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[Intervention Protocol]

Cough augmentation techniques for people with chronic neuromuscular disorders

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of cough augmentation techniques in adults and children with chronic NMD and respiratory muscle weakness.

BACKGROUND

Description of the condition

There are a range of chronic neuromuscular disorders (NMDs) in adults and children, including muscular dystrophies, congenital and metabolic myopathies, neuromuscular junction disorders, peripheral neuropathies, and anterior horn cell diseases (Gozal 2000). People affected by chronic NMDs are at risk of progressive respiratory insufficiency (breathing difficulties that worsen over time), primarily from a combination of respiratory muscle weakness and chest wall abnormalities (Boitano 2006; Finder 2010; Gozal 2000; Panitch 2009).

Infants with NMD generally have normal lungs and normal mucociliary clearance mechanisms at birth, although pulmonary mechanics may be affected from baseline, depending on the underlying NMD. Progressive respiratory insufficiency occurs with advancing age. Chest deformities may develop from infancy because of respiratory muscle weakness and chronic paradoxical breathing patterns, in conjunction with an initially very compliant chest wall (Panitch 2009; Papastamelos 1996). Respiratory muscle weakness causes chronic shallow breathing; the inability to sigh or yawn, which is required to maintain full lung expansion; an ineffective cough with secretion retention; and progressive loss of lung com-

pliance (Fauroux 2008; Panitch 2009). Progressive thoracic deformities such as scoliosis, kyphosis and spinal rigidity, together with fibrosis of the intercostal muscles, further impact on lung function with a progressive decrease in chest wall compliance and ultimately a restrictive pattern of lung disease (Fauroux 2008; Gozal 2000; Panitch 2009). Bulbar weakness and glottic dysfunction, as seen in people with spinal muscular atrophy Type 1 and amyotrophic lateral sclerosis/motor neuron disease (ALS/MND), also impact on the ability to cough effectively (Boitano 2006; Chatwin 2018; Toussaint 2018).

An effective cough is essential to clear pulmonary secretions. If the cough is ineffective, as is the case in people with NMD and respiratory weakness, long-term retention of secretions leads to a vicious cycle of obstruction, infection, inflammation, increased work of breathing, recurrent acute respiratory tract infections, and ultimately chronic lung disease and respiratory failure (Chatwin 2018; Homnick 2007). Respiratory tract infection with altered sputum viscosity and volume, difficulty swallowing (dysphagia), and gastro-oesophageal reflux can all exacerbate secretion retention in people with NMD and respiratory muscle weakness (Finder 2010; Iannaccone 2007).

An effective cough requires: a sufficiently deep inspiration; closure of the glottis with simultaneous contraction of expiratory respiratory muscles to increase intrathoracic pressure; then abrupt opening of the glottis at the start of the expiratory phase to produce a rapid, forceful flow of air from the lungs (Boitano 2006; Chatwin 2018; Toussaint 2018). Any or all of these components may be affected in a person with NMD (Bach 2003; Boitano 2006; Finder 2010; Rokadia 2015).

Bach 1996 suggested that adults require a peak expiratory cough flow (PCF) of 160 L/min for an effective cough. Adults have a normal PCF of 360 L/min to 840 L/min (Leiner 1963; Tzeng 2000). Furthermore, it has been suggested that adults with NMD require a PCF of more than 270 L/min when well, to account for the expected decline in cough flows during intercurrent respiratory infections (Bach 1997). Normal PCF values in children have been published (Bianchi 2008). In children with NMD, an absolute PCF of less than 160 L/min has been shown to be predictive of severe disease, but age or size-adjusted reference values are not available (Dohna-Schwake 2006), and it must be noted that the normal range of PCF in young children is highly variable, with healthy children only able to achieve PCFs of 160L/min on the 5th percentile by six years of age (Bianchi 2008). Therefore, for children over the age of 12 years (when children attain adult PCF (Bianchi 2008)), use of adult values for absolute PCF cut-offs may be appropriate (Hull 2012). Further research to determine age-adjusted PCF is warranted.

Most episodes of respiratory failure in people with NMD are likely to be caused by ineffective coughing during intercurrent chest infections (Bach 2003; Chatwin 2018). The identification of the most effective, safe measures to optimise cough efficacy and promote secretion clearance is therefore vital to optimising pulmonary function, preventing morbidity and improving the quality of life in people with chronic NMD (Toussaint 2018).

Description of the intervention

Many airway clearance techniques are used in clinical practice in people with NMD. Some techniques aim to move secretions from the peripheral to the more central airways (secretion mobilisation techniques), whilst others aim to clear secretions from the central airways (cough augmentation techniques) (Chatwin 2018; Toussaint 2018). Secretion mobilisation and an effective cough are both needed for effective secretion clearance (Finder 2010).

Manual techniques to assist peripheral secretion mobilisation in adults and children with chronic NMD include positioning, chest wall shaking, percussion and vibrations (Chatwin 2018; Toussaint 2018). Other secretion mobilisation techniques that have been suggested for use in people with NMD include breathing exercises (e.g. active cycle of breathing technique, forced expiratory technique, autogenic drainage, positive pressure therapy, oscillatory positive pressure therapy); intermittent positive pressure breathing; chest wall strapping; intrapulmonary percussive ventilation; and high-frequency chest wall oscillation (Anderson 2005; Bott 2009; Chatwin 2018; Douglas 1981; Finder 2010; Hull 2012; Toussaint 2018). Active breathing exercises are effort dependent and therefore may not be useful in people with severe respiratory muscle weakness (Finder 2010; Hull 2012), unless concomitant ventilatory support is given (Chatwin 2018; Toussaint 2018).

Cough augmentation for proximal secretion clearance can be performed using manual or mechanical methods, alone or in combination, to support different components of the cough (Chatwin 2018; Finder 2010; Toussaint 2018). Techniques such as breath or air stacking, glossopharyngeal breathing and mechanical or manual (bagging) single-breath insufflations, augment inspiration in order to achieve sufficient inspiratory lung volumes before a cough (Bott 2009; Chatwin 2018; Toussaint 2018). People can achieve lung insufflation using positive pressure devices including ventilators (invasively or noninvasively) and intermittent positive pressure breathing (IPPB) devices, with set pressure or volume limits, or both. They may achieve breath or air stacking independently (with glottic closure) or through use of an external self-inflating manual resuscitator bag with a one-way valve, if needed, to prevent air leak (Chatwin 2018; Toussaint 2018). For breath stacking, a person takes or receives multiple inspiratory breaths, without exhalation between breaths, until they achieve maximal insufflation capacity (MIC) (Bach 2007; Chatwin 2018; Marques 2014; Toussaint 2018). Thereafter, the individual releases the breath in a spontaneous or assisted forced expiratory manoeuvre or cough (Chatwin 2018; Marques 2014). MIC refers to the maximum tolerable inspiratory lung volume (Bach 2007; Chatwin 2018; Kang 2000). Glossopharyngeal breathing or 'frog breathing', which does not use any external equipment, requires the person with NMD to actively 'gulp' air into the lungs until MIC is reached, using glottic

closing and opening (Bach 2007; Chatwin 2018; Nygren-Bonnier 2009; Toussaint 2018).

Mechanical exsufflation and manually assisted cough (MAC), in which the thorax or abdomen or both are manually compressed, aim to improve expiratory flow rates by rapidly increasing intra-abdominal or intrathoracic pressure, or both (Anderson 2005; Chatwin 2018; Finder 2010; Toussaint 2018).

Mechanical insufflation-exsufflation (MI-E) supports both insufflation and exsufflation, using a device which delivers a preset positive pressure into the airways for a set duration during inspiration (insufflation), immediately followed by an abrupt change to a preset negative exsufflation pressure, thereby simulating a cough with high expiratory flow rates (Anderson 2005; Chatwin 2018; Fauroux 2008; Morrow 2013; Toussaint 2018).

How the intervention might work

Both inspiratory and expiratory cough augmentation techniques aim to optimise cough efficacy by improving PCF when respiratory muscles are too weak to independently achieve sufficient flow rates for secretion clearance. The mechanism by which PCF is affected differs amongst different cough augmentation techniques (Chatwin 2018; Toussaint 2018).

Inspiratory cough augmentation techniques aim to augment inspiratory lung volumes to those required for an effective cough (maximal insufflation capacity). By increasing inspiratory volume, these techniques enhance expiratory flow bias during a spontaneous or assisted cough, thereby effectively mobilising secretions (Chatwin 2018). Inhaling a large volume of air before the compressive and expiratory phases of the cough optimises the length-tension relationship of expiratory muscles and generates higher intrathoracic pressures and PCF (Boitano 2006; Chatwin 2018).

Expiratory cough augmentation techniques, whether manual or mechanical, aim to assist the weak expiratory muscles in generating sufficient intra-abdominal and intrathoracic pressures or increase the expiratory flow generated during the cough, or both. The overall aim is to increase PCF enough to effectively clear secretions from the central airways (Boitano 2006; Chatwin 2018; Toussaint 2018).

Some investigators have suggested that combining inspiratory and expiratory cough augmentation techniques could optimise cough clearance in people with NMD (Boitano 2006; Chatwin 2018; Hull 2012; Sivasothy 2001; Trebbia 2005; Toussaint 2018).

Why it is important to do this review

Cough augmentation techniques are essential to prevent progression to respiratory failure in people with NMD (Bach 2003; Chatwin 2018); however, it is still unclear what technique/s offer the most clinical benefit with the least risk of harm.

Any application of positive pressure to the lungs carries a risk of complications including abdominal distention, discomfort, gastro-oesophageal reflux, cardiovascular effects such as changes in blood pressure and cardiac arrhythmia, and pneumothorax (Chatwin 2018; Homnick 2007; Morrow 2013; Toussaint 2018). Pneumothorax has been described in adults following the use of MI-E (Suri 2008) and long-term non-invasive positive pressure ventilation (Vianello 2004). There may be greater risk of barotrauma and volutrauma in infants and young children with NMD compared to older children or adults, considering their different respiratory anatomy and physiology. Application of positive pressure will affect the lungs differently according to, for example, type of lung disease, lung volumes, and respiratory system compliance and resistance, all of which vary with age and NMD condition (Gattinoni 2003; Gattinoni 2010). The effects of MAC may be altered by chest wall compliance, which is almost twice that of controls in infants with NMD (Papastamelos 1996), and may be substantially reduced in adults with NMD (Gozal 2000; Panitch 2009). During MI-E specifically, applied insufflation volume is not usually measured in clinical practice, and a rapid swing to negative pressure follows insufflation. The combination of high applied tidal volume together with atelectrauma associated with repeated expansion and collapse of lung units has been associated with lung injury in the context of invasive mechanical ventilation (Albuali 2007; Saharan 2010). The safety of MI-E is not clear in this regard.

Some cough augmentation techniques recommended in international guidelines for the treatment of people with NMD require equipment or expertise that are not readily available in lower-resourced environments (Bott 2009; Chatwin 2018; Finder 2004; McCool 2006; Rosière 2009; Toussaint 2018; Wang 2007; Wang 2010), whilst cheaper and more readily available techniques may be equally effective (Anderson 2005; Finder 2010). Currently, people living with NMD and their caregivers generally manage their airway clearance according to perceived need, and clinical management is responsive to changes in the patient's condition (Toussaint 2018). The management approach also depends on availability of equipment and local expertise, which may vary substantially at a global level (Toussaint 2018). It is not yet clear what people with NMD and their caregivers value when considering the choice of cough augmentation technique, and this warrants further investigation.

In order to advocate for the best and most appropriate treatment of people with chronic NMD in different sociogeographical contexts, it is necessary to first determine which cough augmentation technique/s, dosages and frequencies are effective and safe for use in people with chronic NMD, using clinically relevant outcome measures.

OBJECTIVES

To assess the efficacy and safety of cough augmentation techniques in adults and children with chronic NMD and respiratory muscle weakness.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), quasi-RCTs and randomised cross-over trials. Quasi-randomised trials are those in which participants are allocated using methods that are partly systematic, such as by case record number, date of birth, or alternation. We will include studies reported as full text and those published as abstract only. There will be no language restrictions.

Types of participants

We will include adults, adolescents and children with a diagnosis of any chronic NMD with respiratory muscle weakness.

Owing to age-related changes in respiratory anatomy and physiology, we plan to stratify participants according to age. For the purposes of this review, 'infants' will refer to children under the age of one year; 'children' from one to 13 years of age; and 'adolescents/adults' over the age of 13 years. We have chosen 13 years as the cut-off for children versus adolescents/adults, as respiratory system development continues until about 12 years of age. We will also stratify participants according to whether the intervention is 'rescue' therapy (i.e. intercurrent acute chest infection in a person with chronic NMD) or maintenance therapy, where possible.

We will exclude participants with the following comorbidities/characteristics.

1. Amyotrophic lateral sclerosis/motor neuron disease (ALS/MND), which is the focus of another review.
2. Acute NMD with likelihood of resolution, e.g. Guillain-Barré syndrome.
3. Spinal cord injuries.
4. Neonates in the first month of life, as they are pathophysiologically and anatomically a unique patient group warranting a separate review.

Types of interventions

We will include trials comparing any cough augmentation technique or combination of techniques, whether provided as maintenance therapy or for treatment of intercurrent respiratory tract infection, with no treatment (unassisted cough), alternative cough augmentation techniques, or combinations thereof. We will allow co-interventions provided that they are provided to each group equally.

Cough augmentation techniques will include, but will not be limited to:

1. manual or mechanical insufflation;
2. breath/air stacking;
3. glossopharyngeal breathing;
4. mechanical insufflation-exsufflation (MI-E);
5. mechanical exsufflation;
6. and manually-assisted cough (MAC).

Types of outcome measures

In formulating primary and secondary outcome measures, we will differentiate between cough augmentation techniques used for rescue therapy (e.g. during intercurrent respiratory exacerbations) and maintenance management.

In addition to the formal outcome measures listed below, we will informally include any valid measure of economic comparison between cough augmentation techniques relative to health outcomes.

The outcomes listed here are not eligibility criteria for this review, but are outcomes of interest within whichever studies we include.

Primary outcomes

1. Number of unscheduled hospital admissions for episodes of acute respiratory exacerbations over one year
2. Duration of hospital stay (days) for 'rescue' use.

Secondary outcomes

1. PCF measured before and after intervention for 'rescue' use and measured over the medium term (between three months and one year) and long term (one year and longer) for maintenance use.
2. Any adverse events, including, but not limited to: pneumothorax, rib fractures, lung injury, aerophagia/abdominal distension, and death.
3. Measures of gaseous exchange (e.g. oxygenation (PaO_2/SaO_2); expired carbon dioxide ($ETCO_2$)) measured before and after the intervention for 'rescue' use, and measured over the medium term (between three months and one year) and long term (one year and longer) for maintenance use.
4. Pulmonary function measured by forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), vital capacity (VC) and peak expiratory flow rate (PEFR), over the short term (less than three months); medium term (between three months and one year) and long term (one year and longer). Where possible, we will present values as percentages predicted according to age, gender and height; or as Global Lung Function Initiative multi-ethnic norm-referenced Z score values (Quanjer 2012).

5. Quality of life measured by any validated measure over the medium term (between three months and one year) and long term (one year and longer) for maintenance use.

6. Validated measures of function, including measures of perceived exertion, exercise tolerance and motor function measured over the medium term (between three months and one year) and long term (one year and longer) for maintenance use.

7. Participant preference for specific cough augmentation techniques, measured as a proportion or percentage of the sample.

Search methods for identification of studies

Electronic searches

The Information Specialist will search the following databases.

1. Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS-Web).
2. Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web).
3. MEDLINE (1946 onwards).
4. Embase (1974 onwards).
5. CINAHL (1937 onwards).

The draft MEDLINE strategy is in Appendix 1. We will use this as the basis for search strategies for the other databases listed.

We will also conduct a search of the US National Institutes for Health Clinical Trials Registry, www.ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/). We will search all databases from their inception to the present, and we will impose no restriction by language of publication, or by publication status (abstract only, 'in press', 'grey' literature, full text, etc.).

Searching other resources

We will search reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information. We will also search for errata or retractions from included studies.

Data collection and analysis

Selection of studies

Two review authors (BM, AH) will independently screen titles and abstracts of all the studies we identify as a result of the search for inclusion, and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication, and two review authors (BM, LC) will independently screen the full text and identify studies for inclusion, and will identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person as arbiter (MZ). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data extraction form for study characteristics and outcome data which has been piloted on at least one study in the review. One review author (BM) will extract study characteristics from included studies . We will extract data on:

1. Study design and setting;
2. Characteristics of participants (e.g. disease severity and age);
3. Eligibility criteria;
4. Intervention details;
5. Outcomes assessed;
6. Source(s) of study funding;
7. Any conflicts of interest among investigators.

Two review authors (AH; LC) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way, resolving disagreements by consensus or by involving a third person if necessary (MT). One review author (BM) will transfer data into Review Manager 5 (RevMan 2014). A second author will check the outcome data entries (AH). Another review author (MZ) will spot-check study characteristics for accuracy against the trial report.

When reports require translation, the translator will extract data directly using a data extraction form, or authors will extract data from the translation provided. Where possible a review author will check numerical data in the translation against the study report.

Assessment of risk of bias in included studies

Two review authors (BM; AH) will independently assess risks of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2017). We will make summary assessments of the risk of bias for each important outcome (across domains) within and across studies comparing the same interventions. We will resolve any disagreements by discussion or by involving another author (LC). We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.

7. Other bias.

We will grade each potential source of bias as high, low or unclear, and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary. Where information on risk of bias relates to unpublished data or correspondence with an author, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol, and will report any deviations from it in the 'Differences between protocol and review' section.

Measures of treatment effect

We will analyse all data for 'rescue' and maintenance use of cough augmentation techniques separately. We will analyse dichotomous data as risk ratios (RRs) and continuous data as mean difference (MD), or standardised mean difference (SMD) for results across studies with outcomes that are conceptually the same but measured in different ways. Where standard errors of the means (SEMs) are reported, we will convert these to standard deviations (SDs) where possible. We will enter data presented as a scale with a consistent direction of effect.

We will calculate a Peto odds ratio (Peto OR) and corresponding 95% confidence interval (CI) for rare adverse events. In the case of statistically significant results, we will calculate the risk difference (RD) and 95% CI and the number needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH) as appropriate.

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to be meaningful. We will report separately types of cough augmentation techniques and different underlying conditions which cannot be pooled (if the number of trials permits).

We will describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

We will include only first-period data from cross-over trials (Higgins 2011). Long-term studies with multiple repeated measures of outcome may be included, in which case we will define outcomes based on the specified time points (Higgins 2011).

Where multiple trial arms are reported in a single trial, we will include only the treatment arms relevant to the review topic. If two comparisons (e.g. treatment A versus no treatment and treatment B versus no treatment) are combined in the same meta-analysis, we will follow guidance in Section 16.5.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid double-counting (Higgins 2011). Our preferred approach will be to halve the control group.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is available as an abstract only). Where this is not possible, we will consider the studies adequate if more than 85% of the participants are included in the outcome analysis or if fewer participants were analysed but sufficient measures were taken to ensure or demonstrate that this did not bias the results. Where this is not clear, we will conduct an intention-to-treat analysis from extrapolated data. If we suspect that missing data may have introduced serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. We will avoid the use of absolute cut-off values, but will interpret I^2 in relation to the size and direction of effects and strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or confidence interval for I^2).

We will use the rough guide to interpretation as outlined in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017), as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If we identify substantial unexplained heterogeneity we will report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small-study biases.

Data synthesis

We will use a random-effects model, as this is more conservative, and explore possible causes of heterogeneity by subgroup analyses if there are sufficient studies to do so. We will conduct meta-analyses where there is minimal clinical or methodological heterogeneity. Where we cannot pool data, we will report the results in narrative form.

If the review includes more than one comparison which cannot be included in the same analysis, we will report the results for each comparison separately.

'Summary of findings' table

We will create separate 'Summary of findings' tables for 'rescue' and maintenance use of cough augmentation techniques, using GRADEpro GDT software, and will present the following outcomes.

1. Number of unscheduled hospital admissions for episodes of respiratory exacerbations over the medium term (between three months and one year) and long term (one year and longer) for maintenance use.
2. Duration of hospital stay (days) for 'rescue' use.
3. PCF measured before and after intervention for 'rescue' use and measured over the medium term (between three months and one year) and long term (one year and longer) for maintenance use.
4. Any adverse events ('rescue' and maintenance).
5. Quality of life measured by any validated measure over the medium term (between three months and one year) and long term (one year and longer) (maintenance use).
6. Participant preference ('rescue' and maintenance).

Two review authors (BM and AH) will independently assess the quality of the body of evidence (studies that contribute data for the prespecified outcomes) using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias). We will use methods and recommendations described in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions (*Schünemann 2017a; Schünemann 2017b). We will resolve any disagreements by discussion or by involving another author (LC). We will assess trial quality (certainty of the evidence) according to the GRADE criteria. We will consider RCTs as high-quality evidence if the five factors above are not present to any serious degree, but may downgrade the quality to moderate, low or very low. We will downgrade evidence once if a quality consideration is serious and twice if very serious. We will justify all decisions to downgrade or upgrade the quality of studies using footnotes, and will make comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses if possible.

1. Infants versus children.
2. Children versus adolescents/adults.

We will use the following outcomes in subgroup analyses.

1. Number of hospital admissions over one year (for maintenance use).
2. Duration of hospital stay (days) for 'rescue' use.

We will use the formal test for subgroup interactions in RevMan 5 (RevMan 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

1. Repeat the analysis excluding unpublished studies (if there are any).
2. Repeat the analysis excluding studies at high risk of bias (e.g. randomised versus quasi-randomised). We will rate studies at overall high risk of bias if there is a high risk of bias for one or more key domains (Higgins 2017)).
3. If there is one or more very large studies, we will repeat the analysis excluding them to determine to what extent they dominate the results.
4. Repeat the analysis using different statistical models (fixed-effect versus random-effects).

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

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The Information Specialist of Cochrane Neuromuscular, Angela Gunn, developed the search strategy in consultation with the review authors.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (OvidSP) draft search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1 randomized controlled trial.pt. (455306)
2 controlled clinical trial.pt. (92216)
3 randomi#ed.ti,ab. (520311)
4 placebo.ab. (186900)
5 drug therapy.fs. (1998447)
6 randomly.ab. (286114)
7 trial.ab. (420183)
8 groups.ab. (1769782)
9 or/1-8 (4153256)
10 exp animals/ not humans.sh. (4432422)
11 9 not 10 (3588435)
12 (assist* adj2 cough*).mp. (227)
13 (breath stack* or air stack*).mp. (62)
14 glossopharyngeal breath*.mp. (60)
15 frog breath*.mp. (5)
16 (mechanical adj4 (insufflation or exsufflation)).mp. (132)
17 manual insufflation.mp. (7)
18 16 or 17 (139)
19 (breath* or resp*).mp. (5770668)

20 18 and 19 (119)
21 or/12-15,20 (394)
22 11 and 21 (69)

CONTRIBUTIONS OF AUTHORS

BM wrote the protocol; MZ, AH, LC, AA and MT all contributed to the final draft of the protocol and have agreed to its contents and their role in the final review.

DECLARATIONS OF INTEREST

BM: BM has no particular conflict of interest to declare in respect of this protocol. She received an unconditional donation of consumables and a Nippy mechanical In-exsufflation device for an ongoing clinical trial of MI-E from *Bakoni Medical* company. BM is principal investigator of a trial which may be eligible for inclusion in later versions of this review, in which case she will recuse herself from that data extraction and analysis.

AH: Received an unconditional donation of equipment and consumables for a clinical trial of MI-E (currently underway) from *Bakoni Medical* company. She is the student investigator of a trial which may be eligible for inclusion in later versions of this Review, in which case she will recuse herself from that data extraction and analysis.

AA: AA is a specialist (paediatric critical care) physician and manages patients with a variety of conditions. He has no particular conflicts of interest to declare in respect of this protocol.

MZ: MZ is a specialist (paediatric pulmonology) and manages patients with a variety of conditions, including a range of NMDs. He has no particular conflicts of interest to declare in respect of this protocol.

LC: No conflicts to declare

MT: No conflicts to declare

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NOTES

This review will partially supersede Mechanical insufflation-exsufflation for people with neuromuscular disorders (Morrow 2013).