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# BMJ Open

## Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review

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## Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on February 15th 2019 (registration number CRD42019117393).

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### Contributions of authors

- SCBN: screen titles, abstracts and full text to identify studies for inclusion or exclusion; extract study characteristics; extract outcome data; transfer data into RevMan; assess risk of bias
- RTC: screen titles, abstracts and full text to identify studies for inclusion or exclusion; extract outcome data; check outcome data entries; spot-check study characteristics for accuracy; assess risk of bias
- IL: development of the text; statistical analysis, revision of the final text
- VRR: development of the text; statistical analysis, revision of the final text
- GAF: discussion about the disagreements the two authors have in any issues; screen studies the other two authors have authored

### Abstract

**Introduction:** Neuromuscular diseases (NMD), defined as chronic disease with different characteristics in which the clinical pattern is based on the place the lesion occurs in a motor unit, are characterized by progressive muscular impairment. The muscle weakness is directly related to respiratory muscles weakness, causing a reduction in vital capacity, especially when associated with mechanical ventilation (MV). Conventional mechanical ventilation weaning in NMD is generally difficult. The weaning process can be conducted in protocols such as: “T” piece or Pressure Support Ventilator. Weaning failure is frequent because of muscle weakness. The aim of the protocol is to assess the effects of different weaning protocols in individuals with NMD receiving invasive MV in weaning success, duration of weaning, duration of stay in the ICU, duration of hospital stay and ICU mortality. **Methods and analysis:** randomized controlled trials and quasi-RCTs will be included. The inclusion criteria of individuals are adults (above sixteen years old) and children (from five to sixteen years old), with a clinical diagnosis of NMD (muscular dystrophy, amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillain Barré Syndrome, severe inherited neuropathies, metabolic

1  
2  
3 myopathies, inflammatory myopathies, mitochondrial diseases) of any gender. All  
4 patients ventilated for at least 48 hours with because of respiratory failure, and clinically  
5 considered ready for will be included. No individuals with other respiratory or  
6 cardiovascular diagnosis associated will be included. The intervention assessed will be  
7 the weaning from MV using a protocol with 30 minutes to two hours of spontaneous  
8 breathing trial at the end point of the protocol. All comparisons of the different  
9 protocols will be considered. **Ethics and dissemination:** All studies included should be  
10 approved by an ethics committee. This will ensure an appropriate ethical approach. The  
11 disclosure of the results will be made through publication in an indexed journal.  
12  
13

### 14 **Strengths and limitations of this study**

15 **Strength points:** (1) to identify the best way to conduct MV weaning in patients  
16 with NMD; (2) the interaction of several professionals with experience in mechanical  
17 ventilation, in NMD and in systematic reviews.  
18

19 **Limitations points:** (3) difficulty in finding articles that meet the inclusion  
20 criteria; (4) very different approaches in the weaning process of patients with NMD; (5)  
21 NMD heterogeneity may influence the interpretation of the results.  
22  
23

### 24 **Introduction**

25 Neuromuscular disease can be defined as a chronic disease with different  
26 characteristics in which the clinical pattern is based on the place the lesion occurs in a  
27 motor unit (Anziska 2013, Rezanina 2012). Neuromuscular diseases are characterized  
28 by progressive muscular impairment, with difficulty in ambulation, swallowing and  
29 ventilation, with progressive reduction of vital capacity and increased work of breathing  
30 (Ambrosino 2009). These changes lead to the development of chronic respiratory  
31 insufficiency, which is an important cause of prolonged ventilatory dependence (Kim  
32 2017).  
33

34 Muscle weakness is directly related to weakness of respiratory muscles,  
35 especially the diaphragm. Diaphragmatic weakness, often found in patients with NMD  
36 causes a reduction in the capacity to generate force, especially when associated with the  
37 use of controlled mechanical ventilation (Vassilakopoulos 2004). Intensive care unit  
38 (ICU) admission may be a cause of neuromuscular disorders (Bach 2010), which is  
39 estimated to occur in up to 62% of critically ill patients in ICU (Epstein 1998). Some  
40 risk factors such as use of sedatives, malnutrition, systemic inflammation, and prolonged  
41 mechanical ventilation may further impair the neuromuscular performance of people  
42 admitted to ICU (Hermans 2015).  
43

44 NMD patients often experience respiratory impairment due to the respiratory  
45 muscles reduced strength. This alteration is caused, in general, by a large proportion of  
46 motor units that innervate the respiratory muscles affecteds (Rezania, 2012).  
47

48 The majority of critically ill patients admitted to ICU require ventilatory support  
49 for acute or chronic respiratory failure (Ambrosino 2009), specially the NMD ones. In  
50 addition, the pattern of neuromuscular abnormalities associated with critical illness,  
51 defined as ICU-acquired weakness (ICUAW) (Kim 2017), can lead to prolonged  
52 mechanical ventilation, a longer hospital stay and increased ventilation (Kim 2017).  
53

54 The emergence of respiratory symptoms, with progressive hypercapnia, can lead  
55 to death from respiratory failure (Ambrosino 2009). Long-term invasive or non-invasive  
56 mechanical ventilation is the main intervention for people who present with acute  
57 respiratory acidosis; progressive decline in vital capacity (< 10 to 15 mL/kg); or  
58 progressive decline in maximal inspiratory pressure (< 20 to 30 cmH<sub>2</sub>O) (Ambrosino  
59 2009).  
60

1  
2  
3 Weaning from mechanical ventilation is the process of transition to spontaneous  
4 ventilation (Zein 2016). In people with neuromuscular diseases, conventional weaning  
5 is generally not possible (Fan 2014).

6 Weaning difficulty mainly occurs in elderly people with prolonged ICU  
7 hospitalization and chronic respiratory diseases or neuromuscular diseases (Tsara 2015).  
8 Therefore, the decision to progress to extubation is more challenging in this group of  
9 people with advanced respiratory muscle weakness, and this can lead to a need for  
10 tracheostomy and prolonged mechanical ventilation (Kim 2017).

11  
12 Difficult weaning can be defined as a failure of initial weaning and a  
13 requirement for up to three trials of spontaneous breathing or seven days of mechanical  
14 ventilation to achieve extubation (Zein 2016; Sklar 2017).

15  
16 The weaning process may be conducted in different protocols such as:

- 17 • “T” piece: in which the patient receives only supplemental oxygen through a T-  
18 shaped tube connected to an endotracheal tube (orotracheal or tracheostomy) (Zein  
19 2016);
- 20 • Continuous positive airway pressure (CPAP): the weaning protocol involves using  
21 a continuous pressure, equal to the previous positive end-expiratory pressure  
22 (PEEP) level used before (Zein 2016);
- 23 • Pressure support: use of progressive lower levels of inspiratory pressure support  
24 until it reaches 5 to 8 cmH<sub>2</sub>O (Zein 2016).

25  
26 Successful weaning is defined as the ability to maintain spontaneous ventilation  
27 without the need for re-intubation and invasive mechanical ventilation for 48 hours after  
28 extubation (Zein 2016). For patients with neuromuscular diseases, due to the difficulty  
29 of weaning, it may be also defined as the absence of a need for tracheostomy and  
30 mechanical ventilation for five days after extubation (Kim 2017).

31  
32 Post-weaning monitoring should observe whether two of the following  
33 findings are present: respiratory acidosis (pH < 7.35; PaCO<sub>2</sub> > 45 mmHg); SpO<sub>2</sub> < 90%  
34 or PaO<sub>2</sub> < 60 mmHg with FiO<sub>2</sub> > 50%; RR > 35 rpm; decreased level of consciousness,  
35 restlessness or excessive sweating; or signs suggestive of respiratory muscle fatigue,  
36 such as the use of accessory muscles or paradoxical movement of the abdomen, in order  
37 to determinate the need to reestablish mechanical ventilation again (Kim 2017, Zein  
38 2016).

39  
40 Weaning failure is a frequent occurrence in people with neuromuscular disease  
41 because of muscle weakness and gradual hypercapnia (Kim 2017). Thus, the indication  
42 of non-invasive ventilation to allow weaning in patients with neuromuscular disease  
43 who do not tolerate a spontaneous breathing test or the tracheostomy indication for  
44 further successful weaning and ICU discharge is indicated (Kim 2017; Tsara 2015) and  
45 this whole process significantly increases health costs with this patient population. In  
46 this way it is necessary to understand the best practices for the most effective weaning  
47 process in this type of patients.

## 48 49 50 51 **Objectives**

52 The aim of this systematic review is to assess the effects of different weaning  
53 protocols in people with neuromuscular diseases receiving invasive mechanical  
54 ventilation. Our secondary aim is to assess how the different protocols affect weaning  
55 success, duration of weaning, duration of stay in the ICU, duration of hospital stay, and  
56 ICU mortality, and also to assess adverse effects.

## 57 58 59 60 **Methods**

## **Eligibility criteria**

Studies will be selected according to the criteria outlined below.

### ***Study designs***

We will include randomised controlled trials (RCTs) and quasi-RCTs (studies with different methods for allocation). Other study types, such as non-randomised trials, cross-over studies and case control studies will be described in the Discussion section of the review, but they will not be included in the Results section. We will include studies reported as full-text, those published as abstract only, and unpublished data. There will be no restrictions as to language.

### ***Participants***

We will consider for inclusion adults (above sixteen years old) and children (from five to sixteen years old) people with a clinical diagnosis of a neuromuscular disease (muscular dystrophy of any origin including Duchenne muscular dystrophy, amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillian Barré Syndrome, severe inherited neuropathies, metabolic myopathies (Pompe disease), inflammatory myopathies, mitochondrial diseases) of any gender.

We will consider all patients ventilated for at least 48 hours with orotracheal tube or tracheostomy because of acute respiratory failure, and considered by physicians to be ready for weaning according to clinical criteria and weaning parameters. No patients with other respiratory or cardiovascular clinical diagnosis associated will be included, nor patients with mixed NMD diagnosis.

If any subset of participants with NMD is analyzed, these patients will be included.

### ***Interventions***

The intervention assessed will be the process of weaning from mechanical ventilation in people with neuromuscular diseases using a protocol with criteria for deciding if the patient is ready for extubation with 30 minutes to two hours spontaneous breathing trial (SBT) at the end point of the protocol.

We will consider the following protocols for inclusion.

1. Pressure support ventilation, with gradual reduction of the support pressure
2. Synchronized intermittent mandatory ventilation, with gradual reduction of respiratory rate and support pressure
3. Continuous positive airway pressure, with gradual reduction of applied pressure
4. 'T' piece, with progressive increase of spontaneous ventilation time.

### ***Comparators***

We will consider any comparisons of the different protocols.

The protocols will also be compared in relation to the classification of weaning outcomes, in order to identify the which protocols develop better outcomes.

- Simple – successful after first attempt;
- Difficult – require up to three attempts (or less than 7 days to reach success);
- Prolonged – require more than 7 days to reach success).

### ***Outcomes***

#### ***Primary outcomes***

1  
2  
3 Weaning success, defined as the ability to maintain spontaneous ventilation  
4 without the need for reintubation and invasive mechanical ventilation for 48 hours after  
5 extubation (Zein 2016).

#### 6 Secondary outcomes

- 8 • Duration of weaning in patients with acute and prolonged mechanical ventilation  
9 – defined as the time between the weaning protocol initiation and the moment of  
10 extubation;
- 11 • Duration of ICU stay in patients with acute and prolonged mechanical ventilation  
12 – defined as the time between ICU admission and ICU discharge;
- 13 • Duration of hospital stay in patients with acute and prolonged mechanical  
14 ventilation – defined as the time between hospital admission and hospital  
15 discharge;
- 16 • ICU mortality rate in patients with acute and prolonged mechanical ventilation –  
17 defined as the mortality rate during ICU stay.
- 18 • Incidence of pneumothorax during mechanical ventilation period.
- 19 • Incidence of ventilation associated pneumonia.

#### 22 Language

23 We will include articles reported in the English languages. A list of possibly  
24 relevant titles in other languages

#### 27 **Information sources**

##### 28 Electronic searches

29 We search the Cochrane Neuromuscular Specialised Register (The Cochrane  
30 Library, current issues), MEDLINE, and EMBASE. We will scan conference abstracts  
31 for relevant studies.

32 We will also search the United States National Institutes of Health Clinical  
33 Trials Registry, ClinicalTrials.gov (ClinicalTrials.gov) and the World Health  
34 Organization International Clinical Trials Registry Portal (apps.who.int/trialsearch/).

35 We will search all databases from their inception to the present, and we will  
36 impose no restriction on language of publication.

37 We will identify non-randomised studies for inclusion in the discussion from the  
38 same search results.

39 We will search reference lists of all relevant and included trials and review  
40 articles for additional references. We will search for errata or retractions of included  
41 trials. We will also search relevant manufacturers' websites for trial information. And  
42 we will search grey literature, in reports of technical research and projects related to  
43 government programs, to identify other studies.

44 We will contact study authors of included trials, to identify additional trials  
45 whether published or unpublished.

46 If no RCTs or quasi-RCTs in this area are not found the authors will review  
47 other well-designed observational studies, where the population (NMD), intervention  
48 (mechanical ventilation weaning) and outcome (weaning success) are clearly  
49 documented, in the 'Discussion' section of the review. We will identify these (non-  
50 randomised studies) via a search in MEDLINE (from inception to the present) and  
51 EMBASE (from inception to the present). This will be done in order to give a  
52 comprehensive descriptive narrative of any non-randomised data.

#### 58 **Search strategy**

1  
2  
3 Search terms will include: 'neuromuscular disease' or all other terms compatible  
4 with clinical diagnoses of these types of diseases, such as 'muscular dystrophy',  
5 'Duchenne muscular dystrophy', 'amyotrophic lateral sclerosis', 'congenital myasthenia',  
6 'myasthenia gravis', 'congenital myopathy', 'spinal muscular atrophy', 'Guillain Barré  
7 Syndrome', 'severe inherited neuropathies', 'metabolic myopathies', 'Pompe disease',  
8 'inflammatory myopathies' and 'mitochondrial diseases' combined with 'mechanical  
9 ventilation' or 'artificial respiration' or 'mechanical ventilation weaning' or 'ventilator  
10 weaning' or 'respirator weaning'; and all the combination between them.  
11  
12

## 13 **Study records**

### 14 *Selection of studies*

15 Two review authors (SCBN, RTC) will independently screen titles and abstracts  
16 of all the potential studies retrieved by the search for inclusion and code them as  
17 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will identify  
18 and exclude duplicates and collate multiple reports of the same study so that each study  
19 rather than each report is the unit of interest in the review. We will retrieve full-text  
20 study reports/publications, and two review authors (SCBN, RCT) will independently  
21 screen the full text and identify studies for inclusion, and identify and record reasons for  
22 exclusion of the ineligible studies.  
23

24 We will resolve any disagreements through discussion or, if required, through  
25 consultation with a third review author (GAFF).  
26

27 We will report the selection process in sufficient detail to complete a PRISMA  
28 flow diagram and 'Characteristics of excluded studies' table.  
29

### 30 *Data extraction and management*

31 We will use a data extraction form that we will initially pilot on at least one trial  
32 included in the review to collect study characteristics and outcome data. One review  
33 author (SCBN) will extract study characteristics from included trials. We will collect  
34 information on study design and setting, participant characteristics (including disease  
35 severity and age), study eligibility criteria, details of the intervention(s) given, the  
36 outcomes assessed, the source of study funding and any conflicts of interest stated by  
37 the investigators.  
38

39 Two review authors (SCBN, RCT) will independently extract outcome data from  
40 included trials. We will note in the 'Characteristics of included studies' table if the trials  
41 did not report outcome data in a usable way. We will resolve any disagreements by  
42 consensus or consult a third review author (GAFF). One review author (SCBN) will  
43 transfer data into Review Manager (RevMan) 5.3 (RevMan 2014). A second review  
44 author (RCT) will check the outcome data entries.  
45

46 The same review author (RCT) will spot-check study characteristics for  
47 accuracy against the trial report. When reports require translation, the translator will  
48 extract data directly using a data extraction form, or we will extract data from the  
49 translation provided. Where possible, a review author will check numerical data in the  
50 translation against the study report.  
51

52 To minimize bias in the review process, the review authors will not screen  
53 studies for inclusion, extract data, or assess the risk of bias in trials they themselves  
54 have authored. In such circumstances, we will involve a third review author (GAFF).  
55

## 56 **Risk of Bias individual studies**

57 Two review authors (SCBN, RCT) will independently assess risk of bias for  
58 each study using the criteria outlined in the Cochrane Handbook for Systematic  
59  
60



1  
2  
3 Reviews of Interventions (Higgins 2011). These authors will resolve disagreements by  
4 discussion or by involving another review author (GAFF).

5 We will assess the risk of bias according to the following domains:

- 6 1. Random sequence generation.
- 7 2. Allocation concealment.
- 8 3. Blinding of participants and personnel.
- 9 4. Blinding of outcome assessment.
- 10 5. Incomplete outcome data.
- 11 6. Selective outcome reporting.
- 12 7. Other bias.

13 We will grade each potential source of bias as high, low, or unclear and provide  
14 a quote from the study report together with a justification for our judgment in the 'Risk  
15 of bias' table. We will summarise the risk of bias judgements across different studies for  
16 each of the domains listed. We will consider blinding separately for different key  
17 outcomes where necessary (for example for unblinded outcome assessment, risk of bias  
18 for all-cause mortality may be very different than for a patient-reported pain scale).  
19 Where information on risk of bias relates to unpublished data or correspondence with a  
20 trialist, we will note this in the 'Risk of bias' table. When considering treatment effects,  
21 we will take into account the risk of bias for the studies that contribute to that outcome.  
22  
23  
24  
25

## 26 **Data Synthesis**

### 27 Measures of treatment effect

28 We will analyze dichotomous data as risk ratios (RR) with corresponding 95%  
29 CI and continuous data as mean difference (MD) with 95% CI, or as standardised mean  
30 difference (SMD) with 95% CI for results across studies with outcomes that are  
31 conceptually the same but measured in different ways. We will enter data presented as a  
32 scale with a consistent direction of effect.  
33

34 We will undertake meta-analyses only where this is meaningful, that is if the  
35 treatments, participants, and the underlying clinical question are similar enough for  
36 pooling to make sense. This will be identified if there are two or more trials with  
37 comparable populations and interventions.  
38

39 Where a single trial reports multiple trial arms, we will include only the arms  
40 relevant to the review question.

41 All data will be pooled according to age group, dividing them into two groups  
42 (adults - over sixteen years old, and children - between five and sixteen years old). After  
43 this grouping the analyzes will be done, firstly, comparing the success rate and failure  
44 rate in each of the groups. Subsequently the data will also be evaluated taking into  
45 consideration the weaning outcomes in simple, difficult and prolonged (as described in  
46 the types of interventions).  
47  
48

### 49 Unit of analysis issues

50 We do not expect to have any cross-over or cluster randomised controlled trials,  
51 since weaning is a one-off event and also due to the lack of control group, since all  
52 patients are submitted to the same intervention, which is weaning from mechanical  
53 ventilation.  
54  
55

### 56 Dealing with missing data

57 We will address non-reported outcomes ("trial-level missing data") with a two-  
58 stage strategy. Firstly, we will search for the study protocol (where possible) to find  
59 whether the information was collected. If no protocol is available, or if the information  
60

was collected but not reported, we will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible. Missing data may also arise if a trial fails to capture outcome data on all participants ("patient-level missing data"). This may occur for many reasons, and is most likely to affect quality of life data. We will have access to individual patient data for one trial, allowing us to undertake sensitivity analyses, and may be able to obtain additional information from other study authors.

Where this is not possible, and we consider the missing data to have introduced serious bias, we will explore the impact of inclusion of such trials 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. If we identify substantial unexplained heterogeneity, we will report both fixed-effect and random-effects results and explore possible causes by prespecified subgroup analysis.

We will follow the rough guide to interpretation outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

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

#### Assessment of reporting biases

If we are able to pool a sufficient number of studies, i.e. more than 10 trials (Higgins 2011), we will create and examine a funnel plot to explore possible small study biases.

#### Data synthesis

We expect heterogeneity among trials and we will use a random-effects model. We will perform a sensitivity analysis with a fixed-effect model. If the review authors agree that there is obvious clinical and methodological heterogeneity amongst eligible studies, such that meta-analysis seems inappropriate, we will undertake a narrative synthesis.

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

#### 'Summary of findings' table

- We will create a 'Summary of findings' table using the following outcomes.
- Weaning success
- Duration of weaning (time difference between weaning protocol initiation and the moment of extubation moment).
- Duration of ICU stay
- Duration of hospital stay
- ICU mortality rate in patients with acute and prolonged mechanical ventilation – defined as the mortality rate during ICU stay.
- Incidence of pneumothorax during mechanical ventilation period.
- Incidence of ventilation associated pneumonia.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes). We will use methods and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) using GRADEpro software (GRADEpro GDT). We will justify all decisions to down- or upgrade the quality of studies using footnotes, and we will make comments to aid readers' understanding of the review where necessary. Two authors will independently grade the quality of the evidence. They will resolve disagreements by discussion and by consultation with a third review author.

#### *Subgroup analysis and investigation of heterogeneity*

- We plan to perform the following subgroup analyses.
- Simple weaning: successful after first attempt
- Difficult weaning: require up to three attempts
- Prolonged weaning: require more than 7 days to reach success
- Children: from five to sixteen years old
- Adults: above sixteen years old

We will use both primary and secondary outcome measures in all subgroup analyses. We will use the formal test for subgroup interactions in Review Manager 5.3 (RevMan 2014).

#### *Sensitivity analysis*

We plan to undertake the following sensitivity analyses.

1. Repeat the analysis by excluding any unpublished studies.
2. Repeat the analysis by excluding studies at high risk of bias (sequence generation, allocation concealment, blinding of personnel, outcome assessment, and attrition).

If there are one or more very large trials, we will repeat the analysis by excluding them to examine how much they dominate the results.

#### *Reaching conclusions*

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

### **Patient and Public Involvement**

In the present protocol of systematic review and in the subsequent systematic review there was no and there will be no involvement of patients or public.

The paper proposes to use results previously authorized and published by other authors, without there being any need for patient or public involvement. The research question was developed based on the questions raised by other authors, most of the time according to the clinical difficulty and necessity of improve the weaning protocols for this population.

The results of the present study will be published in indexed journal so it can be available for NMD patients, in general, and public, specially health professionals.

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

**Declarations of interest**

- SCBN: non-conflicted
- RTC: non-conflicted
- IL: non-conflicted
- VRR: non-conflicted
- GAF: non-conflicted

**References*****Ambrosino 2009***

Ambrosino N, Carpené N, Gherardi M. Chronic respiratory failure care for neuromuscular diseases in adults. *European Respiratory Journal* 2009;34:441-51. [Other: ; Other: ]

***Anziska 2013***

Anziks Y, Sternberg A. Exercise in neuromuscular disease.. *Muscle & Nerve* 2013;48(1):3-20.

***Bach 2010***

Bach JR, Gonçalves MR, Hamdani I, Winck JC. Extubation of patients with neuromuscular weakness. *Chest* 2010;137(5):1033-9.

***Epstein 1998***

Epstein SK, Ciuboratu RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation.. *Am J Respir Crit Care Med* 1998;158:489-93.

***Fan 2014***

Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al. An official American Thoracic Society Clinical Practice Guideline: the diagnosis of intensive care unit-acquired weakness in adults. *Am J Respir Crit Care Med* 2014;190(12):1437-46.

***Hermans 2015***

Hermans G, den Berghe GV. Clinical review: intensive care unit acquired weakness. *Critical Care* 2015;19:274-83.

***Higgins 2011***

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

***Kim 2017***

Kim SM, Kang SW, Choi YC, Park YG, Won YH. Successful extubation after weaning failure by noninvasive ventilation in patients with neuromuscular disease: case series.. *Ann Rehabil Med* 2017;41(3):450-5.

***RevMan 2014***

Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

**Rezanina 2012**

Reznia K, Goldenberg FD, White S. Neuromuscular disorders and acute respiratory failure: diagnosis and management. *Neurologic Clinics* 2012;30(1):161-85.

**Sklar 2017**

Sklar MC, Burns K, Rittayamai N, Lanys A, Rauseo M, Chen L, et al. Effort to breathe with various spontaneous breathing trial techniques. A physiological meta-analysis. *Am J Respir Crit Care Med* 2017;195(11):1477-85.

**Tsara 2015**

Tsara V, Moisiadis N, Antoniadou M, Serasli E. Characteristics and outcome of patients with difficult weaning from mechanical ventilation: an 18 years' experience of a respiratory intermediate unit attached to a pulmonary department. *Hippokratia* 2015;19(1):37-40.

**Vassilakopoulos 2004**

Vassilakopoulos T, Petrof BF. Ventilator-induced diaphragmatic dysfunction. *Am J Respir Care Med* 2004;169:336-41.

**Zein 2016**

Zein H, Baratloo A, Negida A, Safari S. Ventilator weaning and spontaneous breathing trials: an educational review. *Emergency* 2016;4(2):65-71.

## Note from the Editors: Instructions for reviewers of study protocols

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Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

*BMJ Open* will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scored as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

# BMJ Open

## Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Neurology
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## Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on February 15th 2019 (registration number CRD42019117393).

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### Contributorship statement

- SCBN: screen titles, abstracts and full text to identify studies for inclusion or exclusion; extract study characteristics; extract outcome data; transfer data into RevMan; assess risk of bias
- RTC: screen titles, abstracts and full text to identify studies for inclusion or exclusion; extract outcome data; check outcome data entries; spot-check study characteristics for accuracy; assess risk of bias
- IL: development of the text; statistical analysis, revision of the final text
- VRR: development of the text; statistical analysis, revision of the final text
- GAF: discussion about the disagreements the two authors have in any issues; screen studies the other two authors have authored

### Abstract

**Introduction:** Neuromuscular diseases (NMD) are characterized by progressive muscular impairment. The muscle weakness is directly related to respiratory muscles weakness, causing reduction in vital capacity, especially when associated with mechanical ventilation (MV). Conventional MV weaning in NMD is generally difficult. Weaning process can be conducted in protocols such as: “T” piece or Pressure Support Ventilaton. Weaning failure is frequent because of muscle weakness. Protocol aim is to assess the effects of different weaning protocols in NMD patients receiving invasive MV in weaning success rate, duration of weaning, ICU stay, hospital stay and ICU



mortality. **Methods and analysis:** a search will be carried in the Cochrane Neuromuscular Specialised Register, MEDLINE, EMBASE, Web of Science, Scopus, United States National Institutes of Health Clinical Trials Registry, ClinicalTrials.gov and World Health Organization International Clinical Trial Registry Protal, of randomized controlled trials and quasi-RCTs. Inclusion criteria of individuals are adults (above sixteen years old) and children (from five to sixteen years old), with clinical diagnosis of NMD (muscular dystrophy, amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillian Barré Syndrome, severe inherited neuropathies, metabolic myopathies, inflammatory myopathies, mitochondrial diseases) of any gender. All patients ventilated for at least 48 hours due to respiratory failure and clinically considered ready for weaning. Other respiratory or cardiovascular diagnosis associated will not be included. Intervention assessed will be weaning from MV using a protocol with 30 minutes to two hours of spontaneous breathing trial at the end point. All comparisons of different protocols will be considered. **Ethics and dissemination:** Formal ethical approval is not required as primary data will not be collected, since it will be a systematic review. All studies included should have ethical committee approval. The results will be disseminated through a peer-reviewed publication and in conferences and congresses or symposia.

### **Strengths and limitations of this study**

1. (strength): Help to identify the best way to conduct MV weaning in patients with NMD.
2. (limitation): Difficulty in finding articles that meet the inclusion criteria;
3. (limitation): Very different approaches in the weaning process of patients with NMD;
4. (limitation): NMD heterogeneity.

### **Introduction**

Neuromuscular disease can be defined as a chronic and progressive disease, which may present with different clinical characteristics, in which its pattern is based on the location where the injury occurs in a motor unit.<sup>1,2</sup> Neuromuscular diseases are characterized by progressive muscular impairment, with difficulty in ambulation, swallowing and ventilation, with progressive reduction of vital capacity and increased work of breathing.<sup>3</sup> These changes lead to the development of chronic respiratory insufficiency, which is an important cause of prolonged ventilatory dependence.<sup>4</sup>

Muscle weakness is directly related to weakness of respiratory muscles, especially the diaphragm. Diaphragmatic weakness, often found in patients with NMD causes a reduction in the capacity to generate force, especially when associated with the use of controlled mechanical ventilation.<sup>5</sup>

Intensive care unit (ICU) admission, regardless of the presence of NMD, may be a cause of neuromuscular disorders that lead to muscle impairment.<sup>6</sup> It is estimated that such a condition occurs in up to 62% of critically ill patients in the ICU.<sup>7</sup> The NMD patients experience this respiratory impairment, in general, by a large proportion of motor units that innervate the respiratory muscles affected.<sup>2</sup>

Some risk factors such as use of sedatives, malnutrition, systemic inflammation, and prolonged mechanical ventilation may further impair the neuromuscular performance of people admitted to ICU.<sup>8</sup>

The majority of critically ill patients admitted to ICU require ventilatory support for acute or chronic respiratory failure<sup>3</sup>, specially the NMD ones. In addition, the pattern of neuromuscular abnormalities associated with critical illness, defined as ICU-acquired

1  
2  
3 weakness (ICUAW)<sup>4</sup>, can lead to prolonged mechanical ventilation, a longer hospital  
4 stay and increased ventilation.<sup>4</sup>

5 The emergence of respiratory symptoms, with progressive hypercapnia, can lead  
6 to death from respiratory failure.<sup>3</sup> Long-term invasive or non-invasive mechanical  
7 ventilation is the main intervention for people who present with acute respiratory  
8 acidosis; progressive decline in vital capacity (< 10 to 15 mL/kg); or progressive decline  
9 in maximal inspiratory pressure (< 20 to 30 cmH<sub>2</sub>O).<sup>3,9</sup>

10 Weaning from mechanical ventilation is the process of transition to spontaneous  
11 ventilation.<sup>10</sup> In people with neuromuscular diseases, conventional weaning is generally  
12 not possible.<sup>11</sup>

13 Weaning difficulty may occur in different kind of patients, such as elderly with  
14 prolonged ICU hospitalization, people with chronic respiratory diseases or  
15 neuromuscular diseases.<sup>12</sup> Therefore, the decision to progress to extubation is more  
16 challenging in this group of people with advanced respiratory muscle weakness, and this  
17 can lead to a need for tracheostomy and prolonged mechanical ventilation.<sup>4</sup>

18 Difficult weaning can be defined as a failure of initial weaning and a  
19 requirement for up to three trials of spontaneous breathing or seven days of mechanical  
20 ventilation to achieve extubation.<sup>10,13</sup>

21 The weaning process may be conducted in different protocols such as:

- 22 • “T” piece: in which the patient receives only supplemental oxygen through a T-  
23 shaped tube connected to an endotracheal tube (orotracheal or tracheostomy)<sup>10</sup>;
- 24 • Continuous positive airway pressure (CPAP): the weaning protocol involves using  
25 a continuous pressure, equal to the previous positive end-expiratory pressure  
26 (PEEP) level used before<sup>10</sup>;
- 27 • Pressure support: use of progressive lower levels of inspiratory pressure support  
28 until it reaches 5 to 8 cmH<sub>2</sub>O.<sup>10</sup>

29 Successful weaning is defined as the ability to maintain spontaneous ventilation  
30 without the need for re-intubation and invasive mechanical ventilation for 48 hours after  
31 extubation.<sup>10</sup> For patients with neuromuscular diseases, due to the difficulty of weaning,  
32 it may be also defined as the absence of a need for tracheostomy and mechanical  
33 ventilation for five days after extubation.<sup>4</sup>

34 Post-weaning monitoring should observe whether two of the following  
35 findings are present: respiratory acidosis (pH < 7.35; PaCO<sub>2</sub> > 45 mmHg); SpO<sub>2</sub> < 90%  
36 or PaO<sub>2</sub> < 60 mmHg with FiO<sub>2</sub> > 50%; RR > 35 rpm; decreased level of consciousness,  
37 restlessness or excessive sweating; or signs suggestive of respiratory muscle fatigue,  
38 such as the use of accessory muscles or paradoxical movement of the abdomen, in order  
39 to determinate the need to reestablish mechanical ventilation again.<sup>4,10</sup>

40 Weaning failure from invasive ventilation is a frequent occurrence in people  
41 with neuromuscular disease because of muscle weakness and gradual hypercapnia.<sup>4</sup>  
42 Thus, keeping the patient with non-invasive ventilation may be an alternative solution to  
43 discharge the patient from the ICU if indicated, even after a failure weaning trial, and  
44 carry out a future weaning just when and if possible,<sup>4,12</sup> but this whole process  
45 significantly increases health costs with this patient population.

## 46 Objectives

47 The aim of this systematic review is to assess the effects of different weaning  
48 protocols in people with neuromuscular diseases receiving invasive mechanical  
49 ventilation. Our secondary aim is to assess how the different protocols affect weaning  
50 success, duration of weaning, duration of stay in the ICU, duration of hospital stay, and  
51 ICU mortality, and also to assess adverse effects.

## Methods

### Eligibility criteria

Studies will be selected according to the criteria outlined below.

### *Study designs*

We will include randomised controlled trials (RCTs) and quasi-RCTs (experimental study with participants subjected to some type of intervention or control group, and with the same outcome of interest measured. But in this kind of study, also known as non-randomized trial, populations are subjected to any of the groups using other methods of allocating, usually not truly random). Other study types, such as non-randomised trials, cross-over studies and case control studies will be described in the Discussion section of the review, but they will not be included in the Results section. We will include studies reported as full-text, those published as abstract only, and unpublished data. There will be no restrictions as to language.

### *Participants*

We will consider for inclusion adults (above sixteen years old) and children (from five to sixteen years old) people with a clinical diagnosis of a neuromuscular disease (muscular dystrophy of any origin including Duchenne muscular dystrophy, amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillian Barré Syndrome, severe inherited neuropathies, metabolic myopathies (Pompe disease), inflammatory myopathies, mitochondrial diseases) of any gender.

We will consider all patients ventilated for at least 48 hours with orotracheal tube or tracheostomy because of acute respiratory failure, and considered by physicians to be ready for weaning according to clinical criteria and weaning parameters. No patients with other respiratory or cardiovascular clinical diagnosis associated will be included, nor patients with mixed NMD diagnosis.

If any subset of participants with NMD is analyzed, these patients will be included.

### *Interventions*

The intervention assessed will be the process of weaning from mechanical ventilation in people with neuromuscular diseases using a protocol with criteria for deciding if the patient is ready for extubation with 30 minutes to two hours spontaneous breathing trial (SBT) at the end point of the protocol.

We will consider the following protocols for inclusion.

1. Pressure support ventilation, with gradual reduction of the support pressure
2. Synchronized intermittent mandatory ventilation, with gradual reduction of respiratory rate and support pressure
3. Continuous positive airway pressure, with gradual reduction of applied pressure
4. 'T' piece, with progressive increase of spontaneous ventilation time.

### *Comparators*

We will consider any comparisons of the different protocols.

The protocols will also be compared in relation to the classification of weaning outcomes, in order to identify the which protocols develop better outcomes.

- Simple – successful after first attempt;
- Difficult – require up to three attempts (or less than 7 days to reach success);
- Prolonged – require more than 7 days to reach success).

## ***Outcomes***

### ***Primary outcomes***

Weaning success, defined as the ability to maintain spontaneous ventilation without the need for reintubation and invasive mechanical ventilation for 48 hours after extubation.<sup>10</sup>

### ***Secondary outcomes***

- Duration of weaning in patients with acute and prolonged mechanical ventilation – defined as the time between the weaning protocol initiation and the moment of extubation;
- Duration of ICU stay in patients with acute and prolonged mechanical ventilation – defined as the time between ICU admission and ICU discharge;
- Duration of hospital stay in patients with acute and prolonged mechanical ventilation – defined as the time between hospital admission and hospital discharge;
- ICU mortality rate in patients with acute and prolonged mechanical ventilation – defined as the mortality rate during ICU stay.
- Incidence of pneumothorax during mechanical ventilation period.
- Incidence of ventilation associated pneumonia.

## ***Language***

We will include articles reported in English and other languages. There will be no restrictions.

## **Information sources**

### ***Electronic searches***

We will search the Cochrane Neuromuscular Specialised Register (The Cochrane Library, current issues), MEDLINE, EMBASE, Web of Science and Scopus. We will scan conference abstracts for relevant studies.

We will also search the United States National Institutes of Health Clinical Trials Registry, ClinicalTrials.gov (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Portal (apps.who.int/trialsearch/).

We will search all databases from January 2009 to December 2019, and we will impose no restriction on language of publication.

We will identify non-randomised studies for inclusion in the discussion from the same search results.

We will search reference lists of all relevant and included trials and review articles for additional references. We will search for errata or retractions of included trials. We will also search relevant manufacturers' websites for trial information. And we will search grey literature, in reports of technical research and projects related to government programs, to identify other studies.

We will contact study authors of included trials, to identify additional trials whether published or unpublished.

If no RCTs or quasi-RCTs in this area are not found the authors will review other well-designed observational studies, where the population (NMD), intervention (mechanical ventilation weaning) and outcome (weaning success) are clearly documented, in the 'Discussion' section of the review. We will identify these (non-

1  
2  
3 randomised studies) via a search in MEDLINE (from inception to the present),  
4 EMBASE (from inception to the present), Web of Science (from inception to the  
5 present) and Scopus (from inception to the present). This will be done in order to give a  
6 comprehensive descriptive narrative of any non-randomised data.  
7

### 8 9 **Search strategy**

10 Search terms will include: 'neuromuscular disease' or all other terms compatible  
11 with clinical diagnoses of these types of diseases, such as 'muscular dystrophy',  
12 'Duchenne muscular dystrophy', 'amyotrophic lateral sclerosis', 'congenital myasthenia',  
13 'myasthenia gravis', 'congenital myopathy', 'spinal muscular atrophy', 'Guillain Barré  
14 Syndrome', 'severe inherited neuropathies', 'metabolic myopathies', 'Pompe disease',  
15 'inflammatory myopathies' and 'mitochondrial diseases' combined with 'mechanical  
16 ventilation' or 'artificial respiration' or 'mechanical ventilation weaning' or 'ventilator  
17 weaning' or 'respirator weaning'; and all the combination between them.  
18  
19

### 20 21 **Study records**

#### 22 *Selection of studies*

23 Two review authors (SCBN, RTC) will independently screen titles and abstracts  
24 of all the potential studies retrieved by the search for inclusion and code them as  
25 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will identify  
26 and exclude duplicates and collate multiple reports of the same study so that each study  
27 rather than each report is the unit of interest in the review. We will retrieve full-text  
28 study reports/publications, and two review authors (SCBN, RTC) will independently  
29 screen the full text and identify studies for inclusion, and identify and record reasons for  
30 exclusion of the ineligible studies.  
31

32 We will resolve any disagreements through discussion or, if required, through  
33 consultation with a third review author (GAFF).

34 We will report the selection process in sufficient detail to complete a PRISMA  
35 flow diagram and 'Characteristics of excluded studies' table.  
36

#### 37 *Data extraction and management*

38 We will use a data extraction form that we will initially pilot on at least one trial  
39 included in the review to collect study characteristics and outcome data. One review  
40 author (SCBN) will extract study characteristics from included trials. We will collect  
41 information on study design and setting, participant characteristics (including disease  
42 severity and age), study eligibility criteria, details of the intervention(s) given, the  
43 outcomes assessed, the source of study funding and any conflicts of interest stated by  
44 the investigators.  
45

46 Two review authors (SCBN, RTC) will independently extract outcome data from  
47 included trials. We will note in the 'Characteristics of included studies' table if the trials  
48 did not report outcome data in a usable way. We will resolve any disagreements by  
49 consensus or consult a third review author (GAFF). One review author (SCBN) will  
50 transfer data into Review Manager (RevMan) 5.3.<sup>14</sup> A second review author (RTC) will  
51 check the outcome data entries.  
52

53 The same review author (RTC) will spot-check study characteristics for  
54 accuracy against the trial report. When reports require translation, the translator will  
55 extract data directly using a data extraction form. To minimize bias in the review  
56 process, the review authors will not screen studies for inclusion, extract data, or assess  
57 the risk of bias in trials they themselves have authored. In such circumstances, we will  
58 involve a third review author (GAFF).  
59  
60

## Risk of Bias individual studies

Two review authors (SCBN, RTC) will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.<sup>15</sup> These authors will resolve disagreements by discussion or by involving another review author (GAFF).

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 judgment 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 (for example for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, 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.

If we are able to pool a sufficient number of studies, i.e. more than 10 trials,<sup>15</sup> we will create and examine a funnel plot to explore possible small study biases.

## Data Synthesis

### *Measures of treatment effect*

We will analyze dichotomous data as risk ratios (RR) with corresponding 95% CI and continuous data as mean difference (MD) with 95% CI, or as standardised mean difference (SMD) with 95% CI for results across studies with outcomes that are conceptually the same but measured in different ways. We will enter data presented as a scale with a consistent direction of effect.

We will undertake meta-analyses only where this is meaningful, that is if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. This will be identified if there are two or more trials with comparable populations and interventions.

Where a single trial reports multiple trial arms, we will include only the arms relevant to the review question.

All data will be pooled according to age group, dividing them into two groups (adults - over sixteen years old, and children - between five and sixteen years old). After this grouping the analyzes will be done, firstly, comparing the success rate and failure rate in each of the groups. Subsequently the data will also be evaluated taking into consideration the weaning outcomes in simple, difficult and prolonged (as described in the types of interventions).

### *Unit of analysis issues*

We do not expect to have any cross-over or cluster randomised controlled trials, since weaning is a one-off event and also due to the lack of control group, since all

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3 patients are submitted to the same intervention, which is weaning from mechanical  
4 ventilation.  
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7

### 8 Assessment of heterogeneity

9 We will use the  $I^2$  statistic to measure heterogeneity among the trials in each  
10 analysis. If we identify substantial unexplained heterogeneity, we will report both fixed-  
11 effect and random-effects results and explore possible causes by prespecified subgroup  
12 analysis.  
13

14 We will be follow the rough guide to interpretation outlined in the Cochrane  
15 Handbook for Systematic Reviews of Interventions.

- 16 • 0% to 40%: might not be important;
- 17 • 30% to 60%: may represent moderate heterogeneity;
- 18 • 50% to 90%: may represent substantial heterogeneity; and
- 19 • 75% to 100%: considerable heterogeneity.  
20  
21  
22

### 23 Data synthesis

24 If the review includes more than one comparison that cannot be included in the  
25 same analysis, we will report the results for each comparison separately.  
26  
27

#### 28 'Summary of findings' table

- 29 • We will create a 'Summary of findings' table using the following outcomes.
- 30 • Weaning success
- 31 • Duration of weaning (time difference between weaning protocol initiation and the  
32 moment of extubation moment).
- 33 • Duration of ICU stay
- 34 • Duration of hospital stay
- 35 • ICU mortality rate in patients with acute and prolonged mechanical ventilation –  
36 defined as the mortality rate during ICU stay.
- 37 • Incidence of pneumothorax during mechanical ventilation period.
- 38 • Incidence of ventilation associated pneumonia.  
39  
40

41 We will use the five GRADE considerations (study limitations, consistency of  
42 effect, imprecision, indirectness, and publication bias) to assess the quality of a body of  
43 evidence (studies that contribute data for the prespecified outcomes). We will use  
44 methods and recommendations described in the Cochrane Handbook for Systematic  
45 Reviews of Interventions<sup>15</sup> using GRADEpro software (GRADEpro GDT). We will  
46 justify all decisions to down- or upgrade the quality of studies using footnotes, and we  
47 will make comments to aid readers' understanding of the review where necessary. Two  
48 authors will independently grade the quality of the evidence. They will resolve  
49 disagreements by discussion and by consultation with a third review author.  
50  
51

### 52 Subgroup analysis and investigation of heterogeneity

- 53 • We plan to perform the following subgroup analyses.
- 54 • Simple weaning: successful after first attempt
- 55 • Difficult weaning: require up to three attempts
- 56 • Prolonged weaning: require more than 7 days to reach success
- 57 • Children: from five to sixteen years old
- 58 • Adults: above sixteen years old  
59  
60

1  
2  
3 We will use both primary and secondary outcome measures in all subgroup  
4 analyses. We will use the formal test for subgroup interactions in Review Manager  
5 5.3.<sup>14</sup>  
6

### 7 Sensitivity analysis

8 We plan to undertake the following sensitivity analyses.

9  
10 1. Repeat the analysis by excluding studies at high risk of bias (sequence  
11 generation, allocation concealment, blinding of personnel, outcome assessment, and  
12 attrition).

13 If there are one or more very large trials, we will repeat the analysis by  
14 excluding them to examine how much they dominate the results.

### 15 Reaching conclusions

16 We will base our review conclusions only on findings from the quantitative or  
17 narrative synthesis of included trials. We will avoid making recommendations for  
18 practice. Our implications for research will suggest priorities for future research and  
19 outline the remaining uncertainties in the area.  
20  
21

## 22 **Patient and Public Involvement**

23 In the present protocol of systematic review and in the subsequent  
24 systematic review there will be no involvement of patients or public.

25 The paper proposes to use results previously authorized and published by other  
26 authors, without there being any need for patient or public involvement. The research  
27 question was developed based on the questions raised by other authors, most of the time  
28 according to the clinical difficulty and necessity of improve the weaning protocols for  
29 this population.  
30

31 The results of the present study will be published in indexed journal so it can be  
32 available for NMD patients, in general, and public, specially health professionals.  
33  
34

## 35 **Funding statement**

36 This research received no specific grant from any funding agency in the public,  
37 commercial or not-for-profit sectors.  
38  
39

## 40 **Declarations of interest**

- 41 • SCBN: non-conflicted
  - 42 • RTC: non-conflicted
  - 43 • IL: non-conflicted
  - 44 • VRR: non-conflicted
  - 45 • GAF: non-conflicted
- 46  
47

## 48 **Conclusion**

49 This systematic review will provide evidence in different weaning protocols that  
50 can be applied to the NMD patients, analyzing the weaning success rate, leading to  
51 extubation. The hypothesis is that one specific protocol, probably Pressure Support  
52 strategy, has higher success weaning rates.  
53

54 Where sufficient data are available, we will conduct a meta-analysis to confirm  
55 the relationship between the different protocols and duration of weaning, duration of  
56 stay in the ICU, duration of hospital stay and ICU mortality. It will also be able to  
57 assess adverse effects of weaning protocols that fail to lead to extubation.  
58

59 Moreover, if the hypothesis is confirmed, the review will clarify the reasons  
60 Pressure Support weaning strategy interfere to higher success weaning rates.



Overall, the review will complement the evidence base on mechanical ventilation weaning for NMD patients.

## References

1. Anziks Y, Sternberg A. Exercise in neuromuscular disease. *Muscle & Nerve* 2013;48(1):3-20.
2. Rezania K, Goldenberg FD, White S. Neuromuscular disorders and acute respiratory failure: diagnosis and management. *Neurologic Clinics* 2012;30(1):161-85.
3. Ambrosino N, Carpené N, Gherardi M. Chronic respiratory failure care for neuromuscular diseases in adults. *European Respiratory Journal* 2009;34:441-51.
4. Kim SM, Kang SW, Choi YC, Park YG, Won YH. Successful extubation after weaning failure by noninvasive ventilation in patients with neuromuscular disease: case series. *Ann Rehabil Med* 2017;41(3):450-5.
5. Vassilakopoulos T, Petrof BF. Ventilator-induced diaphragmatic dysfunction. *Am J Respir Care Med* 2004;169:336-41.
6. Bach JR, Gonçalves MR, Hamdani I, Winck JC. Extubation of patients with neuromuscular weakness. *Chest* 2010;137(5):1033-9.
7. Epstein SK, Ciuboratu RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. *Am J Respir Crit Care Med* 1998;158:489-93.
8. Hermans G, den Berghe GV. Clinical review: intensive care unit acquired weakness. *Critical Care* 2015;19:274-83.
9. Chevrolet JC, Deléamont P. Repeated Vital Capacity Measurements as Predictive Parameters for Mechanical Ventilation Need and Weaning Success in the Guillain-Barre Syndrome. *Am Rev Respir Dis* 1991;144:S814-18.
10. Zein H, Baratloo A, Negida A, Safari S. Ventilator weaning and spontaneous breathing trials: an educational review. *Emergency* 2016;4(2):65-71.
11. Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al. An official American Thoracic Society Clinical Practice Guideline: the diagnosis of intensive care unit-acquired weakness in adults. *Am J Respir Crit Care Med* 2014;190(12):1437-46.
12. Tsara V, Moisiadis N, Antoniadou M, Serasli E. Characteristics and outcome of patients with difficult weaning from mechanical ventilation: an 18 years' experience of a respiratory intermediate unit attached to a pulmonary department. *Hippokratia* 2015;19(1):37-40.
13. Sklar MC, Burns K, Rittayamai N, Lanys A, Rauseo M, Chen L, et al. Effort to breathe with various spontaneous breathing trial techniques. A physiological meta-analysis. *Am J Respir Crit Care Med* 2017;195(11):1477-85.
14. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
15. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

## PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Pages
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	2, 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4, 5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of	6

		coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7, 8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7, 8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5, 6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7, 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015 Jan 2;349(jan02 1):g7647.

# BMJ Open

## Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Respiratory medicine, Intensive care
Keywords:	Neuromuscular disease < NEUROLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine), Adult intensive & critical care < INTENSIVE & CRITICAL CARE

SCHOLARONE™  
Manuscripts

## Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on February 15th 2019 (registration number CRD42019117393).

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### Contributorship statement

- SCBN: screen titles, abstracts and full text to identify studies for inclusion or exclusion; extract study characteristics; extract outcome data; transfer data into RevMan; assess risk of bias
- RTC: screen titles, abstracts and full text to identify studies for inclusion or exclusion; extract outcome data; check outcome data entries; spot-check study characteristics for accuracy; assess risk of bias
- IL: development of the text; statistical analysis, revision of the final text
- VRR: development of the text; statistical analysis, revision of the final text
- GAF: discussion about the disagreements the two authors have in any issues; screen studies the other two authors have authored

### Abstract

**Introduction:** Neuromuscular diseases (NMD) are characterized by progressive muscular impairment. The muscle weakness is directly related to respiratory muscles weakness, causing reduction in vital capacity, especially when associated with mechanical ventilation (MV). Conventional MV weaning in NMD is generally difficult. Weaning process can be conducted in protocols such as: “T” piece or Pressure Support Ventilaton. Weaning failure is frequent because of muscle weakness. Protocol aim is to assess the effects of different weaning protocols in NMD patients receiving invasive MV in weaning success rate, duration of weaning, ICU stay, hospital stay and ICU

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2  
3 mortality. **Methods and analysis:** a search will be carried in the Cochrane  
4 Neuromuscular Specialised Register, MEDLINE, EMBASE, Web of Science, Scopus,  
5 United States National Institutes of Health Clinical Trials Registry, ClinicalTrials.gov  
6 and World Health Organization International Clinical Trial Registry Protal, of  
7 randomized controlled trials and quasi-RCTs. Inclusion criteria of individuals are adults  
8 (above sixteen years old) and children (from five to sixteen years old), with clinical  
9 diagnosis of NMD (muscular dystrophy, amyotrophic lateral sclerosis, congenital  
10 myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillian  
11 Barré Syndrome, severe inherited neuropathies, metabolic myopathies, inflammatory  
12 myopathies, mitochondrial diseases) of any gender. All patients ventilated for at least 48  
13 hours due to respiratory failure and clinically considered ready for weaning. Other  
14 respiratory or cardiovascular diagnosis associated will not be included. Intervention  
15 assessed will be weaning from MV using a protocol with 30 minutes to two hours of  
16 spontaneous breathing trial at the end point. All comparisons of different protocols will  
17 be considered. **Ethics and dissemination:** Formal ethical approval is not required as  
18 primary data will not be collected, since it will be a systematic review. All studies  
19 included should have ethical committee aproval. The results will be disseminated  
20 through a peer-reviewed publication and in conferences and congresses or symposia.  
21  
22  
23  
24

### 25 **Strengths and limitations of this study**

- 26 1. This study will help to identify the best way to conduct MV weaning in  
27 patients with NMD, improving the outcomes of this population when using  
28 MV.
- 29 2. It will be difficult to find articles that meet the inclusion criteria leading to  
30 greater difficulty for statistical analysis.
- 31 3. There are very different approaches in the weaning process of patients with  
32 NMD, and that will bring difficult to compare the protocols.
- 33 4. Too many NMD will need to be included because of NMD heterogeneity.  
34  
35

### 36 **Introduction**

37 Neuromuscular disease can be defined as a chronic and progressive disease,  
38 which may present with different clinical characteristics, in which its pattern is based on  
39 the location where the injury occurs in a motor unit.<sup>1,2</sup> Neuromuscular diseases are  
40 characterized by progressive muscular impairment, with difficulty in ambulation,  
41 swallowing and ventilation, with progressive reduction of vital capacity and increased  
42 work of breathing.<sup>3</sup> These changes lead to the development of chronic respiratory  
43 insufficiency, which is an important cause of prolonged ventilatory dependence.<sup>4</sup>  
44  
45

46 Muscle weakness is directly related to weakness of respiratory muscles,  
47 especially the diaphragm. Diaphragmatic weakness, often found in patients with NMD  
48 causes a reduction in the capacity to generate force, especially when associated with the  
49 use of controlled mechanical ventilation.<sup>5</sup>

50 Intensive care unit (ICU) admission, regardless of the presence of NMD, may be  
51 a cause of neuromuscular disorders that lead to muscle impairment.<sup>6</sup> It is estimated that  
52 such a condition occurs in up to 62% of critically ill patients in the ICU.<sup>7</sup> The NMD  
53 patients experience this respiratory impairment, in general, by a large proportion of  
54 motor units that innervate the respiratory muscles affected.<sup>2</sup>  
55

56 Some risk factors such as use of sedatives, malnutrition, systemic inflammation,  
57 and prolonged mechanical ventilation may further impair the neuromuscular  
58 performance of people admitted to ICU.<sup>8</sup>  
59  
60

1  
2  
3 The majority of critically ill patients admitted to ICU require ventilatory support  
4 for acute or chronic respiratory failure<sup>3</sup>, specially the NMD ones. In addition, the pattern  
5 of neuromuscular abnormalities associated with critical illness, defined as ICU-acquired  
6 weakness (ICUAW)<sup>4</sup>, can lead to prolonged mechanical ventilation, a longer hospital  
7 stay and increased ventilation.<sup>4</sup>  
8

9 The emergence of respiratory symptoms, with progressive hypercapnia, can lead  
10 to death from respiratory failure.<sup>3</sup> Long-term invasive or non-invasive mechanical  
11 ventilation is the main intervention for people who present with acute respiratory  
12 acidosis; progressive decline in vital capacity (< 10 to 15 mL/kg); or progressive decline  
13 in maximal inspiratory pressure (< 20 to 30 cmH<sub>2</sub>O).<sup>3,9</sup>  
14

15 Weaning from mechanical ventilation is the process of transition to spontaneous  
16 ventilation.<sup>10</sup> In people with neuromuscular diseases, conventional weaning is generally  
17 not possible.<sup>11</sup>

18 Weaning difficulty may occur in different populations, such as elderly with  
19 prolonged ICU hospitalization, people with chronic respiratory diseases or  
20 neuromuscular diseases.<sup>12</sup> Therefore, the decision to progress to extubation is more  
21 challenging in this group of people with advanced respiratory muscle weakness, and this  
22 can lead to a need for tracheostomy and prolonged mechanical ventilation.<sup>4</sup>  
23

24 Difficult weaning can be defined as the requirement of up to three spontaneous  
25 breathing trials in a period of no longer than seven days of mechanical ventilation to  
26 achieve extubation.<sup>10,13</sup>  
27

28 The weaning process may be conducted in different protocols such as:

- 29 • “T” piece: in which the patient receives only supplemental oxygen through a T-  
30 shaped tube connected to an endotracheal tube (orotracheal or tracheostomy)<sup>10</sup>;
- 31 • Continuous positive airway pressure (CPAP): the weaning protocol involves using  
32 a continuous pressure, equal to the previous positive end-expiratory pressure  
33 (PEEP) level used before<sup>10</sup>;
- 34 • Pressure support: use of progressive lower levels of inspiratory pressure support  
35 until it reaches 5 to 8 cmH<sub>2</sub>O.<sup>10</sup>  
36

37 Successful weaning is defined as the ability to maintain spontaneous ventilation  
38 without the need for re-intubation and invasive mechanical ventilation for 48 hours after  
39 extubation.<sup>10</sup> For patients with neuromuscular diseases, due to the difficulty of weaning,  
40 it may be also defined as the absence of a need for tracheostomy and mechanical  
41 ventilation for five days after extubation.<sup>4</sup>  
42

43 Post-weaning monitoring should observe whether two of the following  
44 findings are present: respiratory acidosis (pH < 7.35; PaCO<sub>2</sub> > 45 mmHg); SpO<sub>2</sub> < 90%  
45 or PaO<sub>2</sub> < 60 mmHg with FiO<sub>2</sub> > 50%; RR > 35 rpm; decreased level of consciousness,  
46 restlessness or excessive sweating; or signs suggestive of respiratory muscle fatigue,  
47 such as the use of accessory muscles or paradoxical movement of the abdomen, in order  
48 to determinate the need to reestablish mechanical ventilation again.<sup>4,10</sup>  
49

50 Weaning failure from invasive ventilation is frequent in people with  
51 neuromuscular disease due to muscle weakness and gradual hypercapnia.<sup>4</sup> In this way  
52 the non-invasive ventilation, even after weaning failure, is an option. And a future  
53 weaning can be conducted when and if clinically possible.<sup>4,12</sup> Although this whole  
54 process significantly increases health costs with this patient population.  
55

## 56 Objectives

57 The aim of this systematic review is to assess the effects of different weaning  
58 protocols in people with neuromuscular diseases receiving invasive mechanical  
59 ventilation. Our secondary aim is to assess how the different protocols affect weaning  
60

1  
2  
3 success, duration of weaning, duration of stay in the ICU, duration of hospital stay, and  
4 ICU mortality, and also to assess adverse effects.  
5

## 6 **Methods**

### 7 **Eligibility criteria**

8  
9 Studies will be selected according to the criteria outlined below.  
10  
11

### 12 ***Study designs***

13 We will include randomized controlled trials (RCTs) and quasi-RCTs  
14 (experimental study with participants subjected to some type of intervention or control  
15 group, and with the same outcome of interest measured. But in this kind of study, also  
16 known as non-randomized trial, populations are subjected to any of the groups using  
17 other methods of allocating, usually not truly random). Other study types, such as non-  
18 randomized trials, cross-over studies and case control studies will be described in the  
19 Discussion section of the review, but they will not be included in the Results section.  
20 We will include studies reported as full-text, those published as abstract only, and  
21 unpublished data. There will be no restrictions as to language.  
22  
23  
24

### 25 ***Participants***

26 We will consider for inclusion adults (above sixteen years old) and children  
27 (from five to sixteen years old) people with a clinical diagnosis of a neuromuscular  
28 disease (muscular dystrophy of any origin including Duchenne muscular dystrophy,  
29 amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital  
30 myopathy, spinal muscular atrophy, Guillian Barré Syndrome, severe inherited  
31 neuropathies, metabolic myopathies (Pompe disease), inflammatory myopathies,  
32 mitochondrial diseases) of any gender.  
33

34 We will consider all patients ventilated for at least 48 hours with orotracheal  
35 tube or tracheostomy because of acute respiratory failure, and considered by physicians  
36 to be ready for weaning according to clinical criteria and weaning parameters. No  
37 patients with other respiratory or cardiovascular clinical diagnosis associated will be  
38 included, nor patients with mixed NMD diagnosis.  
39

40 If any subset of participants with NMD is analyzed, these patients will be  
41 included.  
42

### 43 ***Interventions***

44 The intervention assessed will be the process of weaning from mechanical  
45 ventilation in people with neuromuscular diseases using a protocol with criteria for  
46 deciding if the patient is ready for extubation with 30 minutes to two hours spontaneous  
47 breathing trial (SBT) at the end point of the protocol.  
48

49 We will consider the following protocols for inclusion.

- 50 1. Pressure support ventilation, with gradual reduction of the support pressure
- 51 2. Synchronized intermittent mandatory ventilation, with gradual reduction of  
52 respiratory rate and support pressure
- 53 3. Continuous positive airway pressure, with gradual reduction of applied  
54 pressure
- 55 4. 'T' piece, with progressive increase of spontaneous ventilation time.  
56  
57

### 58 ***Comparators***

59 We will consider any comparisons of the different protocols.  
60



1  
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3 The protocols will also be compared in relation to the classification of weaning  
4 outcomes, in order to identify the which protocols develop better outcomes.

- 5 • Simple – successful after first attempt;
- 6 • Difficult – require up to three attempts (or less than 7 days to reach success);
- 7 • Prolonged – require more than 7 days to reach success).
- 8
- 9

### 10 ***Outcomes***

#### 11 Primary outcomes

12 Weaning success, defined as the ability to maintain spontaneous ventilation  
13 without the need for reintubation and invasive mechanical ventilation for 48 hours after  
14 extubation.<sup>10</sup>

#### 15 Secondary outcomes

- 16 • Duration of weaning in patients with acute and prolonged mechanical ventilation  
17 – defined as the time between the weaning protocol initiation and the moment of  
18 extubation;
- 19 • Duration of ICU stay in patients with acute and prolonged mechanical ventilation  
20 – defined as the time between ICU admission and ICU discharge;
- 21 • Duration of hospital stay in patients with acute and prolonged mechanical  
22 ventilation – defined as the time between hospital admission and hospital  
23 discharge;
- 24 • ICU mortality rate in patients with acute and prolonged mechanical ventilation –  
25 defined as the mortality rate during ICU stay.
- 26 • Incidence of pneumothorax during mechanical ventilation period.
- 27 • Incidence of ventilation associated pneumonia.
- 28
- 29
- 30
- 31

### 32 ***Language***

33 We will include articles reported in English and other languages. There will be  
34 no restrictions.

### 35 **Information sources**

#### 36 Electronic searches

37 We will search the Cochrane Neuromuscular Specialised Register (The  
38 Cochrane Library, current issues), MEDLINE, EMBASE, Web of Science and Scopus.  
39 We will scan conference abstracts for relevant studies.

40 We will also search the United States National Institutes of Health Clinical  
41 Trials Registry, ClinicalTrials.gov (ClinicalTrials.gov) and the World Health  
42 Organization International Clinical Trials Registry Portal (apps.who.int/trialsearch/).

43 We will search all databases from January 2009 to December 2019, and we will  
44 impose no restriction on language of publication.

45 We will identify non-randomized studies for inclusion in the discussion from the  
46 same search results.

47 We will search reference lists of all relevant and included trials and review  
48 articles for additional references. We will search for errata or retractions of included  
49 trials. We will also search relevant manufacturers' websites for trial information. And  
50 we will search grey literature, in reports of technical research and projects related to  
51 government programs, to identify other studies.

52 We will contact study authors of included trials, to identify additional trials  
53 whether published or unpublished.

54 If no RCTs or quasi-RCTs in this area are not found the authors will review  
55 other well-designed observational studies, where the population (NMD), intervention  
56

(mechanical ventilation weaning) and outcome (weaning success) are clearly documented, in the 'Discussion' section of the review. We will identify these (non-randomized studies) via a search in MEDLINE (from inception to the present), EMBASE (from inception to the present), Web of Science (from inception to the present) and Scopus (from inception to the present). This will be done in order to give a comprehensive descriptive narrative of any non-randomized data.

## Search strategy

Search terms will include: 'neuromuscular disease' or all other terms compatible with clinical diagnoses of these types of diseases, such as 'muscular dystrophy', 'Duchenne muscular dystrophy', 'amyotrophic lateral sclerosis', 'congenital myasthenia', 'myasthenia gravis', 'congenital myopathy', 'spinal muscular atrophy', 'Guillain Barré Syndrome', 'severe inherited neuropathies', 'metabolic myopathies', 'Pompe disease', 'inflammatory myopathies' and 'mitochondrial diseases' combined with 'mechanical ventilation' or 'artificial respiration' or 'mechanical ventilation weaning' or 'ventilator weaning' or 'respirator weaning'; and all the combination between them.

An example of the search strategy is available as a Supplementary File.

## Study records

### *Selection of studies*

Two review authors (SCBN, RTC) will independently screen titles and abstracts of all the potential studies retrieved by the search for inclusion and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. 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 retrieve full-text study reports/publications, and two review authors (SCBN, RTC) will independently screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies.

We will resolve any disagreements through discussion or, if required, through consultation with a third review author (GAFF).

We will report 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 that we will initially pilot on at least one trial included in the review to collect study characteristics and outcome data. One review author (SCBN) will extract study characteristics from included trials. We will collect information on study design and setting, participant characteristics (including disease severity and age), study eligibility criteria, details of the intervention(s) given, the outcomes assessed, the source of study funding and any conflicts of interest stated by the investigators.

Two review authors (SCBN, RTC) will independently extract outcome data from included trials. We will note in the 'Characteristics of included studies' table if the trials did not report outcome data in a usable way. We will resolve any disagreements by consensus or consult a third review author (GAFF). One review author (SCBN) will transfer data into Review Manager (RevMan) 5.3.<sup>14</sup> A second review author (RTC) will check the outcome data entries.

The same review author (RTC) 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. To minimize bias in the review

1  
2  
3 process, the review authors will not screen studies for inclusion, extract data, or assess  
4 the risk of bias in trials they themselves have authored. In such circumstances, we will  
5 involve a third review author (GAFF).  
6

### 7 **Risk of Bias individual studies**

8  
9 Two review authors (SCBN, RTC) will independently assess risk of bias for  
10 each study using the criteria outlined in the Cochrane Handbook for Systematic  
11 Reviews of Interventions.<sup>15</sup> These authors will resolve disagreements by discussion or  
12 by involving another review author (GAFF).  
13

14 We will assess the risk of bias according to the following domains:

- 15 1. Random sequence generation.
- 16 2. Allocation concealment.
- 17 3. Blinding of participants and personnel.
- 18 4. Blinding of outcome assessment.
- 19 5. Incomplete outcome data.
- 20 6. Selective outcome reporting.
- 21 7. Other bias.

22  
23 We will grade each potential source of bias as high, low, or unclear and provide  
24 a quote from the study report together with a justification for our judgment in the 'Risk  
25 of bias' table. We will summarise the risk of bias judgements across different studies for  
26 each of the domains listed. We will consider blinding separately for different key  
27 outcomes where necessary (for example for unblinded outcome assessment, risk of bias  
28 for all-cause mortality may be very different than for a patient-reported pain scale).  
29 Where information on risk of bias relates to unpublished data or correspondence with a  
30 trialist, we will note this in the 'Risk of bias' table. When considering treatment effects,  
31 we will take into account the risk of bias for the studies that contribute to that outcome.  
32

33 If we are able to pool a sufficient number of studies, i.e. more than 10 trials,<sup>15</sup>  
34 we will create and examine a funnel plot to explore possible small study biases.  
35

### 36 **Data Synthesis**

#### 37 *Measures of treatment effect*

38 We will analyze dichotomous data as risk ratios (RR) with corresponding 95%  
39 CI and continuous data as mean difference (MD) with 95% CI, or as standardised mean  
40 difference (SMD) with 95% CI for results across studies with outcomes that are  
41 conceptually the same but measured in different ways. We will enter data presented as a  
42 scale with a consistent direction of effect.  
43

44 We will undertake meta-analyses only where this is meaningful, that is if the  
45 treatments, participants, and the underlying clinical question are similar enough for  
46 pooling to make sense. This will be identified if there are two or more trials with  
47 comparable populations and interventions.  
48

49 Where a single trial reports multiple trial arms, we will include only the arms  
50 relevant to the review question.  
51

52 All data will be pooled according to age group, dividing them into two groups  
53 (adults - over sixteen years old, and children - between five and sixteen years old). After  
54 this grouping the analysis will be done, firstly, comparing the success rate and failure  
55 rate in each of the groups. Subsequently the data will also be evaluated taking into  
56 consideration the weaning outcomes in simple, difficult and prolonged (as described in  
57 the types of interventions).  
58

#### 59 *Unit of analysis issues*

60

We do not expect to have any cross-over or cluster randomized controlled trials, since weaning is a one-off event and also due to the lack of control group, since all patients are submitted to the same intervention, which is weaning from mechanical ventilation.

If we are able to find cluster randomized controlled trials with different clusters of different NMD, we will conduct this analysis.

#### Assessment of heterogeneity

We will use the  $I^2$  statistic to measure heterogeneity among the trials in each analysis. If we identify substantial unexplained heterogeneity, we will report random-effects results and explore possible causes by prespecified subgroup analysis.

We will follow the rough guide to interpretation outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

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

#### Data synthesis

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

#### 'Summary of findings' table

- We will create a 'Summary of findings' table using the following outcomes.
- Weaning success
- Duration of weaning (time difference between weaning protocol initiation and the moment of extubation moment).
- Duration of ICU stay
- Duration of hospital stay
- ICU mortality rate in patients with acute and prolonged mechanical ventilation – defined as the mortality rate during ICU stay.
- Incidence of pneumothorax during mechanical ventilation period.
- Incidence of ventilation associated pneumonia.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes). We will use methods and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions<sup>15</sup> using GRADEpro software (GRADEpro GDT). We will justify all decisions to down- or upgrade the quality of studies using footnotes, and we will make comments to aid readers' understanding of the review where necessary. Two authors will independently grade the quality of the evidence. They will resolve disagreements by discussion and by consultation with a third review author.

#### Subgroup analysis and investigation of heterogeneity

- We plan to perform the following subgroup analyses.
- Simple weaning: successful after first attempt
- Difficult weaning: require up to three attempts
- Prolonged weaning: require more than 7 days to reach success
- Children: from five to sixteen years old

- Adults: above sixteen years old

We will use both primary and secondary outcome measures in all subgroup analyses. We will use the formal test for subgroup interactions in Review Manager 5.3.<sup>14</sup>

#### Sensitivity analysis

We plan to undertake the following sensitivity analyses.

1. Repeat the analysis by excluding studies at high risk of bias (sequence generation, allocation concealment, blinding of personnel, outcome assessment, and attrition).

If there are one or more very large trials, we will repeat the analysis by excluding them to examine how much they dominate the results.

#### Reaching conclusions

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

#### **Patient and Public Involvement**

In the present protocol of systematic review and in the subsequent systematic review there will be no involvement of patients or public.

The paper proposes to use results previously authorized and published by other authors, without there being any need for patient or public involvement. The research question was developed based on the questions raised by other authors, most of the time according to the clinical difficulty and necessity of improve the weaning protocols for this population.

The results of the present study will be published in indexed journal so it can be available for NMD patients, in general, and public, specially health professionals.

#### **Funding statement**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

#### **Declarations of interest**

- SCBN: non-conflicted
- RTC: non-conflicted
- IL: non-conflicted
- VRR: non-conflicted
- GAF: non-conflicted

#### **Conclusion**

This systematic review will provide evidence in different weaning protocols that can be applied to the NMD patients, analyzing the weaning success rate, leading to extubation. The hypothesis is that one specific protocol has higher success weaning rates.

Where sufficient data are available, we will conduct a meta-analysis to confirm the relationship between the different protocols and duration of weaning, duration of stay in the ICU, duration of hospital stay and ICU mortality. It will also be able to assess adverse effects of weaning protocols that fail to lead to extubation.

Moreover, if the hypothesis is confirmed, the review will clarify the reasons any weaning strategy interfere to higher success weaning rates.

Overall, the review will complement the evidence base on mechanical ventilation weaning for NMD patients.

## References

1. Anziks Y, Sternberg A. Exercise in neuromuscular disease. *Muscle & Nerve* 2013;48(1):3-20.
2. Rezania K, Goldenberg FD, White S. Neuromuscular disorders and acute respiratory failure: diagnosis and management. *Neurologic Clinics* 2012;30(1):161-85.
3. Ambrosino N, Carpené N, Gherardi M. Chronic respiratory failure care for neuromuscular diseases in adults. *European Respiratory Journal* 2009;34:441-51.
4. Kim SM, Kang SW, Choi YC, Park YG, Won YH. Successful extubation after weaning failure by noninvasive ventilation in patients with neuromuscular disease: case series. *Ann Rehabil Med* 2017;41(3):450-5.
5. Vassilakopoulos T, Petrof BF. Ventilator-induced diaphragmatic dysfunction. *Am J Respir Care Med* 2004;169:336-41.
6. Bach JR, Gonçalves MR, Hamdani I, Winck JC. Extubation of patients with neuromuscular weakness. *Chest* 2010;137(5):1033-9.
7. Epstein SK, Ciuboratu RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. *Am J Respir Crit Care Med* 1998;158:489-93.
8. Hermans G, den Berghe GV. Clinical review: intensive care unit acquired weakness. *Critical Care* 2015;19:274-83.
9. Chevrolet JC, Deléamont P. Repeated Vital Capacity Measurements as Predictive Parameters for Mechanical Ventilation Need and Weaning Success in the Guillain-Barre Syndrome. *Am Rev Respir Dis* 1991;144:S814-18.
10. Zein H, Baratloo A, Negida A, Safari S. Ventilator weaning and spontaneous breathing trials: an educational review. *Emergency* 2016;4(2):65-71.
11. Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al. An official American Thoracic Society Clinical Practice Guideline: the diagnosis of intensive care unit-acquired weakness in adults. *Am J Respir Crit Care Med* 2014;190(12):1437-46.
12. Tsara V, Moisiadis N, Antoniadou M, Serasli E. Characteristics and outcome of patients with difficult weaning from mechanical ventilation: an 18 years' experience of a respiratory intermediate unit attached to a pulmonary department. *Hippokratia* 2015;19(1):37-40.
13. Sklar MC, Burns K, Rittayamai N, Lanys A, Rauseo M, Chen L, et al. Effort to breathe with various spontaneous breathing trial techniques. A physiological meta-analysis. *Am J Respir Crit Care Med* 2017;195(11):1477-85.
14. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
15. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

**SEARCH STRATEGY – MEDLINE 1946 to Present with Weekly Update (Ovid)**

1. exp Neuromuscular Diseases/co, di, mo, nu, pa, ph, pp, pc, rh, th [Complications, Diagnosis, Mortality, Nursing, Pathology, Physiology, Physiopathology, Prevention & Control, Rehabilitation, Therapy]
2. Myotonic Dystrophy/ or Muscular Dystrophy, Duchenne/ or dystrophy.mp.
3. muscular dystrophy.mp. or exp Muscular Dystrophies/
4. Myasthenia Gravis/ or myasthenia.mp.
5. congenital myasthenia.mp. or exp Myasthenic Syndromes, Congenital/
6. myopathy.mp. or \*Muscular Diseases/
7. Myopathies, Structural, Congenital/ or congenital myopathy.mp.
8. inflammatory myopathy.mp. or \*Myositis/
9. metabolic myopathy.mp. or Mitochondrial Myopathies/
10. pompe disease.mp.
11. spinal muscular atrophy.mp. or exp Muscular Atrophy, Spinal/
12. Polyradiculoneuropathy/ or exp Guillain-Barre Syndrome/ or guillian barre.mp. or Polyneuropathies/
13. Peripheral Nervous System Diseases/ or severe inherited neuropathy.mp.
14. amyotrophic lateral sclerosis.mp. or exp Amyotrophic Lateral Sclerosis/
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. Positive-Pressure Respiration/ or Respiration, Artificial/ or Ventilator Weaning/
17. Weaning/ or weaning.mp.
18. Airway Extubation/ or spontaneous breathing trial.mp.
19. 16 or 17 or 18
20. 15 and 19

## PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Pages
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	2, 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4, 5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of	6



		coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7, 8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7, 8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5, 6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7, 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015 Jan 2;349(jan02 1):g7647.