospitalization or at any time during follow-up,[32] and discharge without re-intubation.[29]

Time points for measuring pulmonary mechanics were 5 min before and after the intervention and 1 h after the intervention. Cough peak flow was measured during and after intubation, mostly using the MI-E device.[30,35,40]

Adverse Events

Adverse events were addressed in 13/20 (65%) studies. For reporting purposes, we grouped adverse events into 3

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Table 5. Reporting of Adverse Events

First Author, Year	Summary of Planned Adverse Events Data Collection			Summary of Adverse Events Reporting
	Respiratory	Hemodynamic	Other	
Clinical Studies				
Sancho et al, 2003[44]				No adverse effects
Soares et al, 2014[35]				No side effects in relation to high MI-E pressures
Khan et al, 2015[42]	Re-intubation and pneumothorax			Re-intubation 2/5 subjects Pneumothorax 1/5 subjects
Farina et al, 2017[33]	Barotrauma, desaturation, atelectasis, hemoptysis	Hemodynamic complications		None detected after MI-E
Coutinho et al, 2018[21]		HR and $\overline{P}_{aw}$		No significant changes
Ferreira de Camillis et al, 2018[23]	↓ Oxygen saturation by 3%	Occurrence of systolic blood pressure < 90 mm Hg		None observed
Sanchez-Garcia et al, 2018[31]	Barotrauma (pneumothorax) or atelectasis, desaturation, hemoptysis, other airway complications		Tolerance (need for additional sedatives or analgesic medication)	No adverse events observed, well tolerated
Sanchez-Garcia et al, 2019[28]				No adverse events observed
Volkes et al, 2019[41]				Safe and feasible, no adverse effects
Guarnieri et al, 2020[43]				No adverse events observed
Martínez-Alejos et al, 2021[24]	Pneumothorax,S_{aO_2} consistently ↓ < 85% or > 10% from baseline	HR, systolic blood pressure or diastolic blood pressure ↑ or ↓ > 20% from baseline		10 episodes of brief desaturations or hemodynamic variations were documented during expiratory rib cage compressions + MI-E
Surveys				
Prevost et al, 2010[37]				Complications (not defined) rare in neuromuscular disease subjects; in other patient groups unknown
Rose et al, 2016[8]	Mucus plugging requiring tracheostomy, pneumothorax,hemoptysis	Bradycardia/asystole, hypotension, arrhythmias	Chest pain	Mucus plugging requiring tracheostomy (10/43, 23%) Pneumothorax (4/43, 9%) Hemoptysis (3/43, 7%) Bradycardia/asystole (8/43, 19%)Hypotension (7/42, 16%)Arrhythmias (6/43, 14%) Chest pain (8/43, 19%)

*Remaining articles did not explicitly report on adverse events.
Adverse events (to include definitions when provided): (13/28, 46%).*
MI-E = mechanical insufflation-exsufflation
HR = heart rate
$\overline{P}_{aw}$ = mean airway pressure
S_{aO_2} = arterial oxygen saturation

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Table 6. Reported Barriers and Facilitators to Mechanical Insufflation-Exsufflation Use

Theoretical Domains Framework Domain	Description
Knowledge and skills	A perceived lack of skills (skills) and knowledge (knowledge) was generally seen as a barrier to use, with the suggestion that clinicians may be more skilled using the device via a tracheostomy interface in comparison to an ETT.[8,11]
Beliefs about consequences	Expected or potential outcomes (beliefs about consequences) were focused on positive clinical experiences.[8,11,36]
Intention	A positive intent to practice (intention).[11]
Environmental context and resources	A lack of resources, funding, and senior culture (environmental context) impacting implementation.[8,11,36]
Social influences	Team culture and senior support (social influences) influencing implementation and illustrating the potential impact colleagues.[8,11]

ETT = endotracheal tube

commonly occurring categories, namely respiratory, hemodynamic, and other (Table 5).

Of the 13 studies, 10 studies reported no occurrence of adverse events in relation to MI-E. Three studies did report on the occurrence of adverse events.[8,24,42] Documented adverse events included oxygen desaturation (< 85%),[24] hemodynamic variation (increase or decrease of heart rate or blood pressure > 15–20% from baseline),[8,24] re-intubation,[42] pneumothorax,[8,42] mucus plugging,[8] hemoptysis,[8] and chest pain.[8]

Barriers and Facilitators to MI-E Use

We found no qualitative studies to include in the scoping review; however, 3 survey studies reported qualitative data from open-ended questions.[8,11,36] Themes illustrating barriers and facilitators to MI-E use were grouped under 6 of the 14 Theoretical Domains Framework domains: knowledge, skills, beliefs about consequences, intention, environmental context and resources, and social influences (Table 6). Barriers to MI-E use in the critically ill included the impact of team culture, a lack of clinical experience, and the need for additional resources and training with the device. Conversely, data illustrated positive intention to use the device with this subject group, with positive experiences described to date.

Discussion

In this scoping review, we mapped current and emerging evidence on MI-E use in invasively ventilated critically ill adults. We included 25 completed studies and 3 trial registrations published between January 1990–April 2021. Findings show that MI-E is predominantly used in ICU patients who have difficulties in weaning and sputum clearance. Studies predominantly investigated MI-E use in subjects with NMD and acute spinal cord injuries that does not reflect the heterogeneous nature of invasively ventilated critically ill adults. Perceived contraindications to MI-E use in the acutely intubated population related to the use of increased positive pressure. There was variation in MI-E device setup and the amount of details reported across studies. Only 3 studies reported on occurrence of adverse events. Qualitative data pertaining to subject and clinician experience of using MI-E in this subject group were lacking.

During invasive ventilation, positive-pressure breaths are delivered followed by a passive expiration. In contrast, MI-E delivers both positive- (insufflation) and negative- (exsufflation) pressure breaths. Therefore, it is noteworthy that we found the use of positive pressure to be a perceived contraindication, whereas negative pressure was not considered a contraindication or precaution for use of MI-E in invasively ventilated critically ill adults. In these patients, lung recruitment and de-recruitment are important considerations.[45,46] Barotrauma and volutrauma associated with large V_Ts are well documented, and low-volume lung-protective ventilation is standard of care, particularly for patients with acute lung injury.[45] However, de-recruitment of lung units can have an equally adverse impact on oxygenation and effective ventilation while attenuating lung injury.[46] To date, no studies have examined the extent of de-recruitment or possible adverse events in relation to a negative-pressure exsufflation breath using MI-E.

Our review data indicate that MI-E is mainly studied with insufflation and exsufflation pressures of 40 cm H_2O. The use of asymmetrical pressure settings and customization of pressure settings to endotracheal size have not yet been studied in invasively ventilated critically ill adults. Previous studies in an NMD non-ICU population[47] illustrate that asymmetrical (ie, pressure settings to enhance the expiratory flow +30: −40 cm H_2O) may enhance expiratory flow. One bench study examining the impact of an artificial airway on MI-E flows[48] found higher pressures were required to overcome resistance to flow, particularly

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in narrower ETT sizes. Detail of flows, use of oscillations, and timings were reported infrequently, which makes extrapolation of device setup into a clinical setting challenging. It is difficult to know whether these omissions are simply a lack of reporting detail or whether the full potential of MI-E settings was not used; this has been commented and queried previously.[47] It should be acknowledged that advanced settings such as oscillations have not been available to clinicians for the duration of the data collection period; this may, therefore, have impacted on reporting of this feature. Data are needed to optimize the physiological impact of MI-E in invasively ventilated critically ill patients and to provide evidence-based guidance for our practice of care, training, and education.

We found multiple outcomes reported across studies including re-intubation rates, wet sputum weight, and respiratory parameters. The appropriateness of wet sputum weight as a primary outcome for examining the efficacy of MI-E is questionable.[11,49] Although sputum clearance is important to quantify in invasively ventilated critically ill patients, a linear relationship does not exist between sputum quantity and disease severity.[3] Consistency in the selection of outcome measures across MI-E studies would allow for meta-analyses, thus strengthening the overall evidence base. Development of a core outcome measure set, as recommended by the COMET Initiative (https://www.comet-initiative.org, *Accessed September 2021*), that specifically focuses on airway clearance in the invasively ventilated critically ill adult population is warranted.

Only 3 studies reporting occurrence of an adverse event including pneumothoraces, hemodynamic instability, and oxygen desaturation. Changes in hemodynamic parameters during MI-E were transient and did not require trial protocol cessation. Case reports of pneumothoraces have previously been described in an adult NMD non-ICU population[50,51] following MI-E, although no causal relationship could be confirmed due to the use of MI-E.[50-53]

A common barrier to MI-E use was a perceived lack of skills and knowledge, suggesting an important opportunity for training and education. A European survey among ICU nurses showed that the knowledge related to respiration/ventilation was scored relatively low, although that would not be expected within this field of care.[54] With MI-E being part of respiratory care, further qualitative inquiry to explore barriers and facilitators in greater detail could provide useful data to inform the optimal clinical implementation of research findings.

Strength and Limitations

Strengths of our scoping review are the use of systematic and transparent prespecified protocol, a search strategy with no methodological or language restrictions, appraisal of risk of bias using the Mixed Methods Appraisal Tool, and use of a theoretical framework to explore barriers and facilitators. We acknowledge that bench studies were excluded that may have provided additional data on MI-E settings in order to inform future research protocols.

Summary

This scoping review of MI-E use in invasively ventilated critically ill adults reports data on 28 studies. We conclude that there is little consistency in how MI-E is used and reported. This limits the strength of the overall body of evidence and the ability, therefore, to make recommendations about best practices. More studies are required, including more transparent reporting of device settings for the invasively ventilated critically ill patient. Additionally, we recommend development of a core outcome measure set for airway clearance in this population to promote consistency in outcome reporting in future intervention trials important to patients, clinicians, and researchers.

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Appendix 3: Search strategy terms

Additional file 1

Search strategy for the use of mechanical insufflation-exsufflation in invasively ventilated critically ill patients: a scoping review

UPDATE: 24-2-2020 t/m 15-6-2020

15-6-2020:

Databases:			
Medline. Embase, Cinahl, Central, Web of Science	Before deduplication	After deduplication	After deduplication original document
Total	128	112	76

Searches Before deduplication:

MEDLINE (OVID):

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to June 12, 2020

Search Strategy:

#	Searches	Results
1	(cough* adj2 assist*).ti,ab,kw.	261
2	(CoughAssist* or Pegaso* or Cofflator* or Cof-flator* or cough machine*).ti,ab,kw.	64

3	(cough* adj2 augment*).ti,ab,kw.	79
4	Cough/rh [Rehabilitation]	19
5	(in-exsufflator* or in-exsufflation*).ti,ab,kw.	44
6	(insufflat* adj1 exsufflat*).ti,ab,kw.	135
7	MI-E.ti,ab,kw.	76
8	(direct* adj2 cough*).ti,ab,kw.	60
9	(cough* adj2 flow* adj5 (improv* or increas* or enhanc* or expan* or exten*)).ti,ab,kw.	58
10	(respiratory muscle* adj2 (aid* or support*)).ti,ab,kw.	33
11	(recruit* adj2 (lung volume or aveolar)).ti,ab,kw.	116
12	((lung or alveolar) adj1 recruit* adj2 (manoeuv* or maneuv*)).ti,ab,kw.	311
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	1018
14	exp Animals/ not (exp Animals/ and Humans/)	4706900
15	(comment or editorial or letter or interview or news).pt. or (letter or editorial or comment).ti. or respiratory muscle training.ti,kw.	2128982
16	13 not 14 not 15	849
17	exp Pediatrics/ or (pediatr* or paediatr* or child* or newborn* or infant*).ti.	1144485
18	(exp Child/ or exp Infant/) not exp Adult/	1662619
19	16 not 17 not 18	715
20	limit 19 to ed=20200224-20200615	19

EMBASE (OVID): Database(s): **Embase Classic+Embase** 1947 to 2020 June 12

Search Strategy:

#	**Searches**	**Results**
1	(cough* adj2 assist*).ti,ab,kw.	492
2	(CoughAssist* or Pegaso* or Cofflator* or Cof-flator* or cough machine*).ti,ab,kw.	116
3	(cough* adj2 augment*).ti,ab,kw.	115
4	exp coughing/rh	11
5	(in-exsufflator* or in-exsufflation*).ti,ab,kw.	79
6	(insufflat* adj1 exsufflat*).ti,ab,kw.	238

7	MI-E.ti,ab,kw.	140
8	(direct* adj2 cough*).ti,ab,kw.	81
9	(cough* adj2 flow* adj5 (improv* or increas* or enhanc* or expan* or exten*)).ti,ab,kw.	89
10	(respiratory muscle* adj2 (aid* or support*)).ti,ab,kw.	57
11	(recruit* adj2 (lung volume or aveolar)).ti,ab,kw.	194
12	((lung or alveolar) adj1 recruit* adj2 (manoeuv* or maneuv*)).ti,ab,kw.	476
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	1651
14	(exp animal experiment/ or exp animal model/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experiment/)	6693167
15	13 not 14	1486
16	editorial/ or letter/ or (letter or editorial or comment).ti. or respiratory muscle training.ti,kw.	1782014
17	15 not 16	1429
18	exp pediatrics/ or (pediatr* or paediatr* or child* or newborn* or infant*).ti.	1501891
19	exp child/ not exp adult/	2214791
20	17 not 18 not 19	1196
21	limit 20 to dd=20200224-20200615	26

CINAHL (EBSCO):

13 hits - Publicatiedatum: 20200201-20200631

S17	S15 NOT S16
S16	(MH "Animals+") NOT (MH "Human")
S15	S13 not S14
S14	(PT comment or editorial or letter or news) OR TI (comment or editorial or letter)
S13	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12

S12	TI ((lung or alveolar) N1 recruit* N2 (manoeuv* ormaneuv*)) OR AB ((lung or alveolar) N1 recruit* N2 (manoeuv* or maneuv*))
S11	TI (recruit* N2 (“lung volume” or alveolar)) OR AB (recruit* N2 (“lung volume” or alveolar))
S10	TI (respiratory muscle* N2 (aid* or support*)) OR AB (respiratory muscle* N2 (aid* or support*))
S9	TI (cough* N2 flow* N5 (improv* or increas* or enhanc* or expan* or exten*)) OR AB (cough* N2 flow* N5 (improv* or increas* or enhanc* or expan* or exten*))
S8	TI direct* N2 cough* OR AB direct* N2 cough*
S7	TI “MI-E” OR AB “MI-E”
S6	TI insufflat* N1 exsufflat* OR AB insufflat* N1 exsufflat*
S5	TI ((in-exsufflator* or in-exsufflation*) OR AB ((in-exsufflator* or in-exsufflation*)
S4	(MH "Cough/RH")
S3	TI cough* N2 augment* OR AB cough* N2 augment*
S2	TI (CoughAssist* or Pegaso* or Cofflator* or Cof-flator* or cough machine*) OR AB (CoughAssist* or Pegaso* or Cofflator* or Cof-flator* or cough machine*)
S1	TI cough* N2 assist* OR AB cough* N2 assist*

Cochrane Library:

ID	Search	Hits
#1	(cough* near/2 assist*):ti,ab,kw	74
#2	(CoughAssist* or Pegaso* or Cofflator or Cof-flator* or (cough next machine*)):ti,ab,kw	26
#3	(cough* near/2 augment*):ti,ab,kw	29
#4	MeSH descriptor: [Cough] explode all trees and with qualifier(s): [rehabilitation - RH]	2
#5	(in-exsufflator* or in-exsufflation*):ti,ab,kw	20
#6	(insufflat* near/1 exsufflat*):ti,ab,kw	47
#7	(MI-E):ti,ab,kw	53
#8	(direct* near/2 cough*):ti,ab,kw	18
#9	((cough* near/2 flow* near/5 (improv* or increas* or enhanc* or expan* or exten*))):ti,ab,kw	15
#10	(((respiratory next muscle*) near/2 (aid* or support*))):ti,ab,kw	4
#11	(recruit* near/2 (lung volume or alveolar)):ti,ab,kw	501
#12	(((lung or alveolar) near/1 recruit* near/2 (manoeuv* or maneuv*))):ti,ab,kw	182
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	678
#14	(respiratory muscle training):ti,ab,kw	1831
#15	#13 not #14	666
#16	(pediatr* or paediatr* or child* or newborn* or infant*):ti	100349
#17	#15 not #16	579
#18	MeSH descriptor: [Pediatrics] explode all trees	659
#19	#17 not #18 with Cochrane Library publication date Between Feb 2020 and Jun 2020, in Cochrane Reviews, Trials	26

WEB OF SCIENCE:

44 hits

Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, ESCI.

TOPIC: ((((cough* NEAR/2 assist*)) OR ((CoughAssist* or Pegaso* or Cofflator* or Cof-flator* or cough machine*)) OR ((cough* NEAR/2 augment*)) OR (("in-exsufflator" or "in-exsufflators" or "in-exsufflation" or "in-exsufflations")) OR ((insufflat* NEAR/1 exsufflat*)) OR ("MI-E") OR ((direct* NEAR/2 cough*)) OR ((cough* NEAR/2 flow* NEAR/5 (improv* or increas* or enhanc* or expan* or exten*))) OR ((("respiratory muscle" or "respiratory muscles") NEAR/2 (aid* or support*))) OR ((recruit* NEAR/2 ("lung volume" or alveolar))) OR (((lung or alveolar) near/1 recruit* near/2 (manoeuv* or maneuv*))))) *NOT* **TOPIC:** (respiratory muscle training) *NOT* **TITLE:** (pediatr* or paediatr* or child* or newborn* or infant*) *NOT* **TOPIC:** ((animals NOT humans)) *NOT* **DOCUMENT TYPES:** (Bibliography OR Correction OR Correction, Addition OR Discussion OR Editorial Material OR Letter OR Meeting Abstract OR News Item OR Note)

Refined by: PUBLICATION YEARS: (2020)

Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years

Appendix 4: Pilot data extraction discussion points

There were no major discrepancies during the piloting phase of the data extraction form. Minor differences were seen and discussed which included:

- Both authors (ES and WS) highlighted the data extraction form did not enable the MI-E caregiver to be recorded. This was therefore collected as an additional data point on the data extraction form.
- Some differences in how MI-E terminology had been interpreted. Definitions of some data collection points were added. For example, MI-E cycles and MI-E sets.
- It was apparent that both authors (ES and WS) were used to using different devices due to some terminology that was added to the data collection form. WS predominantly used the Philips E70 device, whereas ES had access to both the E70 and Breas Medical Clearway device. Terminology in the data extraction form was edited to be generic and, in some cases, drop down option boxes were used, for example, for MI-E mode and interface used.
- It was already apparent after the piloting phase of 5 papers that there would likely be a lot of detail missing, particularly regarding MI-E set up. We decided to continue and collect this information as felt that a lack of detail would be a useful finding for future discussion and consideration.

Appendix 5: Interview topic guide (Chapter 2)

Themes for discussion:

Clinician role

Clinical application

Knowledge base

Infrastructure

Topic Guide:

1. Tell me about your experiences of MI-E in an acutely intubated patient?

Probes

   a. (physio) How often have you used it/which patients/what indications?
   b. (nurse) Who have you seen the device used with?
   c. (doctor) Have you asked about MI-E being used on intubated patients? Which patients and why? Who would you not want it used on and why?

2. What do you see as the benefits of using MI-E in the intubated patient?

3. What do you see as the risks or adverse consequences of using MI-E in the intubated patient?
   Probes: have you seen any positive/negative experiences with this device?
   How do you think patients cope with this device?

4. What skills do you think are important for a clinician when using MI-E in the intubated population?

5. What resources would you need to provide an MI-E treatment in the intubated patient on your unit?

6. From your experience, how are decisions made in your unit about when and who to use MI-E with?
   Probes: who makes the decisions? What do others in your ICU think about MI-E?

7. What do you know about the evidence for MI-E use in the intubated ICU patients?

8. Are you aware of any hospital/unit guidelines or clinical protocols regarding MI-E use in the intubated patient in your institution?

9. Is there anything else that you would like to add?

Appendix 6: Interview study advert

UWE Bristol | University of the West of England

NHS University Hospitals Bristol and Weston NHS Foundation Trust

Barriers and enablers to MI-E use in ICU

Are you a **Physiotherapist, nurse or doctor** currently working in ICU?

Would you be willing to talk to me about your experiences of mechanical insufflation-exsufflation ('cough assist') in intubated critically ill adults?

This research is part of my PhD to enable effective and optimal use of this device in the wider ICU population. If you would be interested in participating in an online interview or would like to know more please contact [redacted]
Thank you

Appendix 7: Interview Participant Information Sheet

Barriers and facilitators to the use of Mechanical Insufflation-Exsufflation (MI-E) in UK Intensive Care Units (ICU): a qualitative analysis informed by the Theoretical Domains Framework

Participant Information Sheet

You are invited to take part in a project taking place at the University of the West of England, Bristol (UWE). It is funded by the National Institute of Health Research (NIHR). Before you decide whether to take part, it is important for you to understand why the project is being done and what it will involve. Please read the following information carefully and if you have any queries or would like more information please contact Ema Swingwood, Faculty of Health and Applied Sciences (HAS), UWE (contact details below).

Who is organising and funding the project?

The project lead is Ema Swingwood as part a NIHR Clinical Doctoral Research Fellowship. Dr Sarah Voss, Prof Lousie Rose, Dr Lyvonne Tume, Dr Jeremy Bewley, Dr George Ntoumenopoulos and Professor Fiona Cramp are co-Investigators. The team's bios and details of their work are available at;

What is the aim of the project?

The MERIT study is investigating the feasibility of using MI-E to facilitate weaning and prevent extubation failure. Timely liberation of a patient from invasive ventilation has positive outcomes and therefore weaning strategies remain a research and quality improvement priority. The role of MI-E in this process remains under-researched but preliminary studies indicate it may facilitate extubation and reduce re-intubation rates.

Our UK survey examined the use of this device in an ICU population by physiotherapists. We found that results covered 3 main themes: the need for training and experience; resource availability and the culture of ICU. Further understanding of these is important. We aim to explore these themes further through the use of interviews with clinicians (physiotherapists, nurses and doctors) working in ICU. Results will be used to develop education packages and inform future research trials.

Why have I been invited to take part?

In order for us to better understand the use of MI-E in intubated patients, we are inviting clinicians (physiotherapists, nurses and doctors) working in ICU to take part in a research project. Although you will not receive any extra benefit from taking part, research like this helps to continually improve treatment and care to patients now and into the future.

Do I have to take part?

You do not have to take part in this project. It is up to you to decide whether or not you want to be involved. If you do decide to take part, you will be asked to provide recoded consent. If you do decide to take part, you are able to withdraw from the project without giving a reason. This will be possible from the date you give verbal recorded consent upto the point that interviews are transcribed. If you want to withdraw from the project within this period, please contact Ema Swingwood (contact details below).

What will happen to me if I take part and what do I have to do?

If you agree to take part you will be asked to take part in an online interview. This will be conducted by Ema Swingwood. The interview will take approximately 45-60 minutes. The subject and focus of the discussion will be your opinions and experience of MI-E use in the ICU setting. Your answers will be fully anonymised.

Your interview will take place via an online platform called Microsoft Teams and will be recorded. A unique identifier will be used to re-identify you, so that your data can be withdrawn if you choose to withdraw from the evaluation within the period. At the point of transcription, your voice recording will be deleted. Your data will be anonymised at this point and will be analysed with interview data from other anonymised participants.

If you are willing to be interviewed for the project, please contact *researcher details to be inserted.*

What are the benefits of taking part?

If you take part in the project, you will be helping us to gain a better understanding of the factors that can influence MI-E within ICU. We hope that results will help inform an education package for the use of this device in the intubated population.

What are the possible risks of taking part?

We do not foresee or anticipate any significant risk to you in taking part in this project. If, however, you feel uncomfortable at any time you can ask for the interview to stop. If you need any support during or after the interview then the researchers will be able to put you in touch with suitable support agencies. The project team are experienced in conducting interviews, which have been designed by a team of people with expertise in the subject area.

What will happen to your information?

All the information that you give will be anonymised at the point of transcription. Hard copy material linking your name with your project identifier will be kept in a locked and secure setting to which only the researchers will have access in accordance with the University's and the Data Protection Act 2018 and General Data Protection Regulation requirements. Voice recordings will be destroyed securely immediately after anonymised transcription. Your anonymised data will be analysed together with other interview and file data, and we will ensure that there is no possibility of identification or re-identification from this point. However, where the nature of your professional role carries with it a risk of your being identifiable through your interview data, we will send your sections of the draft project report where your data have been used; you will then have a veto as to whether that section remains as it is.

Where will the results of the project be published?

A Report will be written containing our project findings. This Report will be available on the University of the West of England's open-access Research Repository. We also plan to publish results in a peer-reviewed journal.

A hard copy of the Report will be made available to all project participants if you would like to see it. Key findings will also be shared both within and outside the University of the West of England. Anonymous and non-identifying direct quotes may be used for publication and presentation purposes.

Who has ethically approved this project?

The project has been reviewed and approved by HAS Faculty Research Ethics Committee (UWE). Any comments, questions or complaints about the ethical conduct of this project can be addressed to the Research Ethics Committee at the University of the West of England at:

[redacted]

What if something goes wrong?

If you have any concerns or complaints about the conduct of this project, please contact Ema Swingwood (contact details below).

What if I have more questions or do not understand something?

If you would like any further information about the project please contact in the first instance:

Ema Swingwood, Respiratory Physiotherapist, Clinical Doctoral Research Fellow Department of Allied Health Professionals, HAS, UWE.

[redacted]

Thank you for agreeing to take part in this project.

V.1, Ema Swingwood Dec 2020

Appendix 8: Interview Consent Form

Barriers and facilitators to use of Mechanical Insufflation-Exsufflation (MI-E) in UK Intensive Care Units (ICU): a qualitative analysis informed by the Theoretical Domains Framework

Consent Form

This consent form will have been given to you with the Participant Information Sheet. Please ensure that you have read and understood the information contained in the Participant Information Sheet and asked any questions before you sign this form. If you have any questions please contact a member of the research team, whose details are set out on the Participant Information Sheet

If you are happy to take part in a telephone/online interview please sign and date the form. This is your copy. At the start of the interview the lead investigator will ask you to provide verbal (recorded) consent for each point on the consent form.

- I have read and understood the information in the Participant Information Sheet which I have been given to read before being asked to sign this form;
- I have been given the opportunity to ask questions about the project;
- I have had my questions answered satisfactorily by the evaluation team;
- I agree that anonymised quotes may be used in the final Report of this project;
- I understand that my participation is voluntary and that I am free to withdraw at any time until the data has been anonymised, without giving a reason;
- I agree to take part in the project;
- I agree that the interview will be recorded.

Name (Printed)……

Signature…… Date……

V.1, Ema Swingwood Dec 2020

Appendix 9: TDF domains and associated study specific definitions

TDF Domains	Study specific definition
Knowledge	*Description of current knowledge; perceived knowledge and expectations of others, methods of acquiring knowledge and experience and the influence of knowledge on the use of MI-E*
Skills	*Practical skills to enable the application of MI-E, training methods for skill development and the assessment of skills through competencies*
Social/professional role and identity	*The MI-E decision-making process and ICU task orientated roles*
Beliefs about capabilities	*Capabilities of self, other professions and the MI-E device*
Optimism	*A positive outlook on current and future MI-E use*
Beliefs about consequences	*Outcomes and experiences following MI-E use/non-use and the impact of such experiences*
Reinforcement	*Outcomes that influence future MI-E device use (positively and negatively)*
Intentions	*Stages of change linked to device use in an ICU setting*
Goals	*Goals and aspirations for future MI-E practice*
Memory, attention and decision processes	*The decision-making process and associated communication pathways for MI-E use in the intubated population*
Environmental context and resources	*The impact of team culture, physical resources and infrastructure (on the use of MI-E)*
Social influences	*The impact of culture, hierarchy and collaborations*
Emotion	*Feelings of clinicians and patients that impact on device use*
Behavioural regulation	*Describes a change of clinical approach (behaviour) and the introduction of something new (i.e. MI-E)*

Appendix 10: Published protocol

Swingwood et al. Pilot and Feasibility Studies (2023) 9:129
https://doi.org/10.1186/s40814-023-01362-7

Pilot and Feasibility Studies

STUDY PROTOCOL Open Access

Mechanical insufflation-exsufflation to promote extubation success in critically ill adults on intensive care: protocol for a randomised controlled feasibility trial

Ema Swingwood[1,2*], Sarah Voss[1], Lyvonne N. Tume[3], Jeremy Bewley[4], Nicholas Turner[5], George Ntoumenopoulos[6], Louise Rose[7,8] and Fiona Cramp[1]

Abstract

Background Extubation failure, defined as reintubation within 48 h, is associated with increased intensive care unit (ICU) length of stay and higher mortality risk. One cause of extubation failure is secretion retention, resulting from an inability to cough effectively. Mechanical insufflation-exsufflation (MI-E) simulates a cough aiding secretion clearance. However, MI-E is not routinely used in the ICU for invasively ventilated patients. This study aims to determine feasibility and acceptability of a randomised controlled trial (RCT) examining MI-E use to promote extubation success in intubated, ventilated adults.

Methods It is a single-centre, feasibility RCT with semi-structured interviews, economic scoping, and exploratory physiology study.

The feasibility RCT ($n = 50$) will compare standard care to a MI-E protocol including a minimum of two MI-E sessions via the endotracheal tube prior to extubation. Post-extubation, MI-E will be delivered via facemask or mouthpiece up to two times/day for 48 h. MI-E settings will be individualised. All patients will receive standard care (no MI-E) in relation to mechanical ventilation, weaning, rehabilitation, physiotherapy techniques such as positioning, manual airway clearance techniques, manual/ventilator hyperinflation, endotracheal suctioning, and nebulisation. Clinical data collection will occur before, on completion, and 5-min post-physiotherapy sessions (intervention/control arms). Resource use will be calculated for each 24-h period. Analyses will be descriptive and address feasibility outcomes including participant recruitment and attrition, proportion of MI-E treatment sessions completed, dataset completeness, and frequency of adverse events and acceptability.

Semi-structured online interviews informed by the Theoretical Framework of Acceptability (TFA) with patients, clinicians, and family members will explore the acceptability of the MI-E intervention and study processes.

Interview data will be analysed using reflexive thematic analysis based on TFA domains through first-level coding.

The embedded physiology study will use electrical impedance tomography and lung ultrasound to explore lung recruitment and de-recruitment during MI-E in a subset of 5–10 patients.

Discussion This study will examine feasibility and acceptability of a RCT protocol of MI-E to promote extubation success. Study findings will inform design modification and conduct of a future adequately powered trial. Furthermore, the study will contribute and advance the understanding of MI-E use in critically ill intubated adults.

Trial registration ISRCTN 24603037; IRAS 303674

Keywords Cough assist, Extubation failure, Ventilator weaning, Physiotherapy, ICU, Airway clearance, Electrical impedance tomography

Background

Extubation failure is defined as reintubation within 48 h and is associated with increased intensive care unit (ICU) length of stay (LOS) [1] and higher mortality risk [2]. One cause of extubation failure is secretion retention, resulting from an inability to cough effectively [3]. Having an endotracheal tube in place impairs the ability to cough due to abduction of the vocal cords and glottis. As a result, airway clearance strategies are used to aid secretion clearance. Suctioning is used commonly to remove secretions from the endotracheal tube, tracheostomy, or upper airway. This technique however has limited effectiveness in clearing secretions from the lower airways and may cause airway trauma [4, 5].

Mechanical insufflation-exsufflation (MI-E) augments inspiratory and expiratory flow to improve secretion mobilisation, through rapidly alternating positive and negative pressure, approximating a normal cough [6]. A previous randomised controlled trial (RCT) based in Portugal examined MI-E in 75 critically ill adults intubated for > 48 h [7]. Using MI-E, they found reductions in re-intubation rates (48% v 17%), mechanical ventilation duration (mean (SD) 17.8 [6] v 11.7 (3.5) days), and ICU LOS post-extubation (9.8 (6.7) v 3.1 (2.5) days (all $p < 0.05$)). More recent trials have demonstrated the superiority of MI-E compared to other airway clearance techniques on physiologic outcomes including sputum weight, static lung compliance, airway resistance, and work of breathing [8, 9]. Recent studies regarding the safety of MI-E in intubated patients indicate that adverse effects such as barotrauma, desaturation, atelectasis, and haemoptysis are rare and transient [10, 11]. However, to date, there is limited adoption of MI-E in ICU [12–14] and limited empirical evidence on its effectiveness [15]. MI-E may be safe and effective in intubated critically ill adults, but more data are required.

During invasive ventilation, positive pressure breaths are delivered followed by a passive expiration. In contrast, MI-E delivers both positive (insufflation) and negative (exsufflation) pressure breaths. Barotrauma and volutrauma associated with large tidal volumes are well documented, with low volume lung-protective ventilation now standard of care, particularly for patients with acute lung injury [16]. However, de-recruitment of lung units due to small tidal volumes can have an equally adverse impact on oxygenation and effective ventilation, attenuating lung injury [17]. To date, no studies have examined the extent of de-recruitment or other adverse events as a result of a negative pressure exsufflation breath applied during MI-E.

We recently conducted a scoping review [18] including 28 studies to map use of MI-E in invasively ventilated critically ill adults. We found MI-E was predominantly used in ICU patients with prolonged weaning from mechanical ventilation and difficulty with sputum clearance. Study populations did not always reflect the heterogeneous nature of invasively ventilated critically ill adults, with some studies enrolling cohorts limited to neuromuscular disease and spinal cord injury. We identified substantial variation in MI-E device settings, timing, and frequency of use across studies.

The recent scoping review [18] also identified a lack of specific qualitative data pertaining to patient and clinician experience of using MI-E. Information was gained through three survey studies which reported qualitative data from open-ended questions around barriers to MI-E in ICU. A common barrier to MI-E use was a perceived lack of skills and knowledge. There were no studies that included patients' opinions or experiences of MI-E use.

This variation in how MI-E is used combined with uncertainty in terms of the evidence of effect on patient outcomes such as promoting weaning success, reducing extubation failure and safety, limits the ability to make practice recommendations and warrants further investigation. Therefore, the aim of this study is to determine the feasibility of a RCT of MI-E to promote extubation success for intubated, mechanically ventilated critically ill adults.

Our objectives are to determine trial feasibility based on the following feasibility end points:

1. Ability to recruit and retain the proposed 50 participants
2. Ability to collect outcome data (including follow up data) and to examine dataset completeness
3. Acceptability of the MI-E intervention from the perspectives of patients, family, and members of the

interprofessional team including doctors, nurses, and physiotherapists.

Methods

The protocol conforms to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline [19] and describes a single-centre, individual parallel group, randomised, feasibility RCT with semi-structured interviews, economic scoping, and the incorporation of an exploratory physiology study. A study flow chart is illustrated in Fig. 1; schedule for enrolment, intervention, and follow-up is shown in Table 1, with associated SPIRIT checklist presented in supplementary information 1.

Feasibility RCT

The study will be conducted in a 21-bed general adult ICU, within a large UK National Health System (NHS) teaching hospital. The unit has approximately 1250 admissions annually and typically admits adults with any condition except cardiac or neurosurgery

Participant identification, recruitment, and allocation

Eligibility A research team member will screen all ICU patients on a daily basis against the study eligibility criteria. Our inclusion criteria comprise the following:

- Adult (≥ 16 years)
- Expected to require invasive mechanical ventilation for > 48 h
- Clinician identified pre-extubation problems with secretion management defined as poor/weak cough effort and/or secretion load difficult to clear with usual airway clearance management, i.e. suctioning, manual techniques, and positioning (as assessed by the treating physiotherapy clinical team)

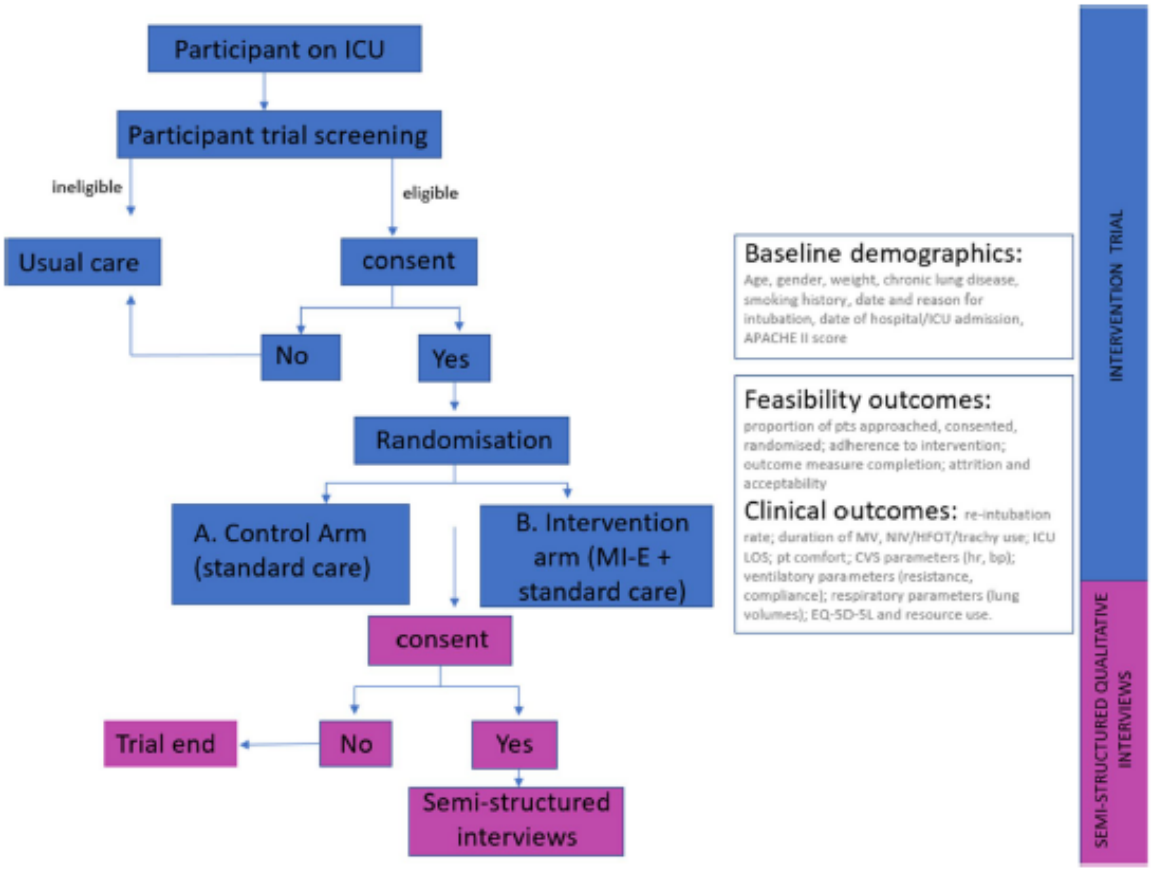

Fig. 1 Study flow chart

Table 1 Schedule for enrolment, intervention, and follow-up

	Data	Timepoint						
		Enrollment	Baseline	Pre-intervention	During intervention	5 min post intervention	Duration of study period	6-month follow-up
Enrolment	Eligibility screening	X						
	Consent	X						
	Allocation	X						
Intervention	Standard care				X			
	MI-E intervention				X			
Assessments: baseline demographic outcome	Demographics (age, gender, predicted body weight, history of lung disease, smoking history)		X					
	Reason for intubation		X					
	Date of hospital and ICU admission		X					
	Date of intubation		X					
	Ventilator settings		X					
	Airway type and size		X					
	APACHE II score		X					
Assessments: clinical outcomes	Use of HFOT, NIV, tracheostomy						X	
	Use of physiotherapy interventions				X			
	LUS score			X		X		
	Patient pain/discomfort (CPOT; NRS)			X		X		
	CVS parameters (HR, SBP, DBP)			X		X		
	Ventilator parameters (vent settings, resistance, compliance)			X		X		
	Respiratory parameters (RR, SpO_2)			X		X		
Assessments: health economics	• Resource use (staffing requirements, suction frequency, consumable use, antibiotic use, physiotherapy on-call use) • QoL (EQ-5D-5L)				X			X
Assessments: safety	Adverse events				X	X	X	

Abbreviations: *APACHE II* Acute Physiology and Chronic Health Evaluation, *CPOT* Critical Care Pain Observation Tool, *DBP* Diastolic blood pressure, *HFOT* High-flow oxygen therapy, *hr* Heart rate, *ICU* Intensive care unit, *LUS* Lung ultrasound, *NIV* Noninvasive ventilation, *NRS* Numeric rating scale, *SBP* Systolic blood pressure, *RR* Respiratory rate, *SpO2* Peripheral oxygen saturations, *QoL* Quality of life

- Identified as 'ready to wean or weaning' by the treating clinical team and on a spontaneous mode of ventilation, for example continuous positive airway pressure (CPAP) or pressure support ventilation (PSV)

Our exclusion criteria comprise the following:

- Positive end-expiratory pressure (PEEP) > 10 cmH_2O
- Fraction of inspired oxygen (FiO_2) > 0.7
- Hemodynamic/cardiovascular instability as defined as noradrenaline infusion of > 0.25 mg/kg or arrhythmia requiring intervention
- Recent untreated pneumothorax (current admission with no chest drain in situ)
- Unable to use MI-E pre-/post extubation (contraindications to facemask use including facial/cranial trauma, recent facial surgery; active upper gastrointestinal bleeding/uncontrolled vomiting; recent upper abdominal/thoracic surgery with at risk anastomosis; acute air trapping, i.e. status asthmaticus)
- Pre-existing neuromuscular condition affecting respiratory muscles
- Pre-existing use of MI-E in the community
- Pre-existing permanent tracheostomy

- Treatment withdrawal expected within 24 h or not expected to survive
- Re-admission to ICU following index admission within same hospital episode
- Previous participation in the study

Randomisation and allocation concealment

Using the online randomisation system 'Sealed Envelope™' (that conceals allocation), an ICU research team member will randomise a patient once informed consent/informed advice has been obtained and demographic data collected. Participants will be randomised using a 1:1 allocation to either (A)-control arm (standard care) or (B)-intervention arm (MI-E plus standard care). Blinding of participants, clinicians, and outcome assessors will not be possible due to the nature of the intervention.

Study arms

A. Control arm (standard care) Patients will receive standard care in relation to mechanical ventilation, ventilator weaning, rehabilitation, standard physiotherapy techniques such as positioning, manual techniques (percussion, expiratory vibrations, expiratory shakes), manual/ventilator hyperinflation, endotracheal suctioning, and nebulisation. The use of MI-E will not be permitted in the standard care control arm. Respiratory physiotherapy treatments will be individualised to patient need at the discretion of the treating physiotherapist and not protocolised. Decisions to extubate and re-intubate will be at the discretion of the attending physician with reason(s) documented.

B. Intervention arm (MI-E plus standard care) For the intervention arm, we will use the MI-E device, Clearway 2 (Breas Medical Ltd., Stratford-Upon-Avon, Warwickshire, UK). This device is reusable between patients with single-use circuit, filter, and interface (mouthpiece, facemask, and flexible catheter mount).

Whilst intubated, treatment will include a minimum of two MI-E sessions via the endotracheal tube (with cuff inflated) following randomisation and prior to extubation. MI-E settings (mode, pressure, timings, flow) will be individualised to each patient based on patient tolerance, chest expansion, and secretion clearance (as assessed by treating physiotherapist, see supplementary file 2). There will be no minimum/maximum time between MI-E sessions. Following extubation (and up to 48 h), patients will receive MI-E delivered via facemask or mouthpiece up to 2 times each day.

Outcomes

Feasibility outcomes are listed in Table 2. Clinical endpoints will be collected to understand the feasibility of their collection informing conduct of a future adequately powered trial and not to conduct hypothesis testing related to causation. Feasibility will be assessed using pre-defined progression criteria (Table 3).

Data collection

Prior to randomisation, the research team will collect baseline demographic and clinical characteristic data from the electronic medical record. Data include general demographics, reason for intubation, date of hospital and ICU admission, date of intubation, admission Acute Physiology and Chronic Health Evaluation (APACHE II), baseline ventilator settings, and airway type and size (Table 1).

Clinical outcomes (Table 1) will be measured before, on completion, and 5 min after physiotherapy sessions for both study arms. We have selected exploratory clinical outcomes using the core outcome measure set for critical care ventilation trials [20]. In addition, we will record the number and type of physiotherapy treatments provided, patient pain/discomfort, cardiovascular parameters, ventilatory parameters, and respiratory parameters (see Table 1 for further details).

Table 2 Feasibility outcomes

Feasibility outcome	Measurement detail
Proportion of eligible patients approached, consented, and randomised	Screening log and randomisation records
Proportion of MI-E treatment sessions completed	Case report form
Proportion of recruited patients with all clinical outcomes recorded	Case report form
Frequency of adverse events	Case report form
Attrition (participant withdrawal and loss to follow-up)	Case report form and withdrawal records
Acceptability of intervention and trial processes to participants and clinicians	Qualitative interviews Acceptability of intervention measure (AIM)/intervention appropriateness measure (IAM)/feasibility of intervention measure (FIM)
Acceptability of outcome measures to participants and clinicians	Qualitative interviews

Table 3 Progression criteria (based on feasibility parameters)

	Summary	Action required
Go (green)	**Recruitment**: > 70% expected recruitment target **Follow-up**: > 75% data completeness **Adherence**: > 75% adherence to intervention	Feasible to continue to main trial
Amend (amber)	**Recruitment**: 50–70% of expected recruitment target **Follow-up**: 65–75% data completeness **Adherence**: 65–75% adherence to intervention	Identify remediable factors; discuss with trial management group
Stop (red)	**Recruitment**: < 50% of expected recruitment target **Follow-up**: < 65% data completeness **Adherence**: < 65% adherence to intervention	Do not progress to main trial, unless there is a strong case that unanticipated remediable factors have been identified

To assess the feasibility of collecting data for a cost-utility analysis in a future trial, we will collect the following:

a) EQ-5D-5L at 6-month post-ICU discharge
b) Resource use associated with the MI-E intervention and standard care

We will identify the following resource use during the index admission: MI-E device-associated resource use including staffing requirements (time spent delivering an MI-E treatment, grade/seniority of staff administering treatment) and consumables used. Patient-related resource use will include endotracheal suction frequency by nursing staff (over a 24-h period), use of noninvasive ventilation (NIV), high-flow oxygen therapy (HFOT) and tracheostomy, antibiotic use, physiotherapy on-call use (planned and unplanned), ICU LOS, ICU re-admission and hospital LOS. For the purposes of the feasibility trial, these will be reported as frequencies and time duration (hours).

Clinician training

Training for physiotherapists detailing the study protocol and how to deliver the intervention will occur at the start of the study. Standardised education materials developed by the research team will be distributed to all clinicians with the opportunity to practice intervention set up and delivery.

Outcome description

- *Re-intubation rate*: Re-intubation rate will be calculated for the 48 h following extubation. This is the planned primary outcome for the future planned trial.
- *Pain scores*: We will measure pain using the 'numeric rating scale' (NRS) [21] and the Critical Care Pain Observation Tool (CPOT) [22]. All patients will have CPOT measured. The CPOT is a valid measure to determine pain presence with four domains: facial expressions, body movements, compliance with the ventilator or vocalisation, and muscle tension. Each domain is scored 0–2 with a maximum score of eight. A CPOT score > 2 indicates pain presence. The NRS is a self-reported measure where patients rate pain presence and severity on a scale from 0 (no pain) to 10 (worst pain possible). During PPI work, patients highlighted the importance of including a patient-reported outcome. The NRS will be measured in addition to the CPOT. If a patient is unable to rate pain, we will use the CPOT only. We will document pain presence before and after a physiotherapy session.
- *Cardiovascular, ventilator, and respiratory parameters*: These measures include heart rate, systolic and diastolic blood pressure, ventilator settings, airway resistance and lung compliance, peripheral oxygen saturations, and respiratory rate measured pre- and post physiotherapy in both the intervention and control arms.
- *Acceptability*: We will use three validated questionnaires to measure acceptability: acceptability of intervention measure (AIM), intervention appropriateness measure (IAM) and feasibility of intervention measure (FIM) [23]. These will be measured immediately post-MI-E intervention.

Statistics and data analysis

Sample size calculation As this is a feasibility trial, a formal sample size calculation based on statistical power to detect a specified treatment effect size is not appropriate. We have selected a sample size of 50 participants based on measurement of feasibility parameters with adequate precision. The participating ICU admits approximately 1250 patients annually with potentially four to five eligible patients each week (minimum of 200 per year). We anticipate recruiting 50 over a 12-month period would be achievable, with an estimated recruitment rate of 25% and a confidence interval width of 0.12.

Statistical analysis plan The analysis and reporting of this study will be consistent with the CONSORT guidelines

extension to feasibility studies [24]. This study is not designed or powered to carry out formal hypothesis testing. Participant flow through the study will be summarised and presented in a flow diagram. Descriptive statistics for patient characteristics will be reported overall and by treatment group: as means or medians with measures of dispersion for continuous outcomes (as appropriate given distribution) and frequencies and percentages for categorical outcomes. Only descriptive statistics will be used in the physiology sub-study due to the small sample size proposed. Patient-reported and clinical feasibility outcomes will be presented and assessed for completeness of data.

Safety reporting The attending consultant physician is responsible for assessing all adverse reactions and adverse events (AEs) and categorising seriousness, expectedness, and relatedness. A list of events that can be expected during this trial, or within this patient population, can be found below.

- Accidental extubation during the intervention
- Cardiovascular changes (including but not exclusive to hypo/hypertension, brady/tachycardia, arrhythmias)
- Pneumothorax
- Sputum plugging during the intervention
- Pulmonary complications such as pneumonia
- Minor skin irritations due to electrical impedance tomography electrode patch application.

We will record occurrence of the following during a MI-E treatment and control arm interventions: HR, SBP, and DBP increase/decrease > 20% baseline and requiring intervention, arrhythmia (requiring intervention), pneumothorax, acute desaturation to < 85% or > 10% below baseline and requiring intervention, accidental extubation, and cardiopulmonary arrest.

It is the responsibility of the sponsor, chief investigator, and delegated individuals to ensure that the dignity, rights, safety, and well-being of research participants are given priority at all times, and appropriate action is taken to ensure their safety. The recording and reporting of safety events will be in accordance with good clinical practice (GCP) guidelines and study sponsor's 'research safety reporting' standard operating procedure.

Semi-structured qualitative interviews

Interviews with healthcare professionals and patients will explore the acceptability of the intervention and enrolment to the study. These interviews aim the following:

- Explore acceptability of the intervention for clinicians, patients, and consultees.
- Investigate potential barriers and facilitators to conducting a full trial.
- Determine outcome measures for a definitive trial.

Study design and recruitment

Interviews with patient participants in the intervention arm and their family members will take place within 6 weeks of discharge from ICU. We will exclude participants who have no recall of their ICU stay or the MI-E intervention. Interviews will be conducted by the chief investigator (E. S.).

Clinician interviews will be conducted with staff from the ICU clinical team including doctors, nurses, and physiotherapists who have had exposure to the MI-E intervention within the preceding 4 weeks. These interviews will be completed by a member of the study team (SV) to eliminate potential bias presented due to a working relationship with ES. These will occur during trial recruitment and within 4 weeks of exposure to a patient in the intervention arm of the trial.

We have based the interview topic guides on the Theoretical Framework of Acceptability (TFA) [25]. Interviews will be completed virtually via an online platform (Microsoft Teams).

Sampling and recruitment

Convenience sampling of 10–15 participants [26] will be used. Clinicians will be approached based on gaining maximal variation sample regarding profession and years of clinical experience. Patients and family members recruited into the study will be approached for consent once the patient has been discharged from ICU.

Interview data collection and analysis

On interview commencement, we will collect clinician demographic data (clinical profession, years working in profession and on ICU, highest educational level obtained) and patient demographics including age, reason for ICU admission, ICU LOS, or family demographics (relationship to patient) as relevant to the interview participant.

Interviews will be digitally recorded and transcribed verbatim by a university-approved transcription service. Transcripts will be checked for accuracy and anonymised. Data will be analysed using reflexive thematic analysis [26, 27] and using TFA domains through first-level coding by ES. Thematically similar responses will be grouped in a process of data reduction and compared across transcripts. Tables will be produced to highlight key thematic content, within each TFA domain with consideration

of responses from both patients and clinicians and with the aim of highlighting similar and discordant themes. Domains will be identified as salient based on their frequency of inclusion and potential strength of impact. NVivo software will be used to support this process.

Embedded exploratory physiology study

Background

During invasive ventilation, positive pressure breaths are delivered followed by passive expiration. In contrast, MI-E delivers both positive (insufflation) and negative (exsufflation) pressure breaths. Lung recruitment and de-recruitment are important considerations in intubated and ventilated patients [16]. Barotrauma and volutrauma associated with large tidal volumes are well documented, with low volume lung-protective ventilation now standard of care, particularly for patients with acute lung injury. De-recruitment of lung units due to small tidal volumes and loss of PEEP through ventilator disconnection can have an equally adverse impact on oxygenation and effective ventilation, attenuating lung injury [16].To date, no studies have examined the extent of recruitment and de-recruitment as a result of positive and negative pressure delivery during MI-E application.

Sub-study aim

To examine lung recruitment and de-recruitment during MI-E application.

Sub-study design

We will use electrical impedance tomography (EIT) (PulmoVista 500, Draeger Medical UK Ltd., Hertfordshire, UK) and lung ultrasound (Venue Go™, GE Healthcare, London, UK) in a subset of patients in the intervention arm. We aim to recruit between five and ten patients.

EIT is a noninvasive, radiation-free technique used at the bedside to provide pulmonary ventilation data in real time [28]. A series of 16 electrodes are placed around the chest wall, through which small electrical currents are passed to measure impedance, conductivity, and permittivity. These measurements result in a 2D image illustrating end inspiratory and end expiratory lung volumes and regional distribution of ventilation. The technique is used clinically and in ICU research studies to examine ventilation strategies, PEEP titration, and effects of positioning [28, 29].

Lung ultrasound score (LUS)

The lung ultrasound score is a semiquantitative scoring method used to illustrate pulmonary aeration [30]. We will use the previously described framework for practical application of the LUS in the ICU [31]. The framework describes six areas of interest per lung. Each hemithorax is divided into anterior, lateral, and posterior regions with each region having an upper and lower position. There is one representation point per area scanned and scored between 0 and 3 as part of this framework. Total scores range between 0 and 36. We will calculate LUS score pre- and post intervention. Scans will be completed by a clinician with Focused Ultrasound in Intensive Care (FUSIC) accreditation.

Data collection and reporting

We will record end-inspiratory and end-expiratory regional ventilation distribution via EIT before, during, and 5 min after the MI-E intervention. The lung ultrasound score will be calculated before and after the MI-E intervention (Table 3). Results will be presented as a case series.

Consent

On initial trial enrolment, patients may lack capacity to provide informed consent. As permitted in the UK, we will use a personal or nominated professional consultee. On regaining capacity, the patient will be informed of trial participation, and informed consent will be sought.

Interview participants will be requested to provide consent at the point of recruitment. Verbal informed consent will also be sought and recorded at the start of each interview.

Study withdrawal and processes

Participants are free to withdraw from any element of the study at any time without providing a reason. Unless specifically stated by the individual, data collected up to that point will be retained for analysis.

Data management

All participants will be assigned a unique study identification number, which will be used in all study-related documentation. A record of names, contact details, hospital numbers, and assigned trial numbers will be stored securely using a password-protected Research Electronic Data Capture (REDCap) database only accessible to members of the research team.

Clinical study data will be inputted directly into REDCap by the treating clinician and subsequently validated by a member of the research team. Study participants completing an online EQ-5D-5L survey will enter data directly through an external user REDCap interface. Data recorded on paper will be entered into the REDCap database (by E. S.).

Password-protected audio digital recording of interviews will be uploaded to a university computer secure drive. All transcriptions will be labelled with a unique

study identification number, edited to ensure respondents are pseudonymised (only clinician profession and banding/grading documented), and stored securely adhering to university data protection policies.

Consent forms (and any other documentation) with personal identifiable data will be stored in a locked filing cabinet (or locked equivalent). Participant details will be anonymised in any publications that result from the trial. At the end of the study, pseudonymised data will be stored in a secure research data storage repository, alongside the other study data (as per sponsor policies).

Study management

A Trial Management Group (TMG) will be responsible for overseeing day-to-day study management. The TMG will meet weekly. We formed a 12-member patient advisory group (PAG) who have informed decisions related to study design and will have ongoing input into study conduct, data analysis, and interpretation and dissemination. Two PAG members will also participate in the Trial Steering Group (TSG) to ensure the patient voice is heard throughout the study. The TSG consists of 5 expert clinicians representing the ICU multi-professional team and has an independent chair. The group meet every 3 months during study conduct.

Discussion

This study will investigate the feasibility of a RCT examining the use of MI-E to promote extubation success in critically ill adults receiving invasive mechanical ventilation. The importance and potential usefulness of completing a feasibility trial are further emphasised when considering the variability in MI-E use in intubated adults and variable outcome reporting as described in our recent scoping review [18]. The lack of qualitative data highlighted in the scoping review will be addressed in this trial through the completion of semi-structured interviews with clinicians, patients, and families. Additionally, the nested physiology study using EIT and LUS will provide a novel insight into the physiological impact of the MI-E device on lung recruitment and de-recruitment. Through the use of both quantitative and qualitative findings, we aim to optimise the design of a definitive trial particularly in relation to intervention and study protocol acceptability whilst also contributing and advancing the understanding of MI-E use in the acutely intubated population.

Trial status

Recruitment commenced on 11th July 2022. The current protocol version (v2.0) is dated 21st March 2022. Recruitment is estimated to be complete by July 2023.

Abbreviations

AE	Adverse events
AIM	Acceptability of Intervention Measure
APACHE II	Acute Physiology and Chronic Health Evaluation
ASB	Assisted Spontaneous Breathing
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous Positive Airway Pressure
CPOT	Critical Care Pain Observation Tool
DBP	Diastolic Blood Pressure
EIT	Electrical Impedance Tomography
FIO_2	Fraction of Inspired Oxygen
FIM	Feasibility of Intervention Measure
FUSIC	Focused Ultrasound in Intensive Care
GCP	Good Clinical Practice
HR	Heart Rate
HFOT	High-flow Oxygen Therapy
IAM	Intervention Appropriateness Measure
ICU	Intensive Care Unit
LOS	Length of Stay
LUS	Lung Ultrasound Score
MI-E	Mechanical Insufflation-Exsufflation
NHS	National Health Service
NIV	Noninvasive ventilation
NRS	Numeric rating scale
PAG	Patient advisory group
PEEP	Positive end-expiratory pressure
REDCap	Research Electronic Data Capture
RCT	Randomised controlled trial
SBP	Systolic blood pressure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TFA	Theoretical Framework of Acceptability
TMG	Trial Management Group
TSG	Trial Steering Group
UK	United Kingdom

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40814-023-01362-7.

Additional file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*.

Additional file 2: Appendix 1. Intervention arm protocol.

Acknowledgements

We would like to thank our patient advisory group and study sponsor, University Hospitals Bristol and Weston, who have been integral in the development of this protocol.

Authors' contributions

Authors ES, FC, SV, LT, LR, JB, and GN provided input to the original study concept and subsequent study design. NT provided statistical expertise. ES prepared the initial draft of the manuscript. All authors read, provided feedback, discussed, and approved the final manuscript. All authors gave approval for manuscript submission.

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Availability of data and materials

This data will be made available in any form to those outside the trial, to include requirements of inspection purposes by the sponsor and/or other regulatory authorities. Individuals interested in study materials may contact the study CI (E. S.).

Declarations

Ethics approvals and consent to participate

The project has been reviewed and approved by Leeds East Research Ethics Committee (IRAS 303674) and has Health Research Authority and Health Care Research Wales approvals dated 11/04/2022.

Consent for publication

Not applicable.

Competing interests

This is an investigator-initiated, designed, and managed research study. Breas Medical, UK, have provided the MI-E devices to the participating ICU free of charge for use in this study. Breas Medical have had no role in the study design and will have no role in study conduct or interpretation of results.

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Publisher's Note

Appendix 11 Feasibility Information for consultee

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

UWE Bristol University of the West of England

A feasibility study examining the use of Mechanical Insufflation Exsufflation to promote extubation success in adult intensive care (The MERIT Study)

Information for Consultee

We feel your relative/friend is unable to decide for himself/herself whether to participate in this research.

To help decide if he/she should join the study, we would like to ask your opinion on whether or not they would want to be involved. We are asking 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 relative/friend 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 will then give you a copy to keep. If you decide that your friend/relative would not wish to take part it will not affect the standard of care they receive in any way. Participants (your relative/friend) will be asked to give consent when they regain capacity and they will be given the PIS to read.

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 relative/friend.

Participant Information Sheet

You are invited to take part in a project taking place at the University of the West of England, Bristol (UWE). It is funded by the National Institute of Health Research (NIHR) and sponsored by University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). Before you decide whether to take part, it is important for you to understand why the project is being done and what it will involve. Please read the following information carefully and if you have any queries or would like more information please contact Ema Swingwood (contact details at the end of this document).

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

What is the project about?

There are about 230,000 adult intensive care admissions each year. Many of these patients require breathing support from a machine and breathing tube. Most adults are successfully removed from the breathing machine (extubation). However, 10-25% of patients are unable to breathe by themselves once the tube has been removed and so it needs to be put back in. One of the main reasons for this is because the patients are unable to cough well enough to clear mucus from their airway.

Having to have the breathing tube put back in leads to worse outcomes for the patient, including prolonging their length of hospital stay and increasing their risk of death. To help with successful extubation, physiotherapists can use a device to help patients cough and clear phlegm from their lungs. The cough device (mechanical insufflation-exsufflation) works by blowing air into the patients' lungs followed by quickly sucking it out. This device can be used before and after extubation. The cough device has only recently been used in the Intensive Care Unit (ICU) setting.

What is the aim of the project?

The aim of this research is to find out if it is possible to carry out a large study to see whether using a cough device in ITU can help patients be successfully removed from breathing support.

Why have I been invited to take part?

We are inviting patients who are currently in hospital on ICU to be involved in the study.

Do I have to take part?

You do not have to take part in this project. It is up to you to decide whether or not you want to be involved. If you do decide to take part, you will be asked to provide consent. If you do decide to take part, you are able to withdraw from the project without giving a reason. If you want to withdraw from the project within this period, please contact Ema Swingwood (contact details below). Deciding not to take part or to withdraw from the study will not affect the standard of care you receive.

What will happen to me if I take part and what do I have to do?

If you agree to take part you will be randomly assigned to either

1. Standard care or

2. The cough device and standard care

In the standard care group there will be no change to the routine care you receive whilst you are on ICU.

In the cough device group, in addition to routine care, you will also receive a physiotherapy treatment using a cough device. This will be conducted by the ICU physiotherapy team who

are all experienced and trained in using this device. The cough device will be used up to twice a day in addition to routine care. The treatment will take place via your breathing tube, on day one of the study. Once the breathing tube is removed, treatment will continue for a further 2-3 days via a facemask. We predict that each treatment session will take around 30-45 minutes.

During this time, we will collect data to see how you are tolerating the treatment and to see how effective it is. In a smaller group of patients (5-10), we will collect some additional measures looking specifically at lung volumes using Electrical Impedance Tomography. This is a non-invasive device that takes measures from the chest wall and creates coloured pictures of the lungs showing the size of each breath.

There will also be a short questionnaire to complete 6 months after you leave ICU. This can be completed over the phone or as a paper version.

If you are willing to be involved in the project, please contact Ema Swingwood (contact details below).

What are the benefits of taking part?

Although you will not receive any direct benefit from taking part in the project, you will be helping us to gain a better understanding of the factors that can influence using the cough device within ICU. The results will help us decide if it is possible to carry out a large study to see whether using a cough device in ICU can help patients be successfully removed from breathing support.

What are the possible risks of taking part?

We do not foresee or anticipate any significant risk to you in taking part in this project. Reported unwanted side effects from using the cough device are extremely rare. If, however, you feel uncomfortable at any time you can ask for the treatment to stop. If you need any support during or after the study then the researchers will be able to put you in touch with suitable support agencies.

What will happen to my information?

We will need to use information from your ICU medical records for this research project. This information will include your name, contact details, age and gender. People will use this information to do the research or to check your records to make sure that the research is being done properly. This information will be stored on a University of Bristol secure database. Any paper documents will be kept in a locked cabinet in a swipe access research office at UHBW.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you

safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. All study related data will be kept securely by the study sponsor (UHBW) for a period of 5 years after the end of the study. We will write our reports in a way that no-one can work out that you took part in the study.

If you wish to find out further information please visit: https://www.hra.nhs.uk/information-about-patients/

Who is organising and funding the project?

The project lead is Ema Swingwood as part a National Institute of Health Research funded Clinical Doctoral Research Fellowship. University Hospitals Bristol and Weston NHS Foundation Trust are the study sponsor. Professor Fiona Cramp (Director of Studies), Dr Jeremy Bewley, Dr George Ntoumenopoulos Professor Louise Rose, Dr Lyvonne Tume, and Dr Sarah Voss, are co-Investigators. Further information on the co-investigators is available at:

Where will the results of the project be published?

A report will be written containing our project findings. This report will be available on the UWE Bristol open-access Research Repository. We also plan to publish results in a peer-reviewed journal.

A hard copy summary report will be made available to all project participants. Key findings will also be shared both within and outside UWE Bristol.

Who has ethically approved this project?

The project has been reviewed and approved by Leeds East Research Ethics Committee (IRAS 303674) and has HRA and HCRW approvals.

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

What if something goes wrong?

If you have any concerns or complaints about the conduct of this project, please contact **Ema Swingwood** (contact details below) or **The UHBW Patient Advice and Liaison Service** (PALS) via telephone 0117 342 1050, email psct@uhbw.nhs.uk or post UHBW PALS, Bristol Royal Infirmary, Marlborough Street, Bristol, BS1 3NU.

What if I have more questions or do not understand something?

If you would like any further information about the project please contact in the first instance:

Appendix 12 Feasibility Consultee Declaration Form

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

UWE Bristol | University of the West of England

A feasibility study examining the use of Mechanical Insufflation Exsufflation to promote extubation success in adult intensive care (The MERIT Study)

Consultee declaration form for research conducted under the Mental Capacity Act 2005 and/or Mental Capacity Act (Northern Ireland) 2016

Participant Identification Number for this study:

CONSULTEE DECLARATION FORM

Please initial box

1. I .....have been consulted about ..... participation in this research project. I confirm that I have read the information sheet dated 21.3.2022 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. In my opinion he/she would have no objection to taking part in the above study. ☐
3. I understand that I can request he/she is withdrawn from the study at any time, without giving any reason and without his/her care or legal rights being affected. ☐
4. I understand that relevant sections of his/her care record and data collected during the study may be looked at by responsible individuals from UHBW or the direct research team, where it is relevant to their taking part in this research. ☐
5. I understand that my personal information will be stored on a University of Bristol secure database which will be accessible only to staff working on the study. ☐

Name of Consultee	Date	Signature
Relationship to participant:		
Person undertaking consultation (if different from researcher):		
Name	Date	Signature
Researcher	Date	Signature

When completed: 1 to be kept in care record, 1 for consultee; 1 for researcher site file (original)

Appendix 13 Feasibility Participant Information Sheet

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

UWE Bristol University of the West of England

Participant Information Sheet

A feasibility study examining the use of Mechanical Insufflation-Exsufflation to enhance extubation success in adult intensive care.

(The MERIT Study)

You are invited to take part in a project taking place at the University of the West of England, Bristol (UWE). It is funded by the National Institute of Health Research (NIHR) and sponsored by University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). Before you decide whether to take part, it is important for you to understand why the project is being done and what it will involve. Please read the following information carefully and if you have any queries or would like more information please contact Ema Swingwood (contact details at the end of this document).

What is the project about?

There are about 230,000 adult intensive care admissions each year. Many of these patients require breathing support from a machine and breathing tube. Most adults are successfully removed from the breathing machine (extubation). However, 10-25% of patients are unable to breathe by themselves once the tube has been removed and so it needs to be put back in. One of the main reasons for this is because the patients are unable to cough well enough to clear mucus from their airway.

Having to have the breathing tube put back in leads to worse outcomes for the patient, including prolonging their length of hospital stay and increasing their risk of death. To help with successful extubation, physiotherapists can use a device to help patients cough and clear phlegm from their lungs. The cough device (mechanical insufflation-exsufflation, figure 1) works by blowing air into the patients' lungs (a big breath in) followed by quickly sucking it out (like a cough). This device can be used before and after extubation. The cough device has only recently been used in the Intensive Care Unit (ICU) setting and is connected to a patients breathing tube when in use (figure 2).

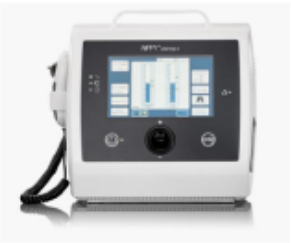

Figure 1: MI-E device

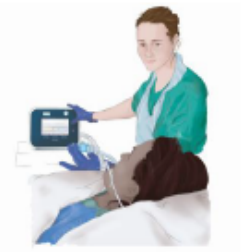

Figure 2: MI-E via breathing tube on ICU

NHS
University Hospitals
Bristol and Weston
NHS Foundation Trust

What is the aim of the project?

The aim of this research is to find out if it is possible to carry out a large study to see whether using a cough device in ICU can help patients be successfully removed from breathing support.

Why have I been invited to take part?

We are inviting patients who are currently in hospital on ICU to be involved in the study.

Do I have to take part?

You do not have to take part in this project. It is up to you to decide whether or not you want to be involved. If you do decide to take part, you will be asked to provide consent. If you do decide to take part, you are able to withdraw from the project without giving a reason. If you want to withdraw from the project within this period, please contact Ema Swingwood or an ICU research nurse (contact details below). Deciding not to take part or to withdraw from the study will not affect the standard of care you receive.

What will happen to me if I take part and what do I have to do?

If you agree to take part you will be randomly assigned to either

1. Standard care or

2. The cough device and standard care

In the standard care group there will be no change to the routine care you receive whilst you are on ICU.

In the cough device group, in addition to routine care, you will also receive a physiotherapy treatment using a cough device. This will be conducted by the ICU physiotherapy team who are all experienced and trained in using this device. The cough device will be used up to twice a day in addition to routine care. The treatment will take place via your breathing tube, on day one of the study. Once the breathing tube is removed, treatment will continue for a further 2 days via a facemask. A treatment session will involve a number of cough cycles (big breath in, followed by big breath out) to help move and clear phlegm that is in your lungs. The physiotherapist will ensure you have sufficient rest in between each cough cycle so that you do not get too tired. We predict that each treatment session will take around 30-45 minutes both for the intervention and the standard care group.

During this time, we will collect data to see how you are tolerating the treatment and to see how effective it is. In a smaller group of patients (5-10), we will collect some additional measures looking specifically at lung volumes using Electrical Impedance Tomography. This is a non-invasive device that takes measures from the chest wall and creates coloured pictures of the lungs showing the size of each breath.

There will also be a short questionnaire to complete 6 months after you leave ICU. This can be completed over the phone or as a paper version.

If you are willing to be involved in the project, please contact Ema Swingwood (contact details below).

What are the benefits of taking part?

It is not known whether the device will help patients in the trial, but the trial will provide information which could enable patients to benefit in the future. The results will help us decide if it is possible to carry out a large study to see whether using a cough device in ICU can help patients be successfully removed from breathing support.

What are the possible risks of taking part?

We do not foresee or anticipate any significant risk to you in taking part in this project. Reported unwanted side effects from using the cough device are extremely rare and include short term changes to your blood pressure, heart rate and oxygen levels. Your tolerance of the device will be monitored throughout by bedside clinicians. If, however, you feel uncomfortable at any time you can ask for the treatment to stop. If you need any support during or after the study then the researchers will be able to put you in touch with suitable support agencies.

What will happen to my information?

We will need to use information from your ICU medical records for this research project. This information will include your name, contact details, age and gender. People will use this information to do the research or to check your records to make sure that the research is being done properly. Your preferred contact details will be used for a study follow up questionnaire following your ICU discharge. This information will be stored on a University of Bristol secure database. Any paper documents will be kept in a locked cabinet in a swipe access research office at UHBW.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. All study related data will be kept securely by the study sponsor (UHBW) for a period of 5 years after the end of the study. We will write our reports in a way that no-one can work out that you took part in the study.

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

If you wish to find out further information please visit: https://www.hra.nhs.uk/information-about-patients/

Who is organising and funding the project?

The project lead is Ema Swingwood as part a National Institute of Health Research funded Clinical Doctoral Research Fellowship. University Hospitals Bristol and Weston NHS Foundation Trust are the study sponsor. Professor Fiona Cramp (Director of Studies), Dr Jeremy Bewley, Dr George Ntoumenopoulos Professor Louise Rose, Dr Lyvonne Tume, and Dr Sarah Voss, are co-Investigators. Further information on the co-investigators is available at:

[redacted]

Where will the results of the project be published?

A report will be written containing our project findings. This report will be available on the UWE Bristol open-access Research Repository. We also plan to publish results in a peer-reviewed journal.

A hard copy summary report will be made available to all project participants. Key findings will also be shared both within and outside UWE Bristol.

Who has ethically approved this project?

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NHS
University Hospitals
Bristol and Weston
NHS Foundation Trust

What if I have more questions or do not understand something?

If you would like any further information about the project please contact in the first instance:

[redacted]

Appendix 14 Feasibility Participant Consent Form

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

UWE Bristol University of the West of England

CONSENT FORM

A feasibility study examining the use of Mechanical Insufflation-Exsufflation to enhance extubation success in adult intensive care.

(The MERIT Study)

Participant Identification Number for this trial:

Please initial box

1. I confirm that I have read the information sheet dated 16.03.2022 (version 2.0) 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 my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities, or from the University Hospitals Bristol and Weston NHS Trust and Research Team, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I understand that my personal information will be stored on a University of Bristol secure database which will be accessible only to staff working on the study. ☐
5. I understand that the information held and maintained by University Hospitals Bristol NHS Foundation Trust may be used to help contact me or provide information about my health status for the purpose of the research study. ☐
6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person seeking consent	Date	Signature

Appendix 15 Clinician MI-E set up guide (appendix 1 within study protocol)

Appendix 1: Intervention arm protocol

Pre -procedure

- Check relevant equipment is ready. Note MI-E circuits may need to be double filtered for infection control purposes.
- Check session contraindications
  - PEEP>10
  - Haemodynamic instability: MAP <60 and >100, HR <50 and >130
  - Severe bronchospasm
- Complete routine airway clearance ensuring no secretions remain in the upper airways
- Note ETT insertion length at teeth and ensure the ETT cuff is adequately inflated
- Record pre-intervention observations into CRF

Procedure

Process step	Process detail	Considerations
1	Ensure closed suction in situ	
2	Attach MI-E to the ETT with one hand holding the MI-E circuit and the other supporting the ETT (figure 1)	
3	Deliver MI-E treatment cycles. Update CRF re intervention detail (mode, pressures, timings, flow, repeats, other physiotherapy techniques used)	-patient positioning -do you need to pre-oxygenate or entrain oxygen into the circuit (figure 2) -starting pressures consider ≥PIP to optimise VT -does the patient have recruitment needs? -does the patient have a secretion load? -are you likely to generate an expiratory flow bias? -are other interventions required to facilitate/augment the expiratory flow bias?
4	Follow each cycle with suctioning of ETT.	It may be beneficial to insert the suction catheter into the ETT either before or during

		exsufflation to optimise secretion clearance
5	Rest on ventilator between cycles OR provide tidal volume breaths via MI-E	To prevent hyperventilation through blowing off CO_2 and/or to minimise potential volutrauma
6	Repeat cycles until secretions are cleared	Regular re-Ax to determine treatment effectiveness
7	Monitor HR, BP and SpO2 throughout	

Post procedure

- Check ETT length and cuff pressure
- Re-auscultate
- Record post intervention observations as per protocol

Figure 1: set up of MI-E device to ETT

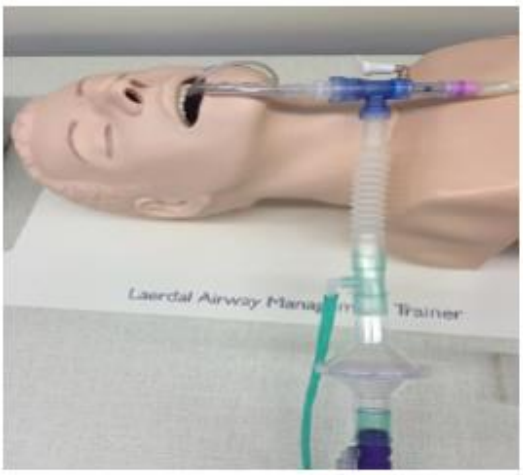
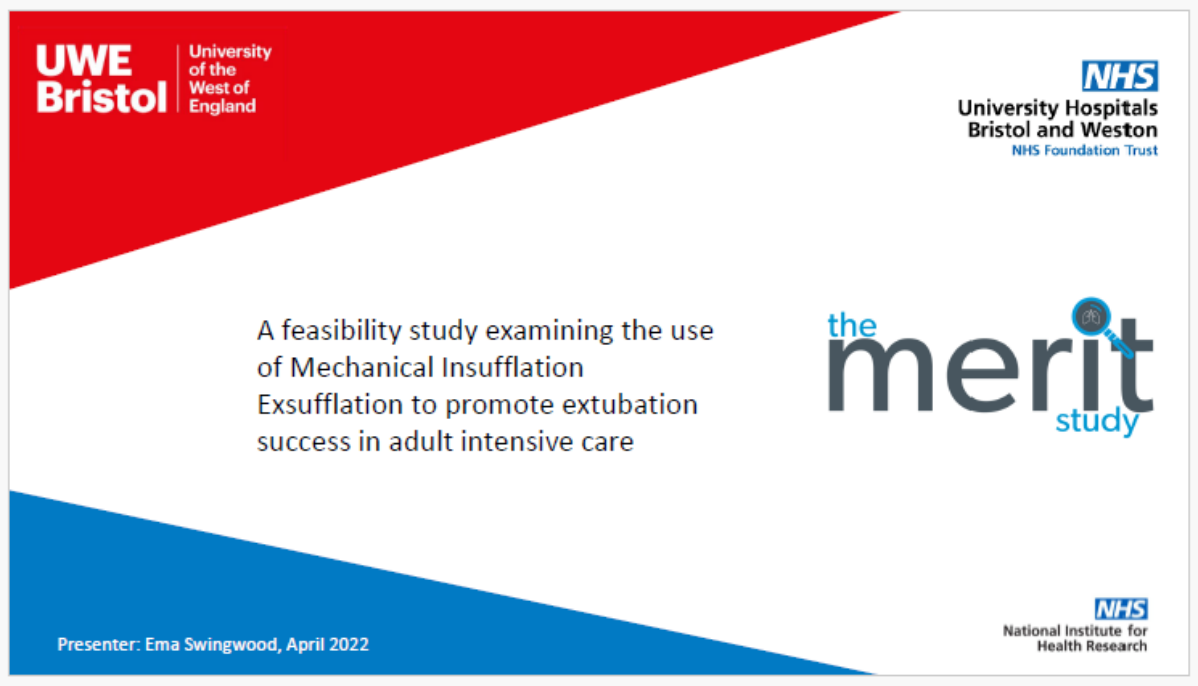
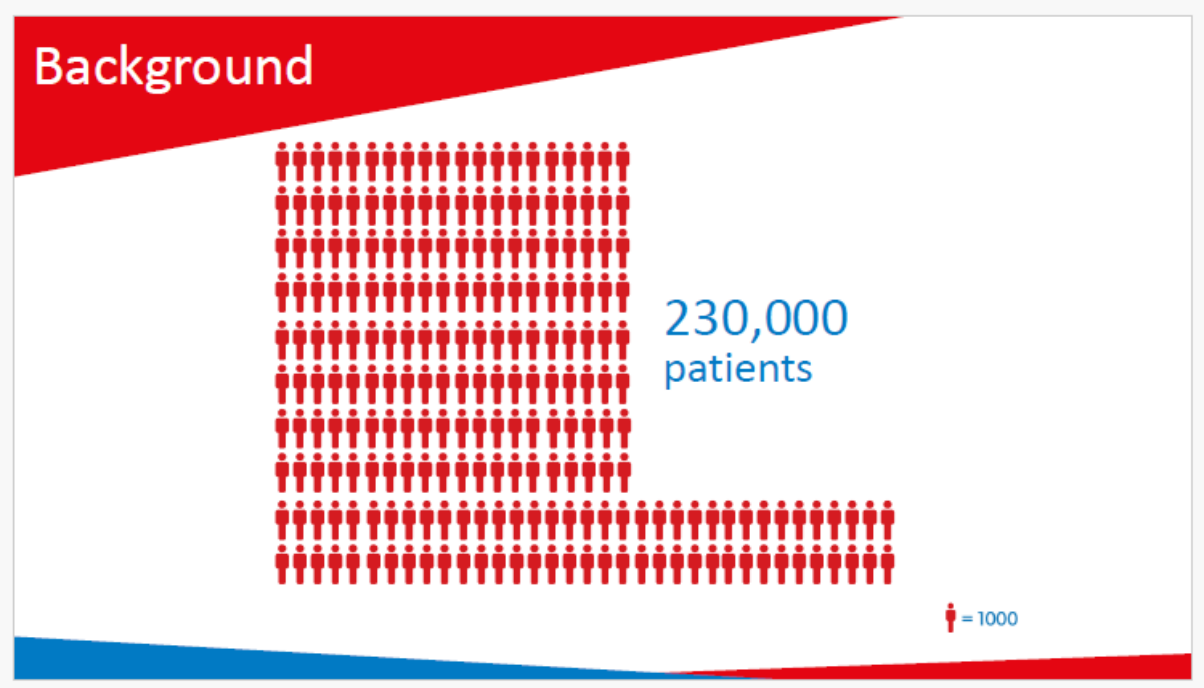


Figure 2: set up of MI-E to ETT to include entrained oxygen into the circuit

Appendix 16 Nurse study training





10-25%

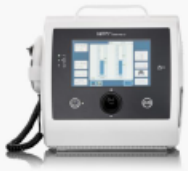
FAIL **initial extubation attempts**

Reintubation within 48 hours and is associated with increased ITU length of stay **(LOS),** impaired quality of life, **and** higher mortality risk.

= 1000

Mechanical Insufflation-Exsufflation

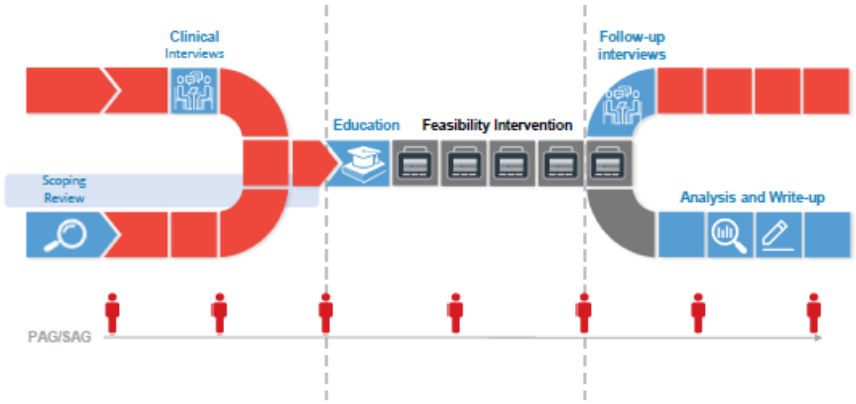
- A non invasive device used to augment cough



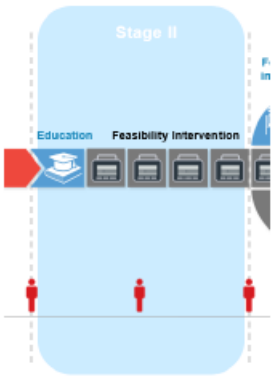
- Delivery of a positive pressure breath (insufflation), rapidly followed by a negative pressure breath (exsufflation)

- Traditionally used in a NMD population-extensive evidence
- ?translation into an intubated population

Research Plan

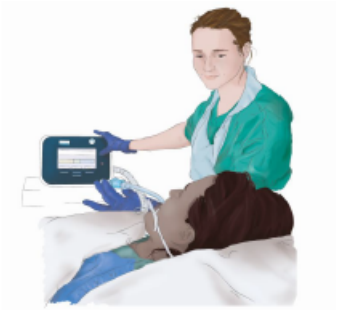


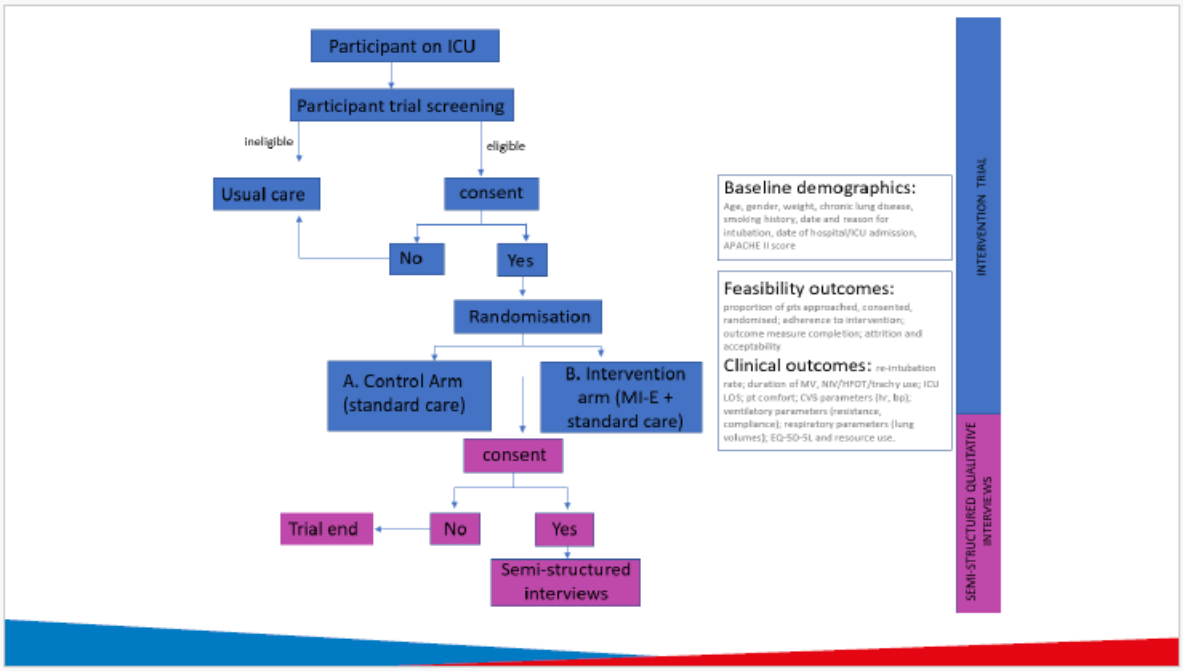
Research Plan: stage II



AIM: *to determine the feasibility of a RCT of MI-E used to promote extubation success in acutely intubated and ventilated patients*

- MI-E v standard care
- 3 day duration
- Feasibility outcomes
- Acceptability





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NHS University Hospitals Bristol and Weston NHS Foundation Trust

Thank you-any questions?

the merit study

[redacted]

NHS National Institute for Health Research

Appendix 17 Doctor study training

UWE Bristol | University of the West of England

NHS University Hospitals Bristol and Weston NHS Foundation Trust

A feasibility study examining the use of Mechanical Insufflation Exsufflation to promote extubation success in adult intensive care

NHS National Institute for Health Research

Presenter: Ema Swingwood, April 2022

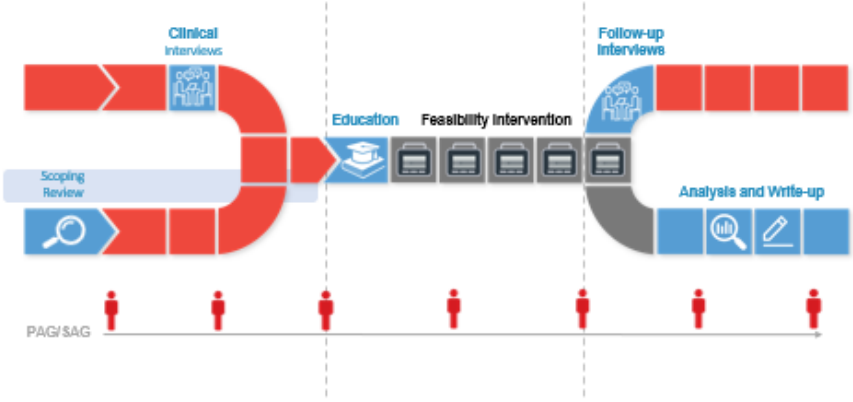
Mechanical Insufflation-Exsufflation

- A non invasive device used to augment cough

- Delivery of a positive pressure breath (insufflation), rapidly followed by a negative pressure breath (exsufflation)
- Traditionally used in a NMD population-extensive evidence

- ?translation into an intubated population

Research Plan



Research Plan: stage II

AIM: *to determine the feasibility of a RCT of MI-E used to promote extubation success in acutely intubated and ventilated patients*

- MI-E v standard care
- 3 day duration
- Feasibility outcomes
- Acceptability

Eligibility

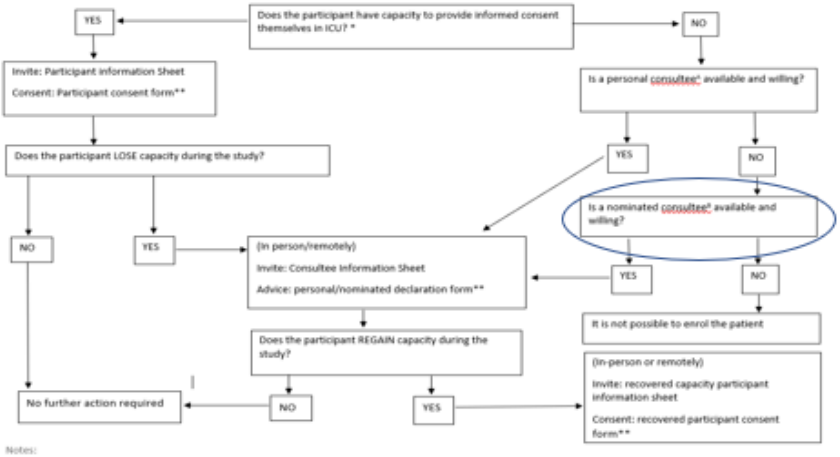
Inclusion criteria

- Adult >16years
- MV >48hrs
- Problems with secretion mx (weak cough/secretion load)
- 'ready to wean' or 'weaning'

Exclusion criteria

- PEEP>10
- FiO2 >0.7
- hemodynamic/cardiovascular instability
- Contraindications to MI-E delivery
- Pre-existing NMD/trachy/MI-E use
- Not expected to survive
- Re-admission to ICU
- Previous MERIT participation

Consent



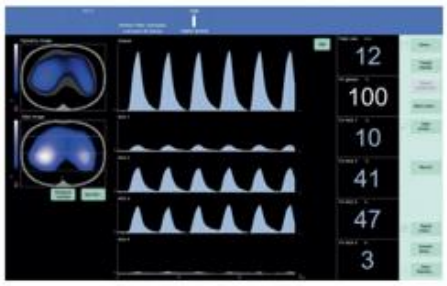
Notes:
*the study invitation and consent process presented here is in line with the Mental Capacity Act 2005 for patients in England and Wales
**The default method of completion is via telephone with witnessed consent or written consent. Staff should update the Screening Log at all relevant timepoints.
^The patients partner, or a friend or carer who is not seeking renumeration for doing so or acting in a professional capacity. ^Nominated Consultee is someone at the participating site appointed by the CI. This may include a member of the care team as long as they are not connected with the project to avoid potential conflict.

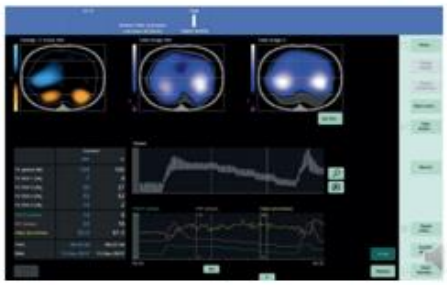
Data collection

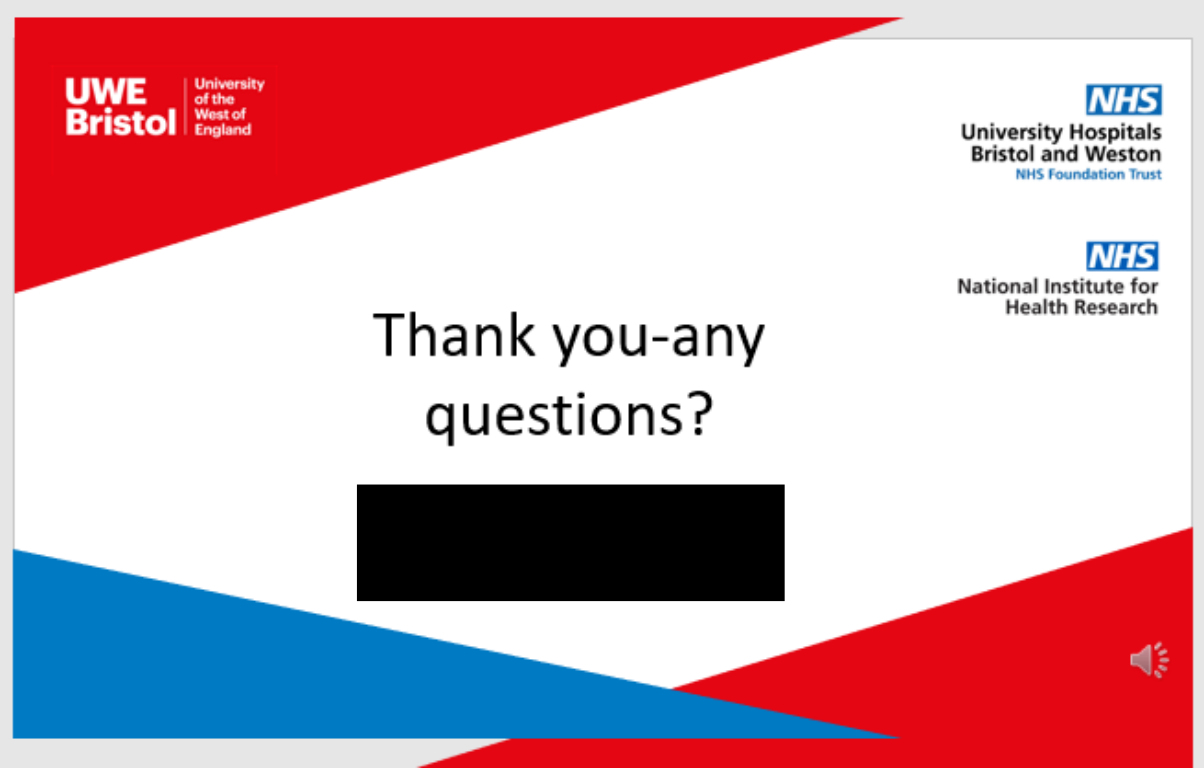
Demographics (baseline) → Intervention data → Resource use → Follow up 6/12 → Interviews

Electrical Impedance Tomography

- Visualisation ventilation distribution
- For intervention arm
- EILV and EELV
- Safety, setting optimisation






UWE Bristol
University of the West of England
NHS
University Hospitals Bristol and Weston
NHS Foundation Trust
NHS
National Institute for Health Research
Thank you-any questions?
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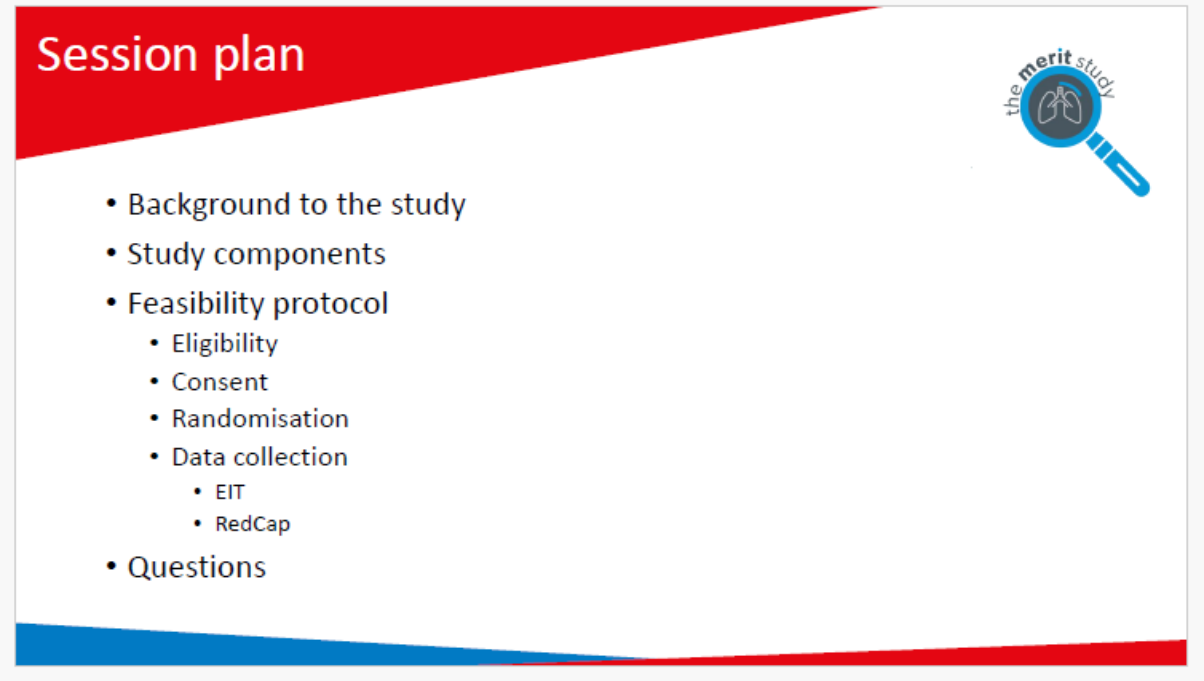
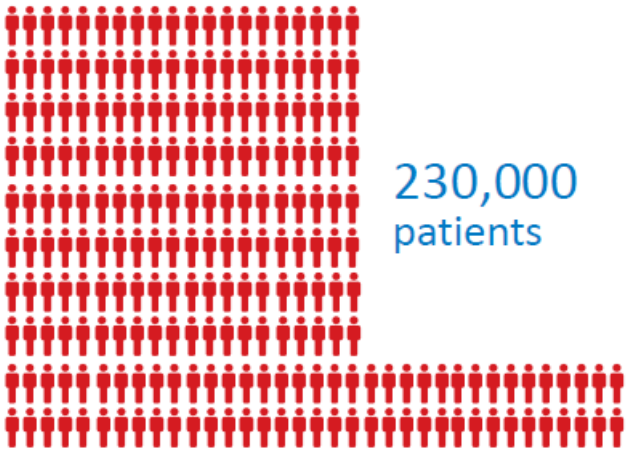
Appendix 18 Physiotherapist study training

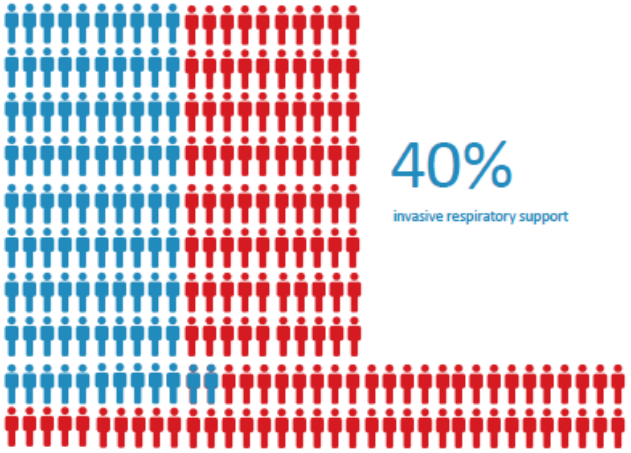


Background



230,000
patients

= 1000



40%
invasive respiratory support

= 1000

10-25%

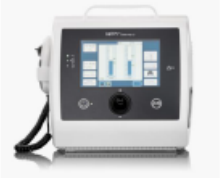
FAIL **initial extubation attempts**

Reintubation within 48 hours and is associated with increased ITU length of stay **(LOS), and** higher mortality risk.

= 1000

Mechanical Insufflation-Exsufflation

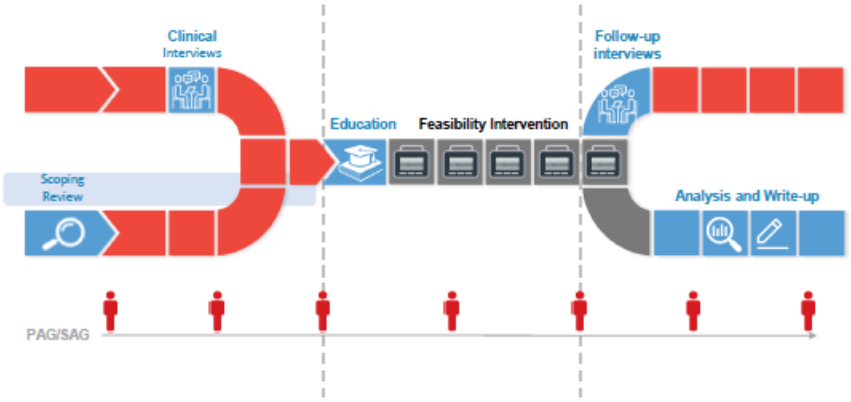
- A non invasive device used to augment cough



- Delivery of a positive pressure breath (insufflation), rapidly followed by a negative pressure breath (exsufflation)

- Traditionally used in a NMD population-extensive evidence
- ?translation into an intubated population

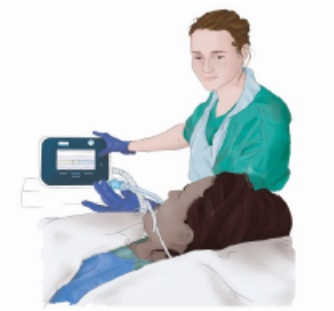
Research Plan



Research Plan: stage II

AIM: *to determine the feasibility of a RCT of MI-E used to promote extubation success in acutely intubated and ventilated patients*

- MI-E v standard care
- 3 day duration
- Feasibility outcomes
- Acceptability



Gonçalves et al. Critical Care 2012, 16:R48
http://ccforum.com/content/16/2/R48

CRITICAL CARE

RESEARCH Open Access

Effects of mechanical insufflation-exsufflation in preventing respiratory failure after extubation: a randomized controlled trial

Miguel R Gonçalves[1,2*], Teresa Honrado[2], João Carlos Winck[3] and José Artur Paiva[2]

- N=75
- A: control v B: MI-E extubation protocol
- MI-E +40:-40, Ti 3s, Te 2s, pause 3s; 8 cycles with abdominal thrust
- Re-intubation rate primary end point

Gonçalves et al. Critical Care 2012, 16:R48
http://ccforum.com/content/16/2/R48

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- N=75
- A: control v B: MI-E extubation protocol
- MI-E +40:-40, Ti 3s, Te 2s, pause 3s; 8 cycles with abdominal thrust
- Re-intubation rate primary end point

Table 2 Postextubation outcomes data

	Group A (n = 40)	Group B (MI-E) (n = 35)
NIV application, n (%)	20 (50%)	14 (40%)
Reasons for NIV (n)		
Respiratory rate > 35 beats/min	5 (25%)	9 (64%)
SpO_2 < 90%	4 (20%)	1 (7%)
20% variation of HR or BP	1 (5%)	-
PaO_2 < 60, $PaCO_2$ >45	10 (50%)	4 (29%)
Total period of MV (days)	17.8 ± 6.4[a]	11.7 ± 3.5[a]
Patients reintubated (n, %)	19 (48%) [a]	6 (17%)[a]
Causes of reintubation (n)		
Respiratory pauses with loss of consciousness	-	1
Respiratory distress after 2-h NIV	6	2
Decreasing level of consciousness	2	-
Intolerance to NIV	2	-
Hypotension (systolic BP < 90 mm Hg for > 30 minutes)	-	1
Secretion encumbrance associated with severe hypoxemia	9	2
NIV failure rate, n (%)	13 (65%) [a]	2 (14%)[a]
Total ICU length of stay	19.3 ± 8.1	16.9 ± 11.1
Postextubation ICU length of stay	9.8 ± 6.7[a]	3.1 ± 2.5[a]

Data are presented as mean ± standard deviation. APS II, New Simplified Acute Physiology Score; COPD, chronic obstructive pulmonary disease; MV, mechanical ventilation; NIV, noninvasive ventilation; NS, nonsignificant. [a]P < 0.05

Does it work?

Effects of Mechanical Insufflation-Exsufflation on Airway Mucus Clearance Among Mechanically Ventilated ICU Subjects

Márcio Luiz Ferreira de Camillis PT, Augusto Savi PT PhD, Regis Goulart Rosa MD PhD, Mariana Figueiredo PT, Ricardo Wickert PT, Luis Guilherme Alegretti Borges PT, Lucas Galant PT PhD, and Cassiano Teixeira MD PhD

Effects of Mechanical Insufflation-Exsufflation on Sputum Volume in Mechanically Ventilated Critically Ill Subjects

Roberto Martínez-Alejos, Joan-Daniel Martí, Gianluigi Li Bassi, Daniel Gonzalez-Anton, Xabier Pilar-Diaz, Thomas Reginault, Philippe Wibart, George Ntoumenopoulos, Oystein Tronstad, Albert Gabarrus, Alice Quinart, and Antoni Torres

Performance of the CoughAssist Insufflation-Exsufflation Device in the Presence of an Endotracheal Tube or Tracheostomy Tube: A Bench Study

Claude Guérin MD PhD, Gaël Bourdin MD, Véronique Leray MD, Bertrand Delannoy MD, Frédérique Bayle MD, Michèle Germain MD, and Jean-Christophe Richard MD PhD

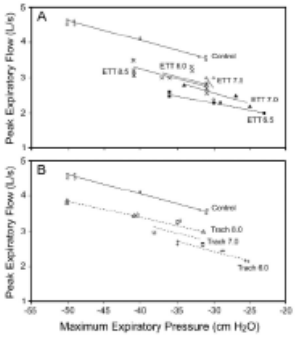


Fig. 3. Regression analysis of the relationship of peak expiratory flow to maximum expiratory pressure with set compliance of 60 mL/cm H_2O and 0 added resistance, with (A) 5 sizes of endotracheal tube (ETT) and (B) 3 sizes of tracheostomy tube (Trach). We made 5 measurements in each condition.

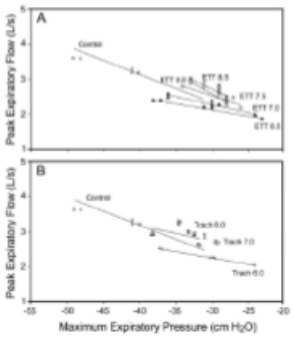


Fig. 4. Regression analysis of the relationship of peak expiratory flow to maximum expiratory pressure with set compliance of 30 mL/cm H_2O and set resistance of 5 cm H_2O/L/s, with (A) 5 sizes of endotracheal tube (ETT) and (B) 3 sizes of tracheostomy tube (Trach). We made 5 measurements in each condition.

- Varying pressure +/-30, 40, 50cm H_2O
- Compliance 30, 60ml/cmH_2O
- Res 0, 5H_2O/L/sec

Narrower inner diameter of tube = lower resultant PEF generated

Safety

The use of mechanical insufflation-exsufflation in invasively ventilated critically ill adults: a scoping review

Ema Swingwood* BSc (Hons), MSc [1,2], Willemke Stilma* MSc, RN[3,4], Lyvonne N Tume PhD, RN[5], Fiona Cramp BSc (Hons), FCSP, PhD[1], Sarah Voss BSc (Hons), PhD[1], Jeremy Bewley MB ChB FFICM[6], George Ntoumenopoulos PhD[7], Marcus Schultz PhD, MD[4,8,9,10], Wilma Scholte op Reimer PhD, RN[11], Frederique Paulus PhD, RN[3,4], Louise Rose PhD, RN[12,13]

- 13/20 studies addressed adverse events (AE)
- 3/13 AE occurrence (CVS instability, re-intubation, mucus plugging, haemoptysis, pneumothoraces, chest pain)

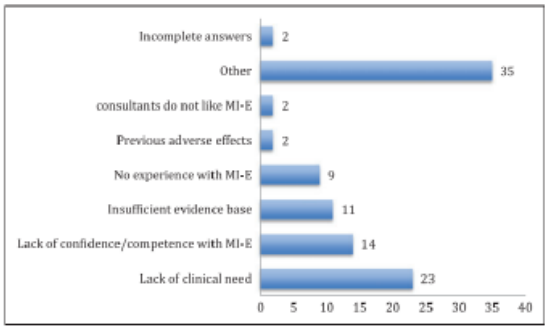
RESEARCH Open Access

Preliminary experience on the safety and tolerability of mechanical "insufflation-exsufflation" in subjects with artificial airway

Miguel Sánchez-García[1*], Paolo Santos[2], Gema Rodríguez-Trigo[3], Fernando Martínez-Sagasti[1], Tomás Fariña-González[1], Ángela del Pino-Ramírez[1], Carlos Cardenal-Sánchez[1], Beatriz Busto-González[1], Mónica Requesens-Solera[1], Mercedes Nieto-Cabrera[1], Francisco Romera-Romero[1] and Antonio Núñez-Reiz[1]

- N=13 (26 sessions) via ETT/trachy
- Measures pre, 5&60mins post MI-E
- *"may be safe and effective-need to confirm in larger studies"*

Barriers to MI-E delivery



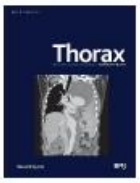
Swingwood et al., 2020

- Clinician interviews n=31
  - Culture
  - Hierarchy of treatments
  - Educational needs
- Lack of consistency
  - In reporting
  - Settings used
  - Outcome measures

ORIGINAL ARTICLE

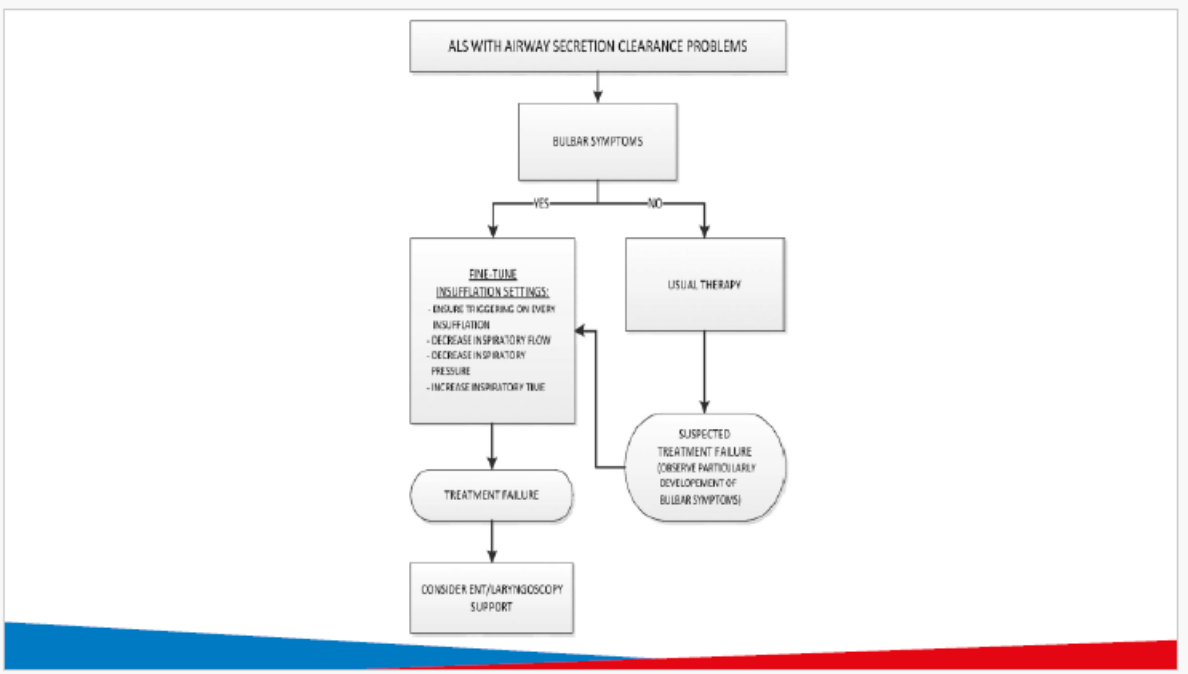
Laryngeal response patterns influence the efficacy of mechanical assisted cough in amyotrophic lateral sclerosis

Tiina Andersen,[1,2,3] Astrid Sandnes,[3] Anne Kristine Brekka,[4] Magnus Hilland,[5] Hege Clemm,[3,6] Ove Fondenes,[1] Ole-Bjørn Tysnes,[7,8] John-Helge Heimdal,[5,8] Thomas Halvorsen,[3,6] Maria Vollsæter,[1,3,6] Ola Drange Røksund[4,6]



Key findings

- aryepiglottic fold adduction during insufflation managed to keep these structures more open with positive pressures of 20-30cmH_2O
- asymmetric treatment pressures with lower insufflation pressures and flows, provided less adduction in the larynx; both at supra-glottic and glottic level
- Instructions did not influence the groups response
- need to fine-tune insufflation settings: see flow chart



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Protocol:

the merit study

Eligibility

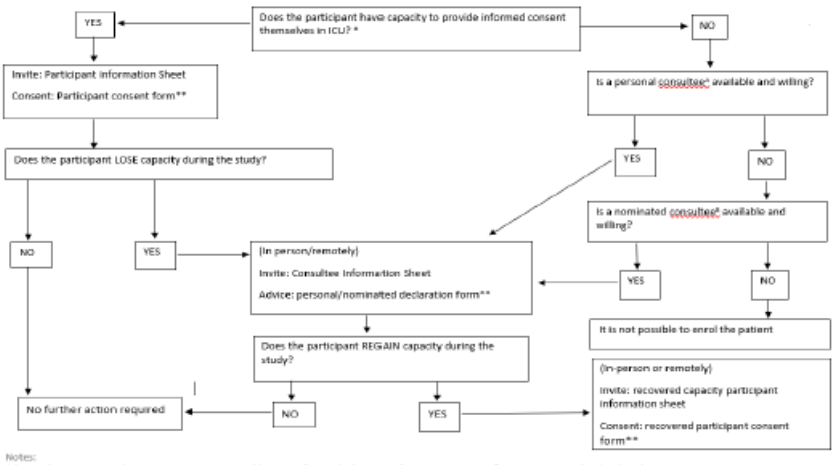
Inclusion criteria

- Adult >16years
- MV >48hrs
- Problems with secretion mx (weak cough/secretion load)
- 'ready to wean' or 'weaning'

Exclusion criteria

- PEEP>10
- FiO2 >0.7
- hemodynamic/cardiovascular instability
- Contraindications to MI-E delivery
- Pre-existing NMD/trachy/MI-E use
- Not expected to survive
- Re-admission to ICU
- Previous MERIT participation

Consent



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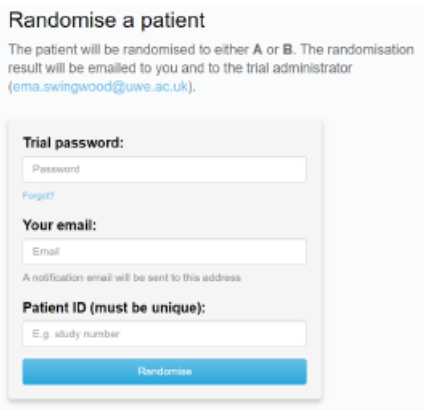
*The patients partner, or a friend or carer who is not seeking remuneration for doing so or acting in a professional capacity; *Nominated Consultee is someone at the participating site appointed by the CI. This may include a member of the care team as long as they are not connected with the project to avoid potential conflict.

Randomisation

- Through a web link or text message service
- Randomised to either:
  - A. control (standard care)
  - B. intervention arm (MI-E plus standard care)
- Trial password: cough123
- Patient ID: BRI001; BRI002 etc (from database)

The MERIT Study | Sealed Envelope (nb this is the test link)



Protocol

A. Control arm (standard care)

- Standard care: ventilation, weaning, physiotherapy
- Decision to extubate/re-intubate from attending physician
- Data collection during PT session in the 24hours preceeding extubation and upto 48hours after (table 4)

B. Intervention arm (MI-E plus standard care)

- Clearway 2
- Intubated a min of 2 MI-E sessions
- Extubated upto 2 Rx's/day for 48hours
- MI-E settings individualised
- Data collection (table 4)
  - Clinical data pre/during/post MI-E
  - Resource use
  - safety

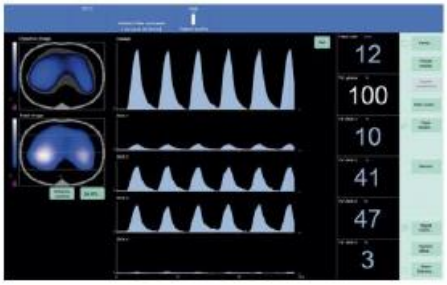
Data collection

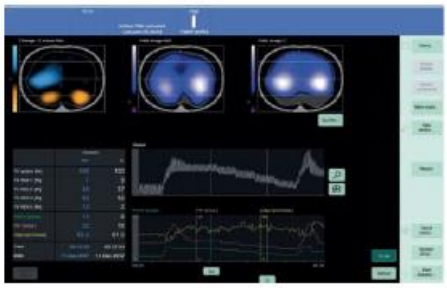
Demographics (baseline) → Intervention data → Resource use → Follow up 6/12 → Interviews

See table 4

Electrical Impedance Tomography

- Visualisation ventilation distribution
- For intervention arm
- EILV and EELV
- Safety, setting optimisation





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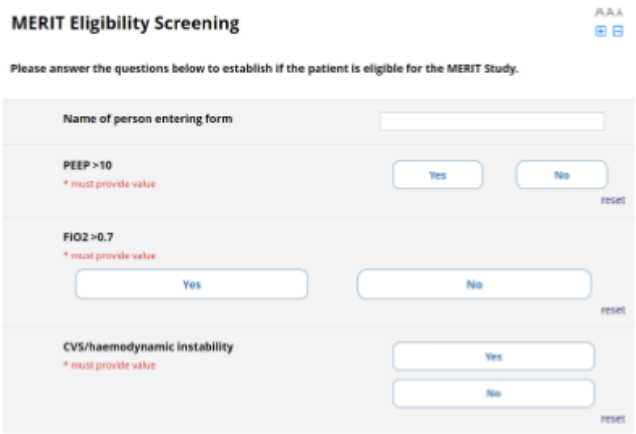

Training

- Recorded presentations
- 'Hands on' simulation
- Live FAQ document
- Study site file
  - Protocol
  - Outcomes measures
  - Paperwork

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Thank you-any questions?

the merit study

[redacted]

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Appendix 19 Physiotherapy study training: short protocol

STUDY PROTOCOL

A feasibility study examining the use of Mechanical Insufflation Exsufflation to promote extubation success in adult intensive care

the merit study

iii. TRIAL SUMMARY

Trial Title	A feasibility study examining the use of Mechanical Insufflation Exsufflation to promote extubation success in adult intensive care
Internal ref. no. (or short title)	The MERIT Study (R&I reference: DT/2020/7038)
Study location	NHS ICU
Study question	Is it feasible to conduct an RCT to evaluate the use of MI-E to promote extubation success in adult ICU?
Trial Design	Single centre, parallel group, individually randomized feasibility RCT with economic scoping, nested EIT exploratory physiology study and nested qualitative study
Trial Participants	Critically ill, intubated adults
Inclusion criteria	• Adult (≥16 years) • Expected to require invasive mechanical ventilation for >48hrs • Clinician identified pre-extubation problems with secretion management defined as poor/weak cough effort (cough peak flow <60L/min) and/or secretion load that are difficult to clear with usual airway clearance management (as assessed by the treating clinical team) • Identified as 'ready to wean or weaning' by the treating clinical team (on a spontaneous mode of ventilation for example CPAP ASB, PSV, APRV with spontaneous effort)
Exclusion criteria	• PEEP >10; • FiO_2 >0.7 • Hemodynamic/Cardiovascular instability (i.e. noradrenaline >0.25mg/kg, arrhythmias requiring intervention); • Recent undrained pneumothorax (current admission with no chest drain in situ); • Unable to continue to use MI-E post extubation (i.e. contraindications to facemask use-facial/cranial trauma, recent facial surgery; active upper gastrointestinal bleeding/uncontrolled vomiting; recent upper abdominal/thoracic surgery with at risk anastomosis) • Pre-existing neuromuscular respiratory condition • Pre-existing routine use of MI-E in the community • Patients with pre-existing permanent tracheostomy • Treatment withdrawal expected within 24hrs or not expected to survive • Re-admission to ICU following index admission • Previous MERIT trial participation

Planned Sample Size	50 ICU patients for intervention study 10-15 participants for follow-up interviews (clinicians) 10-15 participants follow-up interviews (patients/consultees)
Study interventions	
Control arm	Patients will receive standard care including ventilation, weaning, standard physiotherapy techniques such as positioning, manual techniques, manual/ventilator hyperinflation, suctioning, and nebulisers. At present MI-E in the intubated population is not routine clinical care at UHBW. Respiratory physiotherapy treatments will vary across patients as treatments will be delivered at the discretion of the treating physiotherapist based on individual assessment and are not protocolised. Decisions to extubate and re-intubate will be made by the attending physician with reason(s) documented. Clinical data collection will occur during physiotherapy intervention sessions in the 24hours preceding extubation and up to 48 hours post extubation (see table 4/section 6.3).
Intervention arm	The intervention under investigation is MI-E. In this study the MI-E device, Clearway 2 (Breas Medical LTD, Stratford-Upon-Avon, Warwickshire, UK) will be used. The device is reusable between patients with single patient use circuits, filters and interface (mouthpiece, facemask and flexible catheter mount). Whilst intubated, treatment will include a minimum of two MI-E sessions via the endotracheal tube (with cuff inflated) following randomization and prior to extubation. MI-E settings (mode, pressure, timings, flow) will be individualised to each patient based on current ventilator settings, patient tolerance, chest expansion and secretion clearance (see appendix 1). Post extubation (and up to 48hrs), patients will receive MI-E delivered via facemask or mouthpiece up to 2 times/day with MI-E settings individualised and set according to patient tolerance, chest wall expansion and secretion clearance (as assessed by treating physiotherapist).
Study schedule	
Start date	April 2022
Proposed duration	12 months
Proposed end date	April 2023
Outcomes	

Feasibility	• Proportion of eligible patients approached, consented and randomised • Proportion of MI-E treatment sessions completed • Proportion of recruited patients with all outcomes recorded • Attrition (participant withdrawal and loss to follow up) • Acceptability of trial processes to participants and clinicians • Acceptability of outcome measures to participants and clinicians
Clinical*	• Use of HFOT, NIV and tracheostomy • Physiotherapy interventions completed • LUS Score • Pain/discomfort • CVS parameters (HR, SBP, DBP) • Ventilator parameters (resistance, compliance) • Respiratory parameters (RR, SpO_2, EILV**, EILV**) • Adverse events
Health economics	• EQ-5D-5L at 6/12 post intervention • Resource use: treating clinician(s); duration of treatment; equipment used; on-call physiotherapy use (planned and unplanned), suction frequency over 24hours

*****clinical outcomes are collected to understand the feasibility of data collection to inform a definitive trial and not to conduct hypothesis testing

**to be measured in a subset of patients only as part of an add on exploratory physiology study

vi. TRIAL FLOW CHART

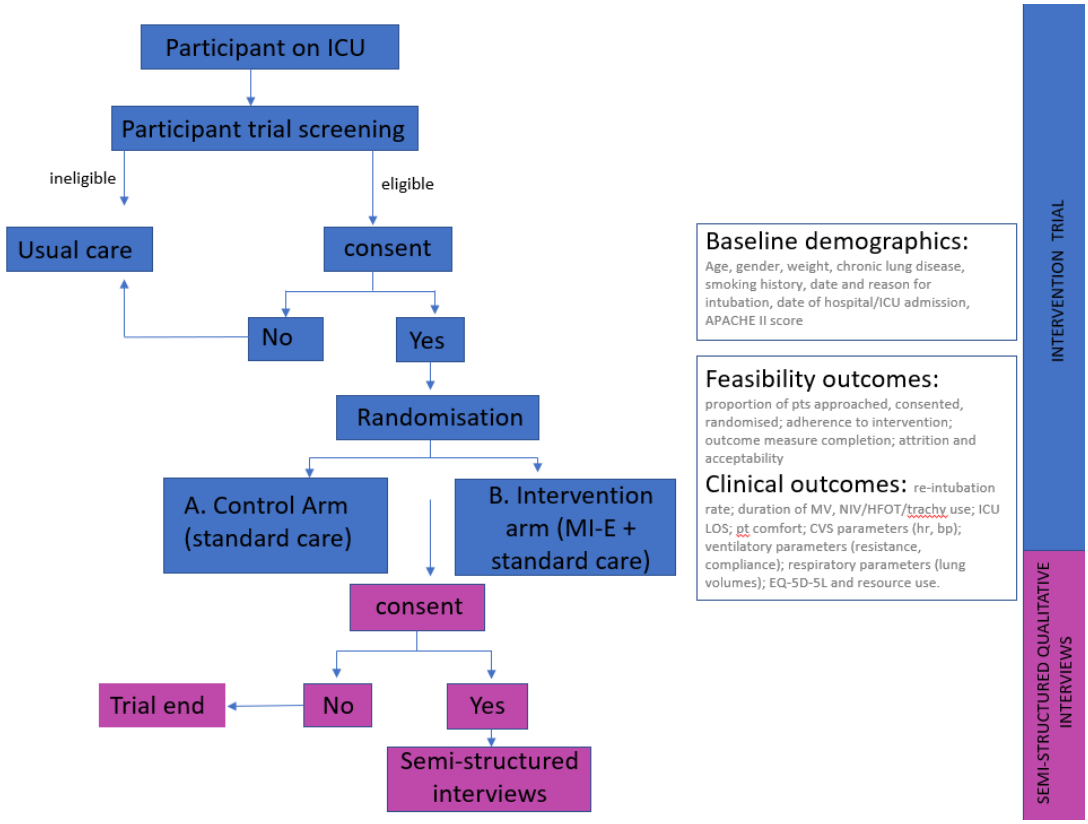
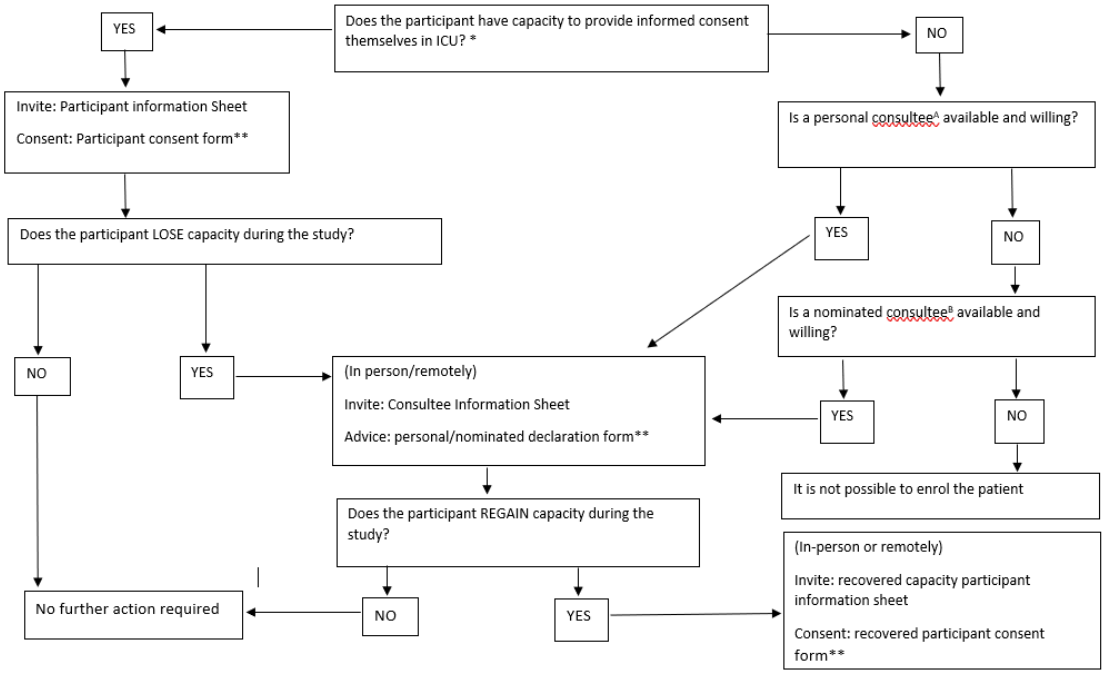


Figure 1: Study summary flow chart



Notes:
*the study invitation and consent process presented here is in line with the Mental Capacity Act 2005 for patients in England and Wales
**The default method of completion is via telephone with witnessed consent or written consent. Staff should update the Screening Log at all relevant timepoints.
[A]The patients partner, or a friend or carer who is not seeking renumeration for doing so or acting in a professional capacity; [B]Nominated Consultee is someone at the participating site appointed by the CI. This may include a member of the care team as long as they are not connected with the project to avoid potential conflict.

Figure 2: Consent process

Randomisation link: [The MERIT Study | Sealed Envelope]

	Data	Baseline	Pre-intervention	During intervention	5 mins post intervention	Duration of ICU stay	6 month follow up	Data location on Philips system
Baseline demographic outcome	Demographics	X						Patient front sheet
	Reason for intubation	X						GICU history and examination
	Date of hospital and ICU admission	X						Demographic form
	Date of intubation	X						GICU history and examination OR medical notes/flowsheet
	Ventilator settings	X	X		X			Flowsheet ventilation
	Airway type and size	X						Flowsheet respiratory
	APACHE II score	X						Appendix 2
Clinical outcomes	Use of HFOT, NIV, tracheostomy					X		Flowsheet ventilation
	Use of physiotherapy interventions			X				Flowsheet medical notes-PT/OT intervention
	LUS score		X		X			Appendix 3
	Patient pain/discomfort		X		X			Flowsheet neuro or self Ax (appendix 4/5)
	CVS parameters (hr, sbp, dbp)		X	X	X			Flowsheet vital signs
	Ventilator parameters (vent settings, resistance, compliance)		X		X			Flowsheet ventilation and from ventilator directly
	Respiratory parameters (RR, SpO_2)		X		X			Flowsheet vital signs and observations screen at bedside
Health economics	-resource use -QOL via EQ-5D-5L			X			X	Flowsheet medical notes-PT/OT intervention and appendix 6
Safety	Adverse events			X	X	X		Ongoing reporting

Table 4: Summary of outcomes and measurements during study period

Appendix 1: Intervention arm protocol

Pre -procedure

- Check relevant equipment is ready. Note MI-E circuits may need to be double filtered for infection control purposes.
- Check session contraindications
    - PEEP>10
    - Haemodynamic instability: MAP <60 and >100, HR <50 and >130
    - Severe bronchospasm
- Complete routine airway clearance ensuring no secretions remain in the upper airways
- Note ETT insertion length at teeth and ensure the ETT cuff is adequately inflated
- Record pre-intervention observations into CRF

Procedure

Process step	Process detail	Considerations
1	Ensure closed suction in situ	
2	Attach MI-E to the ETT with one hand holding the MI-E circuit and the other supporting the ETT (figure 1)	
3	Deliver MI-E treatment cycles. Update CRF re intervention detail (mode, pressures, timings, flow, repeats, other physiotherapy techniques used)	-patient positioning -do you need to pre-oxygenate or entrain oxygen into the circuit (figure 2) -starting pressures consider ≥PIP to optimise VT -does the patient have recruitment needs? -does the patient have a secretion load? -are you likely to generate an expiratory flow bias? -are other interventions required to facilitate/augment the expiratory flow bias?
4	Follow each cycle with suctioning of ETT.	It may be beneficial to insert the suction catheter into the ETT either before or during

		exsufflation to optimise secretion clearance
5	Rest on ventilator between cycles OR provide tidal volume breaths via MI-E	To prevent hyperventilation through blowing off CO_2 and/or to minimise potential volutrauma
6	Repeat cycles until secretions are cleared	Regular re-Ax to determine treatment effectiveness
7	Monitor HR, BP and SpO2 throughout	

Post procedure

- Check ETT length and cuff pressure
- Re-auscultate
- Record post intervention observations as per protocol

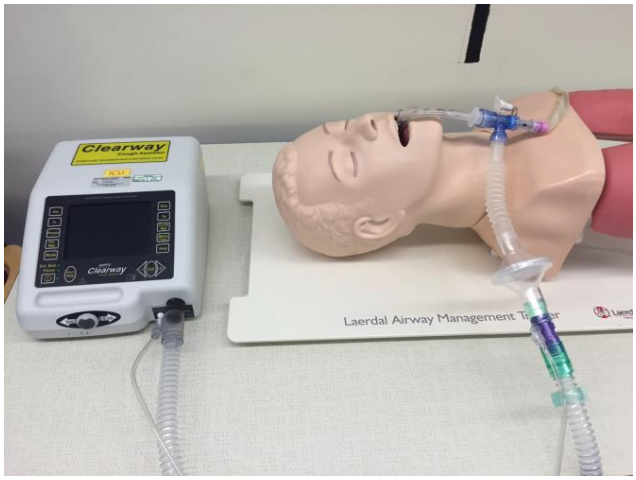


Figure 1: set up of MI-E device to ETT

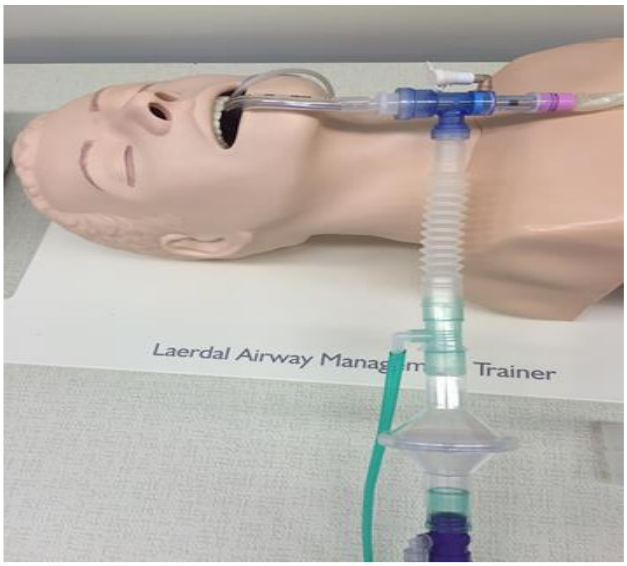


Figure 2: set up of MI-E to ETT to include entrained oxygen into the circuit

Appendix 2: APACHE II

Physiologic Variable	Points								
	+4	+3	+2	+1	0	+1	+2	+3	+4
1. Temperature (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
2. Mean arterial pressure (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
3. Heart rate (/min)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
4. Respiratory rate (/min)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
5. Oxygenation (mmHg) a. A-aDO_2 if FiO_2 ≥0.5 b. PaO_2 if FiO_2 <0.5	500	350-499	200-349		<200 >70	61-70		55-60	<55
6. Acid-base balance a. Arterial pH b. Serum HCO_3 (mEq/l) if no arterial blood gas	≥7.7 ≥52	7.6-7.69 41-51.9		7.5-7.59 32-40.9	7.33-7.49 22-31.9		7.25-7.32 18-21.9	7.15-7.24 15-17.9	<7.15 <15
7. Sodium (mEq/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
8. Potassium (mEq/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
9. Creatinine (mg/dl)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
10. Hematocirt (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<2.5
11. White blood count (×1000/mm^3)	≥40		20-39.9	15.19.9	3-14.9		1-2.9		<1
12. Glasgow Coma Score (GCS)	Score = 15 minus actual GCS								
A. Total Acute Physiology Score (sum of 12 above points)									
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6									
C. Chronic Health Points*									
Total APACHE II Score (add together the points from A+B+C)									

* Chronic Health Points: If the patient has a history of severe organ system insufficiency or is immune-compromised as defined below, assign points as follows:
5 points for non-operative or emergency post-operative patients
2 points for elective post-operative patinets

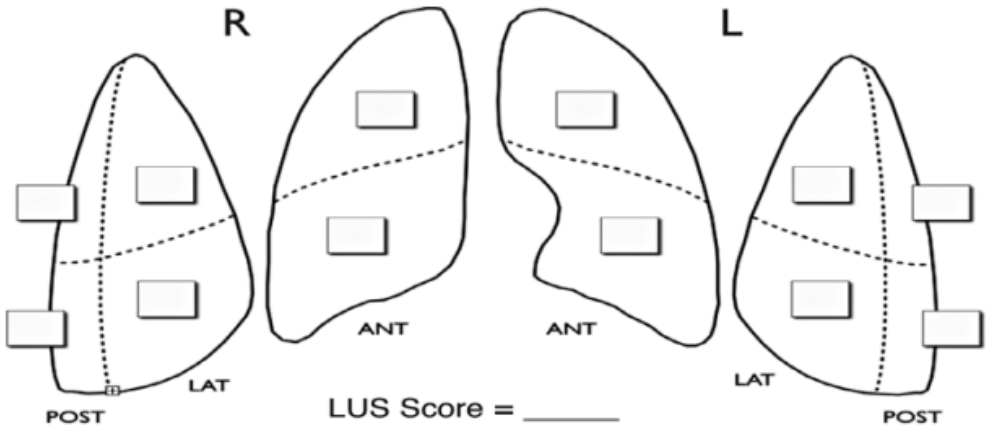
Appendix 3: Lung Ultrasound Score (Via et al., 2012)

LUNG ULTRASOUND

Report Form

PATIENT NAME: ..... GENDER: ☐ M ☐ F DATE OF BIRTH: .....
OPERATOR: ..... EXAM DATE: ..... HOUR ..... STORAGE CODE ....
HISTORY: ....
.....
SPONT VENTILATION: RR = ... Resp Distress: ☐ Yes ☐ No DECUBITUS: ☐ Sup ☐ Lat ☐ Pron ☐ Semirec
MECH VENTILATION: a) Modality: ☐ PCV ☐ DuoPAP ☐ ASV ☐ PSV ☐ SIMV ☐ NIV ☐ CPAP
b) Settings/Pattern: PEEP/Ps = ... /..... Ppeak ..... Pplat ..... RR ..... I:E ..... VT .....
EGA/EAB: pH ..... pCO2 ..... HCO3- ..... BE ..... PO2 ..... P/F ..... SpO2% ..... Hb .....

INDICATION: ☐ DIAGNOSTIC ☐ SCR.EENING ☐ MONITORING ☐ PROCEDURAL GUIDANCE
TYPE OF EXAM: ☐ simplified ☐ comprehensive ☐ focused (ANT / POST)



Legenda: **0** = A-Pattern (or nearly normal); **1** = B-Pattern (B-lines >3/field, well spaced); **2** = B-Pattern (crowded, coalescent +/- subpleural consolidations) **3** = Consolildation* **E**= Effusion*; **Pn** = Pneumothorax**; **NS**= Sliding Abolition; **LP**=Lung Pulse *(3 and E: characterize below in description) **(lindicate Lung Point(s))

DESCRIPTION .....
.....
.....

DIAGNOSIS .....

☐ Suspected ☐ Not made ☐ Second Opinion needed

Signature

Appendix 20 Feasibility interview guides

Feasibility interview guide-clinician interviews (physiotherapy)

- Introductions
- Consent process (read from consent form)
- Demographics: profession, banding, years of ICU experience

- How were you involved in the MERIT study? *Intervention coherence; self efficacy*

- What was your experience of study preparation/training? Is there anything else that would have been useful?

- Patients were allocated to either standard care or the MI-E intervention. How did that make you feel? (Prompt: any examples of when you were content/not content with the allocation?) *affective attitude; burden; ethicality; opportunity costs; perceived effectiveness*

- Thinking about the MI-E device specifically, what do you consider when setting up the device? Were there any challenges in setting up MI-E? How/when do you adjust settings? Did the protocol enable you to do these things? Were there times that you sought advice from colleagues? *Burden; intervention coherence; perceived effectiveness*

- Were you aware of any adverse events/complications occurring? How did this impact you? Would/did you change anything about the use of the device going forwards? *Affective attitude, burden, ethicality, intervention coherence, perceived effectiveness, self-efficacy*

- Has your view of MI-E changed during trial participation – if so how?

- Is there anything that we should have done differently? *Affective attitude, burden, ethicality, intervention coherence, perceived effectiveness, self-efficacy*

- Do you have any additional information that you would like to add?

- Do you have any questions?

END OF INTERVIEW

Feasibility interview guide-clinician interviews (nurse)

- Introductions
- Consent process (read from consent form)
- Demographics: profession, banding, years of ICU experience
- How were you involved in the MERIT study? *Intervention coherence; self efficacy*

- What was your experience of study preparation/training? Is there additional information that would have been useful?

- Any thoughts on the consent process – did you encounter any specific issues?

- Were you aware of any adverse events/complications occurring? How did this impact you? Would/did you change anything about the use of the device going forwards? *Affective attitude, burden, ethicality, intervention coherence, perceived effectiveness, self-efficacy*

- Is there anything that we should have done differently? *Affective attitude, burden, ethicality, intervention coherence, perceived effectiveness, self-efficacy*

- Do you have any additional information that you would like to add?

- Do you have any questions?

END OF INTERVIEW

Feasibility interview guide-clinician interviews (doctor)

- Introductions
- Consent process (read from consent form)
- Demographics: profession, banding, years of ICU experience
- How were you involved in the MERIT study? *Intervention coherence; self efficacy*

- What was your experience of study preparation/training? Is there additional information that would have been useful?
- For a number of participants we gained initial consent using a professional consultee i.e. yourself as the attending consultant. Do you have any thoughts on the consent process – did you encounter any specific issues?
- Were you aware of any adverse events/complications occurring? How did this impact you? Would/did you change anything about the use of the device going forwards? *Affective attitude, burden, ethicality, intervention coherence, perceived effectiveness, self-efficacy*
- Is there anything that we should have done differently? *Affective attitude, burden, ethicality, intervention coherence, perceived effectiveness, self-efficacy*

- Do you have any additional information that you would like to add?

- Do you have any questions?

END OF INTERVIEW

Feasibility interview guide-patient interviews

- Introduction
- Consent process (read from consent form)
- Demographics: age, sex, days in ICU, was this your first ICU stay?

- The consent process on ICU is complex! Initially a doctor provided consent for you to be involved in the study. In time we are able to approach relatives for consent and later, the actual patient. How do you feel about this process? What factors did you consider when deciding whether or not to give consent?

- Can you describe your physio experience on ICU?-any memories of coughing/airway clearance, memories of equipment used, how clinicians interacted with you?-did this help? Could anything have made the experience better for you? *Affective attitude, burden, intervention coherence*

- When we use this device (and other techniques) we measure how well we think it has worked and how well the patient has tolerated the treatment (for example we monitor oxygen levels, how hard you are breathing or how comfortable we think you are). What is important to measure from your perspective?

- Is there anything about the device or trial that you wish you had known before we used it? How best could we have re-layed this information to you?

- Do you have any additional information that you would like to add?

- Do you have any questions?

END OF INTERVIEW

Feasibility interview guide-relative interviews

- Introduction
- Consent process (read from consent form)
- Demographics: relationship to patient

- The consent process on ICU is complex! Initially a doctor provided consent for your relative to be involved in the study? In time we are able to approach relatives for consent and hopefully in time, the actual patient. How do you feel about this process and your potential role? What factors did you consider when deciding whether or not to give consent?
- Did you see a physiotherapy treatment session and specifically the device being used and can you describe this experience?
- When we use this device (and other techniques) we measure how well we think it has worked and how well the patient has tolerated the treatment (for example we monitor oxygen levels, how hard you are breathing or how comfortable we think you are). What is important to measure from your perspective?

- Do you have any additional information that you would like to add?
- Do you have any questions?

END OF INTERVIEW

Probing questions:

Can you tell me more….

Can you explain further….

What happened then…

How did that make you feel…

Appendix 21 Feasibility clinician interviews advert

The MERIT study: exploring experiences of study involvement

*Are you a **Physiotherapist, nurse or doctor** currently working in ICU at the BRI?*

Have you been involved in the MERIT study?

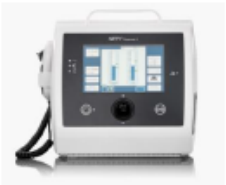
Would you be willing to talk to me about your experiences of trial involvement?

The MERIT study is examining the feasibility of using MI-E (cough assist device) to promote extubation success in adult ICU. An important part of this study is to speak to clinicians (nurses, doctors and physiotherapists) who have been involved in the study to understand their experiences and to explore device acceptability.

This research is part of my PhD to enable effective and optimal use of this device in the wider ICU population.

If you would be interested in participating in an online interview or would like to know more please contact [redacted]

Thank you, Ema



MERIT Study: IRAS ID 303674 v1 25.3.22

Appendix 22 Feasibility clinician interviews participant information sheet

Interviews to explore the experiences of those involved in a feasibility trial examining the use of Mechanical Insufflation-Exsufflation to enhance extubation success in adult intensive care.

Participant Information Sheet

You are invited to take part in a project taking place at the University of the West of England, Bristol (UWE). It is funded by the National Institute of Health Research (NIHR). Before you decide whether to take part, it is important for you to understand why the project is being done and what it will involve. Please read the following information carefully and if you have any queries or would like more information please contact Ema Swingwood.

Background to the project

The overall study is aiming to show if it is possible to carry out a large study to see whether using a cough device can help patients be successfully removed from breathing support whilst they are being treated in an Intensive Care Unit (ICU). This is important because having to have the breathing tube put back in leads to worse outcomes for the patient, including prolonging their length of hospital stay and increasing their risk of death. An important part of the feasibility study is collecting patient views about different aspects of the study.

Why have I been invited to take part?

In order for us to better understand how patients feel about using this device, we are inviting clinicians who took part in the ICU study to talk to us and share their thoughts.

Do I have to take part?

You do not have to take part in this project. It is up to you to decide whether or not you want to be involved. If you do decide to take part, you will be asked to provide recorded consent. You are able to withdraw from the project without giving a reason. This will be possible from the date you give verbal recorded consent up to the point that interviews are transcribed. If you want to withdraw from the project within this period, please contact Ema Swingwood or an ICU research nurse (contact details below).

What will happen to me if I take part and what do I have to do?

If you agree to take part you will be asked to take part in an interview by telephone or video call. This will be conducted by Professor Sarah Voss. The interview will take approximately 45-60 minutes and we will ask about your opinions and experience of the project. Your answers will be fully pseudonymised.

Your interview will take place via telephone or on an online platform called Microsoft Teams and will be recorded. The recording will be saved as an audio only file; the video recording will be permanently deleted. If you decide that you want to withdraw from the study we will use a unique identifier to find your data. The audio recording will be transcribed into a text document by a university approved transcription service and a data processing agreement will be in place. Following transcription, your voice recording will be deleted. Your data will be pseudonymised from this point and will be analysed with interview data from other participants. All pseudonymised interview transcripts will be stored on an encrypted UWE laptop on OneDrive.

If you are willing to be interviewed for the project, please contact Ema Swingwood (contact details below).

What are the benefits of taking part?

It is not known whether the device will help patients in the trial, but the trial will provide information which could enable patients to benefit in the future. The results will help us decide if it is possible to carry out a large study to see whether using a cough device in ICU can help patients be successfully removed from breathing support.

What are the possible risks of taking part?

We do not foresee or anticipate any significant risk to you in taking part in this project. If, however, you feel uncomfortable at any time you can ask for the interview to stop. If you need any support during or after the interview then the researchers will be able to put you in touch with suitable support agencies. The project team are experienced in conducting interviews, which have been designed by a team of people with expertise in the subject area.

What will happen to your information?

All the information that you give will be pseudonymised at the point of transcription. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all personal information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. All study related data will be kept securely by the study sponsor (UHBW)

for a period of 5 years after the end of the study. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason. If you decide that you want to withdraw from the study we will use the unique code number to find your data.

If you wish to find out further information please visit: https://www.hra.nhs.uk/information-about-patients/

Who is organising and funding the project?

The project lead is Ema Swingwood as part a National Institute of Health Research Clinical Doctoral Research Fellowship. The sponsor of the study is University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). Professor Fiona Cramp (Director of Studies), Dr Jeremy Bewley, Dr George Ntoumenopoulos Professor Louise Rose, Dr Lyvonne Tume, and Dr Sarah Voss, are co-Investigators. Further information on the co-investigators is available at:

Where will the results of the project be published?

A Report will be written containing our project findings. This Report will be available on the UWE Bristol open-access Research Repository. We also plan to publish results in a peer-reviewed journal.

A hard copy of a summary report will be made available to all project participants. You will be asked if you would like to see it at interview. Key findings will also be shared both within and outside UWE Bristol. Anonymous and non-identifying direct quotes may be used for publication and presentation purposes.

Who has ethically approved this project?

The project has been reviewed and approved by Leeds East Research Ethics Committee (IRAS 303674) and has HRA and HCRW approvals.

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

What if something goes wrong?

If you have any concerns or complaints about the conduct of this project, please contact Ema Swingwood (contact details below) or **The UHBW Patient Advice and Liaison Service** (PALS) via telephone 0117 342 1050, email psct@uhbw.nhs.uk or post UHBW PALS, Bristol Royal Infirmary, Marlborough Street, Bristol, BS1 3NU.

What if I have more questions or do not understand something?

If you would like any further information about the project please contact in the first instance:

[redacted]

Appendix 23 Feasibility interviews consent form

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

UWE Bristol University of the West of England

CONSENT FORM

Interviews to explore the experiences of those involved in a feasibility trial examining the use of Mechanical Insufflation-Exsufflation to enhance extubation success in adult intensive care.

(The MERIT Study)

Name of Researcher:

Participant Identification Number for this trial:

Please initial box

1. I confirm that I have read the information sheet dated 21.03.22 (version 2.0) or 25.03.22 (version 2.0) (delete as required) 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 my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that anonymised quotes may be used in the final Report of this project; ☐
4. I understand that the information held and maintained by University Hospitals Bristol NHS Foundation Trust may be used to help contact me or provide information about me in direct relation to the study. ☐
5. I understand that anonymised interview transcripts will be stored on University of the West of England OneDrive which will be accessible only to staff working on the study. ☐
6. I agree that the interview can be recorded. ☐
7. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person seeking consent	Date	Signature

Appendix 24 Feasibility interviews patient participant information sheet

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

UWE Bristol University of the West of England

Participant Information Sheet

Interviews to explore the experiences of those involved in a feasibility trial examining the use of Mechanical Insufflation-Exsufflation to enhance extubation success in adult intensive care.

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Background to the project

The overall study is aiming to show if it is possible to carry out a large study to see whether using a cough device can help patients be successfully removed from breathing support whilst they are being treated in an Intensive Care Unit (ICU). This is important because having to have the breathing tube put back in leads to worse outcomes for the patient, including prolonging their length of hospital stay and increasing their risk of death. An important part of the feasibility study is collecting patient views about different aspects of the study.

Why have I been invited to take part?

In order for us to better understand how patients feel about using this device, we are inviting patients who took part in the ICU study to talk to us and share their thoughts.

Do I have to take part?

You do not have to take part in this project. It is up to you to decide whether or not you want to be involved. If you do decide to take part, you will be asked to provide recorded consent. You are able to withdraw from the project without giving a reason. This will be possible from the date you give verbal recorded consent up to the point that interviews are transcribed. If you want to withdraw from the project within this period, please contact Ema Swingwood or an ICU research nurse (contact details below).

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NHS Foundation Trust

What will happen to me if I take part and what do I have to do?

If you agree to take part you will be asked to take part in an interview by telephone or video call. This will be conducted by Ema Swingwood. The interview will take approximately 45-60 minutes and we will ask about your opinions and experience of the project.

Your interview will take place via telephone or on an online platform called Microsoft Teams and will be recorded. The recording will be saved as an audio only file; the video recording will be permanently deleted. The audio recording will be transcribed into a text document by a university approved transcription service and a data processing agreement will be in place. Following transcription, your voice recording will be deleted. Your data will be pseudonymised from this point and will be analysed with interview data from other participants.

If you are willing to be interviewed for the project, please contact Ema Swingwood (contact details below).

What are the benefits of taking part?

It is not known whether the device will help patients in the trial, but the trial will provide information which could enable patients to benefit in the future. The results will help us decide if it is possible to carry out a large study to see whether using a cough device in ICU can help patients be successfully removed from breathing support.

What are the possible risks of taking part?

We do not foresee or anticipate any significant risk to you in taking part in this project. If, however, you feel uncomfortable at any time you can ask for the interview to stop. If you need any support during or after the interview then the researchers will be able to put you in touch with suitable support agencies. The project team are experienced in conducting interviews, which have been designed by a team of people with expertise in the subject area.

What will happen to your information?

We will need to use information from you for this research project. All the information that you give will be pseudonymised at the point of transcription. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Once we have finished the study, we will store the pseudonymised interview transcripts on UWE OneDrive so we can check the results. All study related data will be kept securely by

the study sponsor (UHBW) for a period of 5 years after the end of the study. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason. If you decide that you want to withdraw from the study we will use the unique code number to find your data.

If you wish to find out further information please visit: https://www.hra.nhs.uk/information-about-patients/

Who is organising and funding the project?

The project lead is Ema Swingwood as part a National Institute of Health Research Clinical Doctoral Research Fellowship. The sponsor of the study is University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). Professor Fiona Cramp (Director of Studies), Dr Jeremy Bewley, Dr George Ntoumenopoulos Professor Louise Rose, Dr Lyvonne Tume, and Dr Sarah Voss, are co-Investigators. Further information on the co-investigators is available at:

[redacted]

Where will the results of the project be published?

A Report will be written containing our project findings. This Report will be available on the UWE Bristol open-access Research Repository. We also plan to publish results in a peer-reviewed journal.

A hard copy of a summary report will be made available to all project participants. You will be asked if you would like to see it at interview. Key findings will also be shared both within and outside UWE Bristol. Anonymous and non-identifying direct quotes may be used for publication and presentation purposes.

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NHS Foundation Trust

Who has ethically approved this project?

The project has been reviewed and approved by Leeds East Research Ethics Committee (IRAS 303674) and has HRA and HCRW approvals.

What if something goes wrong?

If you have any concerns or complaints about the conduct of this project, please contact Ema Swingwood (contact details below) or **The UHBW Patient Advice and Liaison Service** (PALS) via telephone 0117 342 1050, email psct@uhbw.nhs.uk or post UHBW PALS, Bristol Royal Infirmary, Marlborough Street, Bristol, BS1 3NU.

What if I have more questions or do not understand something?

[redacted]

Appendix 25 Clinical validation plan

MERIT C050 Clinical Validation Plan

Version 1.1

23 May 2022

Scope

REDCap Project MERIT C050 Clinical (DEV) on BTC Test server:
https://btc-test.bristol.ac.uk/redcap/redcap_v12.0.24/index.php?pid=63

As it is expected that the Eligibility Screening will be completed on an iPad, we suggest using an iPad to run Section 1 of this Validation Plan.

Before starting, check there is no data in the project and you are assigned to the User role 'Core Study Team'. If any of the tests fail, please STOP TESTING IMMEDIATELY and report this to the Development team.

Scenarios

Section 1 – Participant Identification & Eligibility Assessment

1.1 Public survey link works including reCAPTCHA.

1.2 Form displays in expected format – all wording is correct, buttons work on iPad, extra info pop ups display suitably.

1.3 Test eligibility calculation.

1.4 When two screenings are completed in parallel, a unique Study ID is created for each. Eligible and NOT eligible messages display correctly.

1.5 Records correctly created in REDCap.

1.6 Eligible Patients Dashboard shows records where 'Eligibility Result' was 'Eligible'.

1.7 Patient NOT Eligible warning shows on the listed forms if the Eligibility result is NOT Eligible.

Section 2 – Consent

2.1 Form works as expected, ie correct wording, when different options are selected, correct questions displayed.

2.2 Consent not recorded warning shows on the listed forms if the Consent to participate field is blank in the first consent instance.

2.3 Can record a second consent for the same participant.

2.4 Patient did not give consent warning shows on the listed forms if the Consent to participate field is No in the last consent instance.

Section 3 – Randomisation

3.1 Can record date and allocation. EIT question shown if 'Intervention'. If EIT selected, prompt to complete EIT.

Section 4 – Admin forms

4.1 Demographics form displays correct questions and works as expected, ie branching logic correctly shows sub questions.

4.2 Resource use 24hr form displays correctly. Form can be completed more than once for same participant.

4.3 EIT form can be completed if it applies – a warning is shown if 'Included in EIT sub-study' is NOT Yes.

Section 5 – Trial Assessments

Correct questions displayed for each timepoint and randomisation arm:

	Timepoint	***Randomisation arm***
5.1	Baseline obs	Control
5.2	Intervention end obs	Control
5.3	5 mins post intervention obs	Control
5.4	Baseline obs	Intervention
5.5	Intervention end obs	Intervention
5.6	5 mins post intervention obs	Intervention

5.7 Trial Assessments form can be completed a second time for the same participant.

Section 6 – End of Study

6.1 End of Study form displays correctly.

Section 7 – 165 Day Follow Up

7.1 Missing details for Quests report works as expected

7.2 Postal Quests to be sent report works as expected

7.3 Automated survey invitation sent 165 days from date of ICU discharge if online method selected

Section 8 – Withdrawal

8.1 Withdrawal form displays correctly.

8.2 Automated survey invitation is NOT sent if participant has been marked as withdrawn from quest

8.3 ‘Postal Quests to be sent’ report does NOT include a participant marked as withdrawn from quest

Section 9 User Roles

9.1 Study Team user role has restricted access to certain forms

Section 1 – Participant Identification & Eligibility Assessment Tests

Instruction	Open the public survey link: https://btc-test.bristol.ac.uk/redcap/surveys/?s=J8XD77TKELMHFDTD You should see ‘MERIT Study Screening’ with a message ‘To proceed to the survey, please check off the box and click the button below.’ Tick the box and click on ‘Begin survey’
Test 1.1	Does the public survey link take you to the start page and show a box for reCAPTCHA? When you click on ‘Begin survey’, does it take you to the next page?
Test result 1.1	Yes
Instruction	Select 'Submit' to confirm you want to assess if a patient is eligible for the MERIT Study. You should see a page headed ‘MERIT Eligibility Screening’. Name of person entering form: [Elaine Ellington] Answer all 11 questions as ‘No’. Hover over the ‘i’ which is shown on 2 questions (Contraindications to MI-E use and Neuromuscular condition’. Check that further information pops up, is readable and correctly worded.
Test 1.2	Does the form display in the expected format eg logos are desired size, wording is correct including punctuation, extra information pop ups marked ‘i’ display suitably, buttons can be selected easily on an iPad?
Test result 1.2	Yes
Instruction	Check that when you have marked all 11 eligibility questions as ‘Yes’, the ‘Eligibility calculation’ field (which is flagged to be hidden on live) shows ‘22’. Go through each question in turn, changing the answer to No then back to Yes, checking that the calculation changes to 21 each time.
Test 1.3	Does the Eligibility calculation work correctly?
Test result 1.3	Yes
Instruction	Make sure all 11 answers entered by ‘Elaine Ellington’ are ‘No’. Leave this page open ensuring you DO NOT press ‘Submit’. Open a new browser and paste in the public survey link https://btc-test.bristol.ac.uk/redcap/surveys/?s=J8XD77TKELMHFDTD Start a second eligibility screening, entering ‘Name of person entering form’ as ‘Norman Nott’. Answer the first 10 eligibility questions as ‘No’, then answer ‘Pre-existing permanent trachy’ as ‘Yes’. Select ‘Submit’. You should see a page headed ‘Eligibility result’. The field which is to be hidden should show ‘NOT Eligible’ and there should be a red box starting ‘The patient is not eligible.’

<table>
<tr><td></td><td>You should see MERIT Study ID: BRI002 mentioned in both a blue box and in the field which has a check box next to it. Tick the box to confirm you've noted the Study ID and press 'Submit'.

Return to the first screening you started (Elaine Ellington). Check that all 11 eligibility questions are selected as 'No', then press 'Submit'.

You should see a page headed 'Eligibility result'. The field which is to be hidden should show 'Eligible' and there should be a green box starting 'The patient is not eligible.'

You should see MERIT Study ID: BRI001 mentioned in both a blue box and in the field which has a check box next to it. Tick the box to confirm you've noted the Study ID and press 'Submit'.</td></tr>
<tr><td>Test 1.4</td><td>When two screenings were completed in parallel, was a unique Study ID created for each? Did the Eligible and NOT eligible messages display correctly?</td></tr>
<tr><td>Test result 1.4</td><td>Yes</td></tr>
<tr><td>Instruction</td><td>https://btc-test.bristol.ac.uk/redcap/redcap_v12.0.24/DataEntry/record_status_dashboard.php?pid=63
Log into REDCap and go to the Project MERIT C050 Clinical. Look at the Record Status Dashboard. Check that 2 records have been created with the correct Study IDs and information you entered.</td></tr>
<tr><td>Test 1.5</td><td>Were records correctly created in REDCap?</td></tr>
<tr><td>Test result 1.5</td><td>Yes</td></tr>
<tr><td>Instruction</td><td>Open the public survey link: https://btc-test.bristol.ac.uk/redcap/surveys/?s=J8XD77TKELMHFDTD
Name of person entering form: [Ian Inglebury]
Answer the first 3 questions as 'No'.
Submit the form. You will see a pop up saying 'NOTE: Some fields are required!'. Press Okay, then close the screening form without entering anything further.

Screen 4 more Eligible patients by opening the public survey link and using these details:
<table>
<tr><td>Name of person entering form</td><td>Screening Questions</td><td>Expected Stu</td></tr>
<tr><td>Caroline Contralto</td><td>Answer all 11 as 'No'</td><td>BRI004</td></tr>
<tr><td>Abbey Alders</td><td>Answer all 11 as 'No'</td><td>BRI005</td></tr>
<tr><td>William Drew</td><td>Answer all 11 as 'No'</td><td>BRI006</td></tr>
</table>
Return to REDCap Project MERIT C050 Clinical. Change the 'Dashboard displayed' to 'Eligible Patients'.
Check you can see BRI001, BRI004, BRI005 and BRI006.
Check that BRI002 and BRI003 do NOT appear.</td></tr>
<tr><td>Test 1.6</td><td>Does the 'Eligible Patients' Dashboard display the correct records?</td></tr>
<tr><td>Test result 1.6</td><td>Yes</td></tr>
<tr><td>Instruction</td><td>Change the Dashboard back to the Default. Click on Record ID 2 for Study ID BRI002, which takes you to this Participant's Record Home Page.</td></tr>
</table>

	Starting with 'Consent', click on the grey dot for this form. You should see a red warning 'This patient was NOT eligible when screened. DO NOT enter any data.' Select 'Cancel' to close the form without making changes and return to the Record Home Page. Repeat these steps to check the warning is also displayed on the following forms: Randomisation Demographics Resource use 24hr EIT Withdrawal Trial Assessments – in the column 'Baseline obs' Trial Assessments – in the column 'Intervention end obs' Trial Assessments – in the column '5 mins post intervention obs' End of study EQ-5D-5L
Test 1.7	Does the Patient NOT Eligible warning show on the listed forms if the Eligibility result is NOT Eligible?
Test result 1.7	yes

Section 2 – Consent Tests

Instruction	MERIT C050 Clinical, click on form named 'Consent' for Study ID BRI001. Work through the form, trying out all the different combinations, without saving. Check that the questions, wording and branching logic work as you would like. Reset the form and select this option before saving: Participant has capacity to consent: Yes 'Save & Exit Form'
Test 2.1	Are you happy with the Consent form as it is currently presented?
Test result 2.1	Yes
Instruction	Click on form named 'Randomisation' for Study ID BRI001. You should see a red warning 'Consent has not been recorded for this patient. Do NOT enter any data until you have completed the form named Consent.' Select 'Cancel' to close the form without making changes. Check that the warning is also shown on the following forms for BRI001: Demographics Resource use 24hr EIT Withdrawal Trial Assessments – in the column 'Baseline obs' Trial Assessments – in the column 'Intervention end obs' Trial Assessments – in the column '5 mins post intervention obs' End of study EQ-5D-5L
Test 2.2	Does the Consent not recorded warning show on the listed forms if the Consent to participate field on the first consent instance is blank?
Test result 2.2	yes

Instruction	From the Record Status Dashboard, click on the + to record a second consent for BRI001: Participant has the capacity to consent: Yes Consent to participate in MERIT Study: No Reason for no consent/participation: No reason given Mark the form as Complete, Save & Exit form.
Test 2.3	Were you able to record a second consent for the same participant?
Test result 2.3	yes
Instruction	Click on form named 'Randomisation' for Study ID BRI001. You should see a red warning 'This patient DID NOT GIVE CONSENT. Do NOT enter any data.' Select 'Cancel' to close the form without making changes. Check that the warning is also shown on the following forms for BRI001: Demographics Resource use 24hr EIT Withdrawal Trial Assessments – in the column 'Baseline obs' Trial Assessments – in the column 'Intervention end obs' Trial Assessments – in the column '5 mins post intervention obs' End of study EQ-5D-5L
Test 2.4	Does the Consent not recorded warning show on the listed forms if the Consent to participate field is No in the last consent instance?
Test result 2.4	yes
Instruction	Complete the Consent form for Participants BRI004, BRI005 and BRI006 as follows: Participant has the capacity to consent: Yes Consent to participate in MERIT Study: Yes Clinician name taking consent: Dr Mary Myrtle Date of consent: [Today] Mark the form as Complete, Save & Exit form.

Section 3 – Randomisation Tests

Instruction	MERIT C050 Clinical, click on 'Randomisation' for Study ID BRI004, Caroline Contralto. Work through the form, trying out all the different combinations. Check that the questions, wording and branching logic work as you would like. Before you save the form, change the answers to these: Date of randomisation [Today] Treatment arm [Control] Mark form as Complete, Save & Exit. For Study ID BRI005, Abbey Alder, complete Randomisation as follows: Date of randomisation [Today] Treatment arm [Intervention] Included in EIT sub-study? [Leave blank] Mark form as Complete, Save & Exit.

	For Study ID BRI006, William Drew, complete Randomisation as follows: Date of randomisation [Yesterday] Treatment arm [Intervention] Included in EIT sub-study? [No] Mark form as Complete, Save & Exit.
Test 3.1	Are you happy with the Randomisation form as it is currently presented?
Test result 3.2	yes

Section 4 – Admin forms Tests

Instruction	MERIT C050 Clinical, click on form named 'Demographics' for Study ID BRI004. Work through the form, trying out all the different combinations. Check that the questions, wording and branching logic work as you would like.
Test 4.1	Are you happy with the Demographics form as it is currently presented?
Test result 4.1	yes
Instruction	MERIT C050 Clinical, click on form named 'Resource use 24hr' for Study ID BRI004. Work through the form, trying out all the different combinations. Check that the questions, wording and branching logic work as you would like. Save a Resource use 24hr form for participant BRI004. Return to the Record Status Dashboard. Click on the + to record a second Resource use 24hr form for BRI004. Save the second instance.
Test 4.2	Are you happy with the Resource use 24hr form as it is currently presented? Were you able to record a second form for the same participant?
Test result 4.2	yes
Instruction	MERIT C050 Clinical, click on form named 'EIT' for Study ID BRI004. You should see a red message explaining that the questions are not shown because the EIT question in the Randomisation forms is not Yes. Check that this message is also displayed for BRI005. For Participant BRI005, go to the Randomisation form and change 'Included in EIT sub-study' to 'Yes'. This should bring up a blue message 'Please complete the EIT form'. Return to EIT and check the warning has disappeared and the EIT questions are displayed. Do NOT complete the form. To check the full range of warnings, return to the Randomisation form for BRI005 and change 'Included in EIT sub-study?' to No. Check that the EIT form shows the warning again. Finally, return to Randomisation for BRI005, change 'Included in EIT sub-study?' to Yes. Return to EIT and complete the form, checking it contains the questions you would like. Save one instance of the form, then return and complete a second.
Test 4.3	Are you happy with the EIT form as it is presented? Did the warning work as expected? Were you able to complete a second form?
Test result 4.3	yes

Section 5 – Trial Assessments Tests

Instruction	From Record Status Dashboard, for Participant BRI004 click 'Trial Assessments' in the column headed '**Baseline obs**'. Work through the form, trying out all the different combinations. Check that the questions, wording and branching logic are as you would like.
Test 5.1	Are you happy with the Trial Assessments form at Baseline obs for Control arm as it is currently presented?
Test result 5.1	MI-E set up and O2 entrainment does not need to be listed for the control arm. This is now fixed
Instruction	For Participant BRI004, open 'Trial Assessments' in the column headed '**Intervention end obs**'. Work through the form, trying out all the different combinations. Check that the questions, wording and branching logic are as you would like.
Test 5.2	Are you happy with the Trial Assessments form at Intervention end obs for Control arm as it is currently presented?
Test result 5.2	Treatment techniques used- need to be able to select multiple options so this may be better as a tick box rather than dropdown please. This is now fixed
Instruction	For Participant BRI004, open 'Trial Assessments' in the column headed '**5 mins post intervention obs**'. Work through the form, trying out all the different combinations. Check that the questions, wording and branching logic are as you would like.
Test 5.3	Are you happy with the Trial Assessments form at 5 mins post intervention obs for Control arm as it is currently presented?
Test result 5.3	yes
Instruction	From Record Status Dashboard, for Participant BRI005 click 'Trial Assessments' in the column headed '**Baseline obs**'. Work through the form, trying out all the different combinations. Check that the questions, wording and branching logic are as you would like.
Test 5.4	Are you happy with the Trial Assessments form at baseline obs for Intervention arm as it is currently presented?
Test result 5.4	MI-E device set up: no of cycles/no of sets needs to be removed. This is now fixed
Instruction	For Participant BRI005, open 'Trial Assessments' in the column headed '**Intervention end obs**'. Work through the form, trying out all the different combinations. Check that the questions, wording and branching logic are as you would like.
Test 5.5	Are you happy with the Trial Assessments form at Intervention end obs for Intervention arm as it is currently presented?
Test result 5.5	MI-E device set up: no of cycles/no of sets needs to be added. Treatment techniques used- need to be able to select multiple options so this may be better as a tick box rather than dropdown please. This is now fixed
Instruction	For Participant BRI005, open 'Trial Assessments' in the column headed '**5 mins post intervention obs**'. Work through the form, trying out all the different combinations. Check that the questions, wording and branching logic are as you would like. Ensure that you save the form.
Test 5.6	Are you happy with the Trial Assessments form at 5 mins post intervention obs for Intervention arm as it is currently presented?
Test result 5.6	Yes
Instruction	For Participant BRI005, complete a second 'Trial Assessments' in the column headed '**5 mins post intervention obs**'. Save the second instance.

Test 5.7	Were you able to complete the Trial Assessments form a second time for the same participant?
Test result 5.7	yes

Section 6 – End of Study Tests

Instruction	For Participant BRI004 select 'End of study'. Check that the questions, wording and branching logic are as you would like.
Test 6.1	Are you happy with the End of study form as it is currently presented?
Test result 6.1	yes
Instruction	Complete the End of study form for 3 participants as follows:

	BRI004	**BRI005**	**BRI006**
Date of ICU discharge	[164 days ago]	[153 days ago]	[164 days ago]
ICU re-admission	Yes	No	No
Date of ICU re-admission	[7 days ago]	[Field not shown]	[Field not shown]
Date of hospital discharge	[Today]	[2 weeks ago]	[leave blank]
Form Status	Complete	Incomplete	Incomplete

Section 7 – 165 Day Follow Up Tests

Instruction	Under 'Reports' on the left hand side of the page, select 'Missing details for Quests'. Do you see Participants BRI004, BRI005 and BRI006? Update the End of study form for 3 participants to add the following:

	BRI004	**BRI005**	**BRI006**
Questionnaire method	Online	Paper	Online
Email address for online surveys	[Your email address]	[Your email address]	[Your email address]

Mark the forms as Complete, Save & Exit

Return to the 'Missing details for Quests' report and check that no results appear.

Test 7.1	Does the 'Missing details for Quests' report work as expected?
Test result 7.1	yes
Instruction	Under 'Reports', select 'Postal Quests to be sent'. Check that no results appear. Go to 'End of study' for BRI005 and make the 'Date of ICU discharge' one day earlier, ie 154 days ago from today. This Study ID should now appear in the 'Post Quest to be sent' report.
Test 7.2	Does the 'Postal Quests to be sent report' work as expected?
Test result 7.2	BRI005 is listed as a postal/paper questionnaire
Instruction	Go to 'End of study' for BRI004 and make the 'Date of ICU discharge' one day earlier, ie 165 days ago from today. This should trigger the automated survey invitation and you should receive an email.

	Complete the survey.
Test 7.3	Was an automated survey invitation sent?
Test result 7.3	Yes but went into junk-not ideal but I presume nothing can change this? Aware this can not be changed-I have made a note to highlight this to participants

Section 8 – Withdrawal Tests

Instruction	For Participant BRI006, open the Withdrawal form. Check that the questions, wording and branching logic are as you would like. Do not save anything.
Test 8.1	Are you happy with the Withdrawal as it is currently presented?
Test result 8.1	yes
Instruction	Complete the withdrawal form for BRI006 as follows: Withdraw from EQ-5D-5L?: Yes Mark the form as Complete, Save & Exit. Go to 'End of study' for BRI006 and make the 'Date of ICU discharge' one day earlier, ie 165 days ago from today. This would trigger the automated survey invitation if the participant was not marked 'Withdraw from EQ-5D-5L'. An automated survey invitation should NOT be received for this participant. You can check nothing has been scheduled by selecting 'Survey Distribution Tools' from the left hand menu and then looking at the tab 'survey Invitation log' and selecting 'View past invitations'.
Test 8.2	Test passes if you did NOT receive an email for this participant. If you received an invite the test has failed.
Test result 8.2	Passed
Instruction	For Participant BRI005, open the Withdrawal form. Mark 'Withdraw from EQ-5D-5L' as Yes. Leave the form Incomplete, Save & Exit. Select the 'Postal Quests to be sent' report. You should no longer see BRI005 in this report.
Test 8.3	Test passes if 'Postal Quests to be sent' report does NOT include a participant marked as withdrawn from quest.
Test result 8.3	Yes-passed

Section 9 User Roles Tests

Instruction	Log out of REDCap. Contact the development team and ask them to change your User Role from Core Study Team to 'Study Team'. Log back into REDCap and take a look at the forms you can see/edit.
Test 9.1	Are you happy with the Study Team User Role as it is currently specified?
Test result 9.1	Yes