Cough augmentation techniques for people with chronic neuromuscular disorders (Protocol)

Morrow B, Argent A, Zampoli M, Human A, Corten L, Toussaint M

Morrow B, Argent A, Zampoli M, Human A, Corten L, Toussaint M.

Cough augmentation techniques for people with chronic neuromuscular disorders.


DOI: 10.1002/14651858.CD013170.

www.cochranelibrary.com
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Header</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Background</td>
<td>1</td>
</tr>
<tr>
<td>Objectives</td>
<td>3</td>
</tr>
<tr>
<td>Methods</td>
<td>4</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>7</td>
</tr>
<tr>
<td>References</td>
<td>8</td>
</tr>
<tr>
<td>Appendices</td>
<td>10</td>
</tr>
<tr>
<td>Contributions of Authors</td>
<td>11</td>
</tr>
<tr>
<td>Declarations of Interest</td>
<td>11</td>
</tr>
<tr>
<td>Sources of Support</td>
<td>11</td>
</tr>
<tr>
<td>Notes</td>
<td>11</td>
</tr>
</tbody>
</table>
Cough augmentation techniques for people with chronic neuromuscular disorders

Brenda Morrow¹, Andrew Argent², Marco Zampoli³, Anri Human⁴, Lieselotte Corten⁵, Michel Toussaint⁶

¹Department of Paediatrics, University of Cape Town, Cape Town, South Africa. ²Pediatric Intensive Care, Division of Pediatric Critical Care and Children's Heart Disease, Red Cross War Memorial Children's Hospital and University of Cape Town, Cape Town, South Africa. ³Pulmonology, and Paediatric Medicine, Red Cross War Memorial Children's Hospital and University of Cape Town, Cape Town, South Africa. ⁴Physiotherapy Department, School of Health Care Sciences, Sefako Makgatho Health Sciences University, Garankuwa, South Africa. ⁵Department of Health and Rehabilitation Sciences, Division of Physiotherapy, University of Cape Town, Cape Town, South Africa. ⁶Centre for Home Mechanical Ventilation and Specialized Centre for Neuromuscular Diseases, Inkendaal Rehabilitation Hospital, Vlezenbeek, Belgium

Contact address: Brenda Morrow, Department of Paediatrics, University of Cape Town, 5th Floor ICH Building, Red Cross Memorial Children's Hospital, Klipfontein Road, Rondebosch, 7700, Cape Town, South Africa. Brenda.morrow@uct.ac.za.

Editorial group: Cochrane Neuromuscular Group.


Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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-
Cough augmentation techniques for people with chronic neuromuscular disorders (Protocol)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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 (Dohma-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 160 L/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; Bost 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, glosso-phyngal 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). Glosso-phyngal 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; Faouroux 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).

Inspiration 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.

OBJECTIVES

Cough augmentation techniques for people with chronic neuromuscular disorders (Protocol)
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.
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 (PaO₂/SaO₂); expired carbon dioxide (ETCO₂)) 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 (FEV₁), 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).
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.
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) to be used. 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 we will calculate a Peto odds ratio (Peto OR) and corresponding 95% confidence interval (CI) for rare adverse events. In the case of directional effects, we will take into account the direction of effect. Possible ORs will be entered as a scale with a consistent direction of effect.
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.

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.

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.

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

The Methods section of this protocol is based on a template developed by the Cochrane Neuromuscular Disease Group from an original created by the Cochrane Airways Group.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Neuromuscular. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health. Cochrane Neuromuscular is also supported by the MRC Centre for Neuromuscular Disease.
Additional references

Albuali 2007

Anderson 2005

Bach 1996

Bach 1997

Bach 2003

Bach 2007

Bianchi 2008

Boitano 2006

Bott 2009

Chatwin 2018

Deeks 2017

Dohna-Schwake 2006

Douglas 1981

Fauroux 2008

Finder 2004

Finder 2010

Gattinoni 2003

Gattinoni 2010

Gozal 2000

Higgins 2011

Cough augmentation techniques for people with chronic neuromuscular disorders (Protocol)
Cough augmentation techniques for people with chronic neuromuscular disorders (Protocol)

Higgins 2017

Homnick 2007

Hull 2012

Iannaccone 2007

Kang 2000

Leiner 1963

Marques 2014

McCool 2006

Morrow 2013

Nygren-Bonnier 2009

Panitch 2009

Papastamoulos 1996

Quanjer 2012

RevMan 2014 [Computer program]

Rokadia 2015

Rosière 2009

Saharan 2010

Schünemann 2017a

Schünemann 2017b

Sivasothy 2001
Sivasothy P, Brown L, Smith IE, Shneerson JM. Effect of manually assisted cough and mechanical insufflation on cough flow of normal subjects, patients with chronic...

**Suri 2008**

**Toussaint 2018**

**Trebbia 2005**

**Tzeng 2000**

**Vianello 2004**

**Wang 2007**

**Wang 2010**

* 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:
--------------------------------------------------------------------------------
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)
-----------------------------------------------------------------------------------------------

*Cough augmentation techniques for people with chronic neuromuscular disorders (Protocol)*

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
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

SOURCES OF SUPPORT

Internal sources

- University of Cape Town, South Africa.
  Salary

External sources

- National Research Foundation, South Africa.
  Incentive Funding for Rated Researchers Program
NOTES

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