Original research

Routine lung volume recruitment in boys with Duchenne muscular dystrophy: a randomised clinical trial

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ABSTRACT

Background Impaired cough results in airway secretion retention, atelectasis and pneumonia in individuals with Duchenne muscular dystrophy (DMD). Lung volume recruitment (LVR) stacks breaths to inflate the lungs to greater volumes than spontaneous effort. LVR is recommended in DMD clinical care guidelines but is not well studied. We aimed to determine whether twice-daily LVR, compared with standard of care alone, attenuates the decline in FVC at 2 years in boys with DMD.

Methods In this multicentre, assessor-blinded, randomised controlled trial, boys with DMD, aged 6–16 years with FVC >30% predicted, were randomised to receive conventional treatment or conventional treatment plus manual LVR twice daily for 2 years. The primary outcome was FVC % predicted at 2 years, adjusted for baseline FVC % predicted, age and ambulatory status. Secondary outcomes included change in chest wall distensibility (maximum insulation capacity minus FVC) and peak cough flow.

Results Sixty-six boys (36 in LVR group, 30 in control) were evaluated (median age (IQR): 11.5 years (9.5–13.5), median baseline FVC (IQR): 85% predicted (73–96)). Adjusted mean difference in FVC between groups at 2 years was 1.9% predicted (95% CI –6.9% to 10.7%; p=0.68) in the direction of treatment benefit. We found no differences in secondary outcomes.

Conclusion There was no difference in decline in FVC % predicted with use of twice-daily LVR for boys with DMD and relatively normal lung function. The burden associated with routine LVR may outweigh the benefit. Benefits of LVR to maintain lung health in boys with worse baseline lung function still need to be clarified.

Trial registration number NCT01999075.

Key messages

What is the key question?

⇒ Does twice-daily lung volume recruitment (LVR) reduce decline in FVC in boys with Duchenne muscular dystrophy?

What is the bottom line?

⇒ The burden associated with routine LVR may outweigh the benefit in boys with relatively normal lung function.

Why read on?

⇒ This multicentre randomised controlled trial is the first to evaluate the effects of routine lung volume recruitment on decline in FVC % predicted, peak cough flow and chest wall distensibility (maximum insulation capacity minus FVC) over a 2-year period in boys with Duchenne muscular dystrophy, with relatively normal baseline lung function.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a progressive neuromuscular disease that presents in childhood.1 Respiratory complications are the primary cause of morbidity and mortality and consist of nocturnal hypoventilation, chest wall restriction with loss of lung function and impaired cough resulting in retention of airway secretions, atelectasis and pneumonia.2 Respiratory management of DMD aims to maintain lung function, support respiration with non-invasive ventilation and clear the airways of secretions.3-6

Lung volume recruitment (LVR) is an ‘assisted inflation’ technique accomplished by stacking breaths to inflate the lungs to a volume greater than that achieved with spontaneous effort.7,8 Breath stacking aims to expand the lungs, reduce atelectasis, improve ventilation-perfusion matching, increase elastic recoil of the chest wall and increase expiratory airflow and airway wall shear forces to remove secretions. Regular inflation above spontaneous inspiratory capacity is hypothesised to maintain ‘range of movement’ or flexibility of the chest wall and lungs, preventing stiffening and contractures of costovertebral and costochondral joints.9,10 Retrospective studies in individuals with neuromuscular disease indicate LVR slows the decline in FVC,12,13 maintains maximum insulation capacity (MIC)—a measure of chest wall distensibility—11,16-18 and maintains or increases peak cough flow (PCF).11,17 Only one prospective randomised controlled trial of long-term LVR has been published in a cohort of people with amyotrophic lateral sclerosis, a more
Paediatric lung disease

rapidly progressive adult-onset condition. No trials of long-term LVR as the sole intervention exist in children with neuromuscular disease.

Despite this lack of robust evidence, several care guidelines recommend the use of LVR and similar airway clearance techniques for individuals with neuromuscular weakness. Although LVR is advocated for airway clearance, there is clinical equipoise regarding the benefit of regular routine LVR use. We therefore undertook a randomised controlled trial in boys with DMD to assess whether LVR, compared with standard of care alone, attenuates decline in FVC % predicted at 2 years (primary outcome), as well as the effect of LVR on PCF and chest wall distensibility (difference between MIC and vital capacity (VC)). We hypothesised that routine long-term use of LVR twice daily would attenuate FVC decline, maintain chest wall distensibility and compliance (MIC−VC difference) and increase PCF (assisted by LVR), compared with usual care in boys with DMD.

METHODS

Trial design and setting

A prospective, multicentre, single blind, randomised controlled trial of boys with DMD was conducted (Clinicaltrials.gov).

Participants

Children were identified through neuromuscular clinics. Eligibility criteria included: 6–16 years old, DMD confirmed by genetic testing or muscle biopsy, baseline FVC >30% predicted, caregiver willing to provide LVR therapy and fluent in English or French. As there is clinical equipoise on ideal timing for initiation of regular LVR, we also included boys with normal lung function (ie, FVC ≥80% predicted) to evaluate the effect of LVR across a spectrum of disease severity.

Reasons for ineligibility included enrolment in other intervention trials, patient-reported regular (daily) LVR or mechanical in-exsufflation therapy use (outside of a respiratory infection), inability to perform pulmonary function tests, endotracheal or tracheostomy tube, increased susceptibility to pneumothorax (including uncontrolled asthma or obstructive lung disease) or symptomatic cardiomyopathy. A research assistant obtained informed written consent/assent for all participants and caregivers prior to conducting study procedures.

Randomisation

Following baseline assessment, participants were randomised to conventional treatment or conventional treatment plus LVR, for a 2-year period. Concealed randomisation was conducted using an online website housed at the coordinating study site, using a minimisation allocation strategy developed using Taves’ method. The allocation strategy included study site, use of systemic glucocorticoids, baseline FVC (% predicted), degree of scoliosis, age and ambulatory status. Each treatment arm had a 50% chance of allocation when the minimisation scores were balanced, otherwise individuals were assigned according to the minimisation algorithm with an 80:20 allocation probability. Sites were not aware of allocation balance across study centres. The research assistant entered the participant’s information at the time of randomisation, and a treatment arm was allocated immediately. The research assistant informed families of their treatment arm and instructed them not to share this information with the blinded assessor in order to maintain blinding. Blinding was further maintained by not recording treatment allocation in the participant’s medical chart.

Study arms

Participants in the control arm received standard of care for DMD, which included physiotherapy, nutritional support, oral or intravenous antibiotics for respiratory infections, non-invasive ventilation for sleep-disordered breathing and/or use of systemic glucocorticoids.

Participants and caregivers in the intervention arm were taught manual LVR therapy by a respiratory therapist or physiotherapist during an in-person clinic visit of approximately 30 min duration. During the training session, the parent and child were given a demonstration and then tried it independently, until the clinician felt confident in the family’s ability to properly administer LVR.

The provided LVR kit for home use comprised a self-inflating resuscitation bag, one-way valve, mouthpiece and written instructions (LVR kit item number 1034502; Mercury Medical, Florida, USA). Therapy consisted of 3–5 sequential bag compressions with a breath-hold between each, delivered by a caregiver in coordination with the child’s own inspiration to achieve one maximal inflation to MIC, followed by a cough. Insufflation volume was individually titrated and determined by clinical evaluation. This consisted of visual inspection of chest wall excursion and patient comfort, to a maximum of 40 cmH2O due to a pressure-release valve. Three to five maximal inflation repetitions were performed in each session.

Participants were advised to conduct LVR twice daily, prior to meals or at least 2 hours after. In line with clinical practice, LVR technique was re-evaluated at follow-up visits, with additional training provided as necessary.

All participants were permitted to use manual and mechanically assisted cough techniques during acute respiratory exacerbations, if advised by their physician. Brief use of LVR or mechanical in-exsufflator was considered unlikely to affect the primary outcome.

Outcome measures

The primary outcome was FVC % predicted at 2 years. Secondary outcome measures included change in MIC−VC (L), PCF (L/min), total lung capacity (TLC) (L), maximal inspiratory pressure (MIP) (cm H2O) and maximal expiratory pressure (MEP) (cm H2O).

Pulmonary function tests were performed every 6 months by blinded respiratory therapists or pulmonary function technologists as part of standard clinical care, according to American Thoracic Society recommendations. Review of the MIC technique was conducted at all sites during site onboarding. If fatigue prevented repeated manoeuvres, a single trial was included if the flow-volume loop met acceptability criteria. The Stanojevic normative equations were used to calculate % predicted values for FVC and FEV1. Measurements of MIC, MIP, MEP and PCF were performed according to established protocols. TLC was measured with plethysmography.

At this visit, the research assistant obtained LVR adherence data from children in the intervention arm. Adherence data were downloaded from a battery-powered data logger fitted to the LVR kit (Omega OM-CP-State101A data logger, OMEGA Engineering, Inc; Stamford, Connecticut, USA). The data logger was wired to two pressure switches connected in series (Model 7411–711, PSF102 Series pressure switch, TLCtDesignFlex Switches, A World Magnetics Company; Traverse City, Michigan, USA). The data logger measured date-stamped and time-stamped time-at-pressure, enabling calculation of the number of sessions per day. Logger data was supplemented by self-report adherence diaries,
collected by the research assistant every 3 months by telephone or in-person. Intervention adherence, defined through investigator consensus, was considered as at least one LVR session per day on at least 50% of days.

Sample size
The sample size was informed by a survey of Canadian Paediatric Respirologists and Neuromuscular Specialists, which suggested that a 30% relative reduction in decline in FVC % predicted was the minimal clinically important difference. Assuming a decline in FVC of 12% predicted over 2 years, a minimal difference of 3.6% predicted, a SD of 5.5% and a two-sided test, 76 participants would yield 80% power and type I error of 5%. We targeted a sample size of 110 to account for non-compliance, crossovers and loss to follow-up.

Statistical methods
Analyses were conducted in R V4.0.2. The primary analysis was an analysis of covariance (ANCOVA) multivariable model that analysed FVC % predicted at 2 years, adjusted for baseline FVC % predicted as a means of assessing change over time. Age and ambulatory status were also included in the model as they were part of the minimisation strategy. Missing data in an intention-to-treat population was addressed with longitudinal (time-raster) multiple imputation methods using chained equations to account for irregularly timed or missing FVC measurements (mice package V3.11). The linear mixed model included time as a fixed effect and participant as a random effect (lme4 package V1.1.23). A preplanned sensitivity analysis to account for treatment adherence used a complier average causal effect estimation method that applied a propensity score based on overall LVR adherence over the 2-year period (inverse probability weighting applied to control participants). Preplanned analyses were also repeated by subgroups, defined as baseline MIC−VC difference less than or greater than 10% of the FVC to explore whether baseline chest distensibility and recruitment volume was associated with a long-term effect. Time to an absolute decrease of 10% in FVC % predicted between control and intervention groups was compared using a Cox proportional hazards model, adjusting for age and ambulatory status.

Linear mixed models were used for analysis of secondary outcomes. The proportion of missing data for TLC, MIC−VC and assisted-unassisted PCF did not support imputation and descriptive analyses were performed.

RESULTS
Ninety-five boys with DMD were assessed for eligibility; 25 were excluded (figure 1). We enrolled the remaining 70 boys.
However, four did not have reliable or reproducible FVC measurements at baseline and were subsequently excluded. This left 66 participants, of which 36 were randomised to the intervention and 30 to control. Fifty-three participants (76%) completed the 2-year study. Recruitment occurred between December 2013 and September 2016 (predetermined end date); the final study visit was in November 2018. Baseline characteristics were similar between groups (table 1). Median age was 11.5 years (IQR: 9.5–13.5). At baseline, median FVC was 84.8% predicted (IQR: 73.3–95.5); 52 participants had MIC−VC greater than 10% of FVC. Most participants (59/66, 89%) were receiving systemic steroids; the corticosteroid regime was daily deflazacort in the majority of cases. Almost one-third (32%) were wheelchair assisted; 6% used non-invasive ventilation for nocturnal hypoventilation; and no participants used an in-exsufflator. No participants reported new initiation of non-invasive ventilation during the follow-up period. One participant in the non-LVR arm started using an in-exsufflator for respiratory exacerbations during follow-up. Three participants had chest infections requiring antibiotics (two in the LVR arm, one in the conventional treatment group).

Of 330 planned pulmonary function tests, 47 (14%) were not done. Of 283 pulmonary function tests, 217 (77%) were both reliable and reproducible. Of 50 instances (18%), a single reliable measurement was obtained. An additional 16 pulmonary function tests (6%) were neither reliable nor reproducible and were treated as missing.

Twenty (59%) participants were adherent to LVR in year 1, 21 (62%) in year 2 and 14 (41%) were LVR-adherent in both years. There was no crossover between study groups. At each study time point, between one and four participants in the control arm reported rescue LVR treatment, with a range of 1–11 LVR sessions performed per individual.

All 66 children were included in the primary analyses. For the primary analysis, the ANCOVA-estimated adjusted mean difference in FVC between study groups at 2 years was 1.9% predicted (95%CI −6.9 to 10.7; p=0.68; R²=0.66; n=66), with the point estimate in the direction of treatment benefit. Secondary analyses of FVC % predicted at each time point showed no evidence of a time-by-intervention group interaction (p=0.94; R²=0.41; n=66; figure 2). In the pre-protocol analysis adjusted for adherence, the ANCOVA-estimated adjusted mean difference between LVR and standard-of-care groups at 2 years was 2.7% predicted FVC (95%CI −8.3 to 13.6; p=0.64; R²=0.68; n=66). Cox regression of time to absolute 10% decrease in FVC % predicted did not identify a difference between groups (HR 0.7, 95%CI 0.3 to 1.4; p=0.30; n=66; figure 3).

For MIC−VC, PCF assisted − PCF unassisted and TLC, imputation of missing data was not feasible, and observed data were used. Change over time in trajectory of MIC−VC and PCF assisted unassisted were not different between study groups (p=0.79; R²=0.29; n=42 and p=0.88; R²=0.26; n=45, respectively; figure 4a, b). No statistical differences were detected between study groups over time in MIP (p=1.00; R²=0.07; n=66), MEP (p=0.98; R²=0.05; n=66), nor TLC (p=0.88; R²=0.69; n=35; figure 4c–e). A secondary analysis considering change in FVC % predicted over time among subgroups with baseline MIC−VC less than or greater than 10% of the FVC did not detect a difference in the slope of FVC % predicted over time (p=0.19; R²=0.67; n=14, and p=0.13; R²=0.92; n=12, respectively, online supplemental figure S1a, b).

No serious adverse events were reported. One individual in the intervention arm experienced a syncopal episode probably related to LVR and subsequently withdrew from the study. Two individuals had mild chest discomfort resulting in brief interruptions of LVR treatment; one had cough during LVR, which did not result in change in LVR use.

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**Table 1 Baseline characteristics**

<table>
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<tr>
<th>Variable</th>
<th>Overall n=66</th>
<th>Conventional treatment n=30</th>
<th>Conventional treatment +LVR n=36</th>
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<tr>
<td>Age (years), median (IQR)</td>
<td>11.5 (9.5–13.5)</td>
<td>11.5 (9.2–13.0)</td>
<td>11.5 (9.5–13.9)</td>
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<tr>
<td>FVC (%-predicted), median (IQR)</td>
<td>84.8 (73.3–95.5)</td>
<td>85.6 (73.8–98.8)</td>
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<td>Wheelchair assisted, n (%)</td>
<td>21 (32)</td>
<td>10 (33)</td>
<td>11 (31)</td>
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<td>Scoliosis, n (%)</td>
<td>9 (14)</td>
<td>3 (10)</td>
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<tr>
<td>Non-invasive ventilation, n (%)</td>
<td>4 (6)</td>
<td>2 (7)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Steroid use, n (%)</td>
<td>59 (89)</td>
<td>27 (90)</td>
<td>32 (89)</td>
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*There were no differences in baseline characteristics between the intervention and control groups (p>0.05).

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**Figure 2** Secondary analysis of FVC % predicted over time. Marginal means by group with 95% CI from mixed effect model of FVC % predicted, adjusted for age and ambulatory status, at 6-month intervals. LVR, lung volume recruitment.

**Figure 3** Kaplan-Meier curve for a single missing data imputation. LVR, lung volume recruitment.
**DISCUSSION**

In this, to our knowledge, first-ever randomised controlled trial of LVR in children with neuromuscular disease, we found no difference in FVC % predicted at 2 years of follow-up among boys with DMD and relatively normal baseline pulmonary function using twice-daily LVR in addition to usual care compared with usual care alone. As many study participants had normal lung function at baseline, it is not surprising that a large improvement in the downward trajectory of FVC % predicted was not observed with twice-daily LVR. This may be because the expected loss of FVC % predicted over a 2-year period is small in those with relatively normal lung function at baseline. 22 26 34 The use of systemic glucocorticoids in the majority of our study population may have further helped to preserve lung function.21

Our study suggests there may be less benefit of LVR therapy in less advanced disease. Current clinical care guidelines for individuals with DMD recommend implementation of regular LVR treatment when there is evidence of weak cough (ie, PCF below 270 L/min and/or FVC <60% predicted). 4 6 23 As an impact on the decline in FVC was not demonstrated in our cohort of boys with relatively normal lung function, our results suggest that twice-daily LVR may not be necessary when lung function is normal, providing novel, high-quality evidence to support current clinical care guidelines. This is an important finding as LVR represents an additional treatment burden for children and families. This is reflected in our study adherence data, where only 41% of participants were adherent to LVR across both study years. While low, this adherence rate is similar to that reported in children prescribed non-invasive ventilation.39 It will be necessary to further explore the reasons behind the low LVR adherence rates, as LVR likely still has an important role in assisting airway clearance during pulmonary exacerbations in this population, when pulmonary function may be expected to be reduced, as well as for preservation of chest wall compliance.

Furthermore, although differences in FVC % predicted were not detected in our study, LVR may be beneficial for maintenance of other important aspects of lung function in those with relatively normal lung health. We speculate that long-term regular LVR therapy initiated prior to onset of lung function abnormalities may help to preserve distensibility of the chest wall, akin to prevention of other joint contractures with the use of range-of-motion exercises, by preventing stiffening and fixed restriction of the chest wall which maintains the ability to expand the chest and lungs.40 Sustained improvements in respiratory system compliance may delay the onset of respiratory failure, the need for ventilatory support and/or allow adequate non-invasive ventilation at lower airway pressures. Improved airway clearance of secretions may also prevent atelectasis and pneumonia. Such potential benefits of LVR in those with relatively normal lung function will require further exploration. There is thus a paradox where clinical benefit of regular LVR likely exists even among those with normal lung function, although our study was unable to demonstrate it. Future studies may compare measures of chest wall compliance or respiratory symptoms over time when routine LVR is initiated at different thresholds of lung function or age. This may be best accomplished through examination of registry data, as lack of clinical equipoise may preclude inclusion of individuals with more advanced neuromuscular disease in
randomised trials. Understanding of the role of LVR to maintain all aspects of lung and chest wall health will be especially critical as new therapies for DMD appear on the horizon that may ultimately change the trajectory of the natural history of disease.

Due to our recruitment of participants with essentially normal lung function, despite inclusion criteria of FVC >30% predicted, important knowledge gaps remain in those with more advanced disease. These include the optimal timing for LVR introduction, frequency of use and efficacy in maintaining or improving lung function. LVR may be more beneficial in boys with lower baseline lung function and more advanced disease. This was observed in our previous retrospective cohort of individuals with more advanced disease, although differences in MIC–VC over time were not seen between treatment groups in the current study.

This study has several strengths. We used a rigorous multi-centre randomised design that incorporated a minimisation strategy to ensure well-balanced study groups at baseline. Adherence to LVR therapy was objectively recorded with an in-line data logger. Longitudinal follow-up over a 2-year period was achieved.

Our study also has limitations. Although we recruited a nationally representative sample of boys with DMD, due to recruitment challenges (several pharmaceutical trials competed for recruitment of the same population), the study sample was smaller than planned, meaning our study is likely underpowered. Furthermore, low adherence may have limited our ability to detect between-group differences. Despite eligibility criteria that aimed to recruit individuals with a broad range of baseline lung function, most participants had relatively normal lung function. This may have been due to existing regular use of LVR or other airway clearance therapy in those with lower baseline lung function, rendering them ineligible for study participation. While there were no routinely applied criteria for initiation of regular LVR therapy at the time of the study start, guidelines published later in the study period may have influenced clinicians’ LVR prescription practices, thereby decreasing our eligible pool of participants. Finally, although our study had a long intervention period—that is, 2 years, which is a strength—some data were missing. This was mitigated, where possible, by imputation of missing values. These limitations highlight the challenges of conducting large-scale studies in children with neuromuscular disease.

CONCLUSION
In this randomised controlled trial of 66 boys with DMD and relatively normal lung function, we found no difference in rate of decline in FVC % predicted over 2 years when twice-daily LVR was used. This novel, high-quality evidence supports clinical guidelines that recommend LVR initiation only once lung function is below a certain threshold. Therefore, in boys with DMD and normal lung function, the treatment burden of twice-daily routine LVR may outweigh the therapeutic benefit. However, the benefits of LVR as prophylactic regular therapy for boys with DMD with lower lung function still needs further research.

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Contributors SLK conceptualised and designed this study, oversaw the acquisition, analysis and interpretation of study data across all sites and wrote the first draft of this manuscript. SLK serves as the guarantor of this work. CC, JKM, LCM, TTDN, WH, HW, GM, HW, TK, MA, HJ, TD, MW, RCM and HJM contributed substantially to the design of this study and oversaw the analysis and interpretation of the data. VB contributed the analysis and interpretation of the study data. SDA, DJB, DM, HM, LR, NS and LW substantially contributed to the interpretation of the data. HB substantially contributed to the acquisition of the study data. All authors critically revised the manuscript for important intellectual content, gave final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent for publication Not applicable.

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REFERENCES
ONLINE SUPPLEMENT

Figure s1. Estimated FVC %‐predicted from a linear mixed effects model in boys with (a) baseline MIC‐VC <10% of the FVC, and (b) baseline MIC‐VC ≥10% of the FVC.
Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time (STEADFAST)

Katz

Jesse's Journey 2013

Title: Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time (STEADFAST)

Funded By: Jessie’s Journey the foundation for Gene and Cell therapy

Registered: Clinicaltrials.gov #NCT01999075

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Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time (STEADFAST)

Katz

Jesse's Journey 2013

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Protocol Version_ Extension Amendment 3_4 June 2015

**Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time**

(STEADFAST)

Katz

**SCIENTIFIC ABSTRACT**

**Keywords:** Duchenne muscular dystrophy, pulmonary complications, lung volume recruitment, breath-stacking, cough efficacy, maximal insufflation capacity

**Detailed Summary (up to 450 words)**

**Background:** Respiratory complications are the primary cause of morbidity and mortality associated with childhood Duchenne Muscular Dystrophy (DMD). Involvement of the respiratory muscles leads to progressive hypoventilation and/or recurrent atelectasis and pneumonia secondary to decreased cough efficacy. Lung volume recruitment (LVR) is a means of stacking breaths to achieve maximal lung inflation (MIC), prevent micro-atelectasis, and improve cough efficacy. Although it has been recommended by some experts as the “standard of care” for individuals with neuromuscular disease, the strategy has not been widely implemented in DMD given the lack of clinical trials to date to support its efficacy as well as the additional burden of care required in a population already requiring multiple interventions.

**Primary Objective:** To determine whether LVR, in addition to conventional treatment, is successful in reducing decline from baseline in forced vital capacity (FVC) over 2 years (percent predicted, measured according to American Thoracic Society standards), compared to conventional treatment alone in children with DMD.

**Secondary Objectives:** To determine differences between children treated with LVR in addition to conventional treatment, compared to those treated with conventional treatment alone, in: (1) the number of courses of antibiotics, hospitalizations and intensive care admissions for respiratory exacerbations, (2) health-related quality of life, and (3) peak cough flow and other pulmonary function tests.

**Methods:** We propose a 3-year multi-centre randomized controlled trial involving fifteen tertiary care pediatric hospitals across Canada. The study population consists of boys aged 6-16 years with DMD and FVC ≥ 30% of predicted. A sample size of 110 participants will be enrolled. This has been informed by chart review and survey of participating centres to be feasible, and will be re-assessed with an ongoing internal pilot study.

**Intervention:** Participants will be allocated with a minimization procedure to receive conventional treatment (non-invasive ventilation, nutritional supplementation, physiotherapy and/or antibiotics, as decided by the treating physician) or conventional treatment plus twice daily LVR exercises performed with an inexpensive, portable self-inflating resuscitation bag containing a one-way valve and a mouthpiece.

**Data Analysis:** The primary outcome (change in percent predicted FVC over 2 years) will be compared between the two study groups using an analysis of co-variance (ANCOVA) that takes into account baseline FVC and minimization factors.

**Importance:** Decline in pulmonary function among children with DMD negatively affects quality of life and predicts mortality. The relatively simple strategy of LVR has the potential to optimize pulmonary function and reduce respiratory exacerbations, thereby improving quality of life for individuals with DMD. This study is novel in that it is the first randomized controlled trial of LVR. A major strength is that the results will give support or refute recommendations regarding inclusion of LVR in the standard of care for individuals with DMD worldwide.
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LAY LANGUAGE SUMMARY OF PROJECT

Duchenne Muscular Dystrophy is complicated by weak breathing muscles and lung infections. "Lung volume recruitment" is a technique performed using a face mask or mouthpiece and a hand-held resuscitation bag to stack breaths, inflate the lungs and help clear the airways of secretions by increasing the forcefulness of a cough. We believe this will slow down the steady loss of lung function, prevent lung infection, and improve quality of life. Our aim is to compare the outcome of a group of individuals with DMD treated with standard care to another group that also receives lung volume recruitment. If effective, this study will change clinical practice by including twice-daily treatment as part of the standard of care for individuals with DMD, in order to improve their lung health and quality of life.

LAY LANGUAGE DESCRIPTION OF PROJECT DISSEMINATION/KNOWLEDGE TRANSFER STRATEGIES

Publication of the results of this trial in a peer-reviewed journal and presentation at international conferences will educate inter-professional healthcare teams, patients and families about this therapeutic tool. Demonstrating benefits of lung volume recruitment on lung function and quality of life will lead to more widespread adoption and support for this treatment in DMD patients worldwide. The results can be used to inform care recommendations for individuals with DMD and may be incorporated into guidelines for respiratory health maintenance in this population. The results of this study may also be applicable to the care of individuals with other neuromuscular conditions.
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DETAILED PROJECT PROPOSAL

BACKGROUND DATA

Respiratory failure is the primary cause of morbidity and mortality in children with Duchenne Muscular Dystrophy (DMD). In the absence of a definitive treatment for the underlying disease, management focuses on supportive measures to slow the decline in lung function, prevent respiratory infection and improve quality of life. The goal of this study is to determine whether introduction of twice-daily lung volume recruitment (LVR), in addition to current standard treatment, reduces the rate of decline in pulmonary function and the frequency of respiratory exacerbations in children with DMD, compared to the current standard treatment.

REVIEW OF THE LITERATURE

We are aware of only one controlled clinical trial, which compared efficacy of mechanical insufflation at 1 point in time between individuals with and without bulbar involvement with Amyotrophic Lateral Sclerosis (ALS, a neuromuscular condition affecting adults).\(^1\) A systematic review of airway clearance techniques in ALS concluded there was level 2 evidence for the use of mechanical insufflation followed by an assisted cough in improving peak cough flow, but only level 4 evidence that long-term use could prevent pulmonary infections and hospitalizations.\(^2\) There were no systematic reviews on either the use of LVR in improving lung function in neuromuscular disease nor any on the use of LVR in neuromuscular disease in children.

RATIONALE FOR THE PROJECT

A. Duchenne Muscular Dystrophy (DMD) is an important health problem

DMD is a progressive neuromuscular disease presenting in childhood, with an estimated incidence of 1 in 3600-6000 live male births.\(^3\)-\(^6\) There is no definitive treatment for the underlying condition.\(^7,8\) Mortality increases substantially in early adulthood, with a median life expectancy of 25-35 years.\(^7,8\) Respiratory complications are the primary cause of morbidity and mortality, as progressive inspiratory and expiratory respiratory muscle weakness leads to hypoventilation\(^10\)-\(^18\) and/or recurrent pneumonia\(^19,20\) secondary to decreased cough efficacy.\(^21,22\) Decreased chest wall motion due to weakened inspiratory muscles also results in reduced chest wall compliance, with decreased lung volumes leading to micro-atelectasis and reduction in elastic properties of lung tissues.\(^23\) Ultimately, 24-hour ventilatory support is required, necessitating continuous caregiver support, and significant healthcare costs.\(^24\) In Australia, the burden of care for muscular dystrophies is estimated to be $435 million per year, or $125,000 per person annually; total cost to society due to disability and premature death exceeds $1 billion.\(^25\)

B. LVR Techniques are sometimes included in current management strategies:

Respiratory management strategies currently focus on three interrelated areas: 1) non-invasive ventilation for nocturnal hypoventilation; 2) lung volume recruitment (LVR); and 3) airway clearance.\(^21,26-29\) **LVR is a means of stacking breaths to achieve maximal lung insufflation capacity, expanding the chest wall and filling the lungs with air.** Insufflation may also help to maintain chest wall motion and lung compliance.\(^27\)

LVR can be delivered with two technologies: manual insufflations and mechanical insufflation. For manual delivery, the self-inflating resuscitation bag and
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patient interface with a 1-way valve (Appendix 1) is readily available, inexpensive ($70), lightweight, requires no external power, and is easily portable. This technique has been used in adults with neuromuscular disease and described in detail by Dr. McKim (http://www.irrd.ca/education). For mechanical delivery, the Respironics In-exsufflator (http://www.coughassist.com) provides positive pressure breaths, followed by a rapid negative pressure to mimic a cough. It is, however, expensive ($4500-6,000), cumbersome, requires external power, is less easily portable, and is not covered by any Canadian provincial insurance plan. Therefore, we have chosen to study LVR with an inexpensive self-inflating bag.

C. LVR has not been rigorously studied

While LVR has been shown to improve cough efficacy, the effect on slowing the progression of restrictive respiratory impairment has not been evaluated in long-term studies. Most studies performed to date have incorporated LVR as an integral part of an overall approach to care, making it difficult to assess its impact alone on clinical course. Only 3 small studies included children, all of which involved mechanical in-exsufflation. One case series, which studied mostly adults, demonstrated an improvement in maximum insufflation capacity (MIC, the maximum volume of air that can be held in the lungs with a closed glottis after breath-stacking), despite a decrease in forced vital capacity (FVC), over 0.5 – 24 years of follow-up in 282 patients with neuromuscular disease. Integrating the mechanical in-exsufflator into an overall plan of care has also been successful in some case series in avoiding hospitalization, pneumonias, episodes of respiratory failure and tracheostomy. A similar protocol using non-invasive positive pressure ventilation (NPPV) and LVR has been used in a prospective cohort study to avoid intubation and death in episodes of acute respiratory failure in 79.2% of adults with neuromuscular disease. It is difficult to determine however, whether the improved outcomes in these studies were due to NPPV or the mechanical in-exsufflator.

A single cohort study of adults and children using mechanical in-exsufflation twice daily (as per self-report) demonstrated improvement in MIC and PCF over time. In a largely pediatric population there has only been 1 retrospective review of long-term regular (once a day to every 4 hours) use in 62 individuals with neuromuscular disease and impaired cough (age range 3 months to 28.6 years), with a median duration of 13.4 months. 6% of participants experienced an improvement in chronic atelectasis and 8% noted a reduction in frequency of pneumonias, although the number of acute lower respiratory tract infections was too small to permit meaningful comparison with a pre-treatment period.

Our recently completed retrospective cohort study, published in Archives of Physical Medicine and Rehabilitation, describes the trajectory of pulmonary function in adults with DMD, in whom LVR has been used for up to 2 years. The annual change in percent-predicted FVC before introduction of LVR was approximately -4.7 %-predicted per year, which is consistent with literature suggesting the rate of decline of pulmonary function plateaus in adulthood, with severe disease. After LVR introduction, the rate of decline decreased to -0.5 %-predicted/year. The difference between the two rates was 4.2 %-predicted/year (p < 0.001), demonstrating significant benefit of LVR (Appendix 2).

In summary, there are no trials, nor any long-term controlled prospective studies evaluating LVR as a treatment for children with DMD, although the existing literature of

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uncontrolled studies suggests that LVR may be beneficial for adults with neuromuscular disease.

D. Current Standards of Care and Questions Remaining

LVR has been recommended by Bach and Finder as the “standard of care” for neuromuscular patients. The paucity of long-term clinical studies to demonstrate its efficacy has left questions, with several groups worldwide calling for further prospective, controlled studies. It was listed as a top research priority in recent British Thoracic Society Guidelines on “Respiratory Management of Children with Neuromuscular Weakness”. Our recent Survey of Respiratory Management of Neuromuscular Disease revealed that LVR has been adopted for management of intercurrent infections by Pediatric Respiriologists and Neuromuscular Specialists at many Canadian centres (Appendix 3). No centres are routinely prescribing regular LVR use. It is used at only 3 centres and in less than one third of their patients, during periods of clinical stability. Clinical equipoise therefore currently exists regarding the use of regular LVR in children with neuromuscular disease. Given the additional burden of this therapy on children and caregivers, it requires closer evaluation before it can be recommended on a routine basis.

HYPOTHESIS/RESEARCH QUESTIONS

We propose a novel single-blind randomized controlled trial (RCT) of LVR in DMD, allowing evaluation of the impact of its implementation in clinical care.

Primary Question: Will adding twice-daily LVR to the standard treatment received by children with DMD reduce the decline in FVC %-predicted by at least 30% over 2 years?

Secondary Questions: Will adding LVR to standard treatment received by children with DMD:
1. increase time to FVC decline of 10% of predicted from baseline?
2. reduce the number of outpatient antibiotic treatment courses, hospitalizations and/or admissions to intensive care (ICU) for respiratory exacerbations?
3. improve the health-related quality of life (HRQL) of children with DMD?
4. affect the decline of unassisted peak cough flow (PCF), maximum insufflation capacity (MIC), maximal inspiratory and expiratory pressures (MIP, MEP)?

SPECIFIC OBJECTIVES
1. To determine the impact of twice-daily LVR on relative decline in FVC %-predicted and other functional parameters (PCF, MIC, MIP, MEP) over 2 years
2. To determine the impact of twice-daily LVR on antibiotic courses, hospitalizations and ICU days, as well as quality of life, over 2 years
3. To inform care guidelines on LVR therapy for individuals with DMD

PROJECT DESIGN AND RESEARCH METHODOLOGY

1. PROPOSED TRIAL DESIGN & INTERVENTIONS
This will be a multi-centre single-blind parallel RCT. The study will involve 10 tertiary care Pediatric hospitals across Canada (Appendix 4) and will run for 5 years (August 2013- August 2018). The coordinating centre will be the Children’s Hospital of Eastern Ontario (CHEO) in Ottawa, Ontario. Recruitment will take place from August 2013- 30 April 2016. Participants will be randomized 1:1 to conventional treatment.
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alone, or conventional treatment plus LVR. The intervention will occur for 24 months and participants will be followed up in clinic at Baseline, 6, 12, 18 and 24 months. (Appendix 5- Flow Diagram and Activities).

Treatment Groups

Conventional Treatment will be coordinated by the treating physician. This may include: a. Physiotherapy, consisting of percussion, active cycle of breathing and/or postural drainage; b. Nutritional support, consisting of oral or tube-fed dietary supplements; c. Antibiotics (oral or intravenous), if there is evidence of respiratory infection; d. Non-invasive positive pressure ventilation, if there is evidence of nocturnal hypoventilation or sleep-disordered breathing; e. Systemic steroids. e) LVR therapy during acute respiratory exacerbations only.

Intervention Treatment: Conventional treatment plus the use of LVR twice per day.

Interventional Procedures

Caregivers of those who are randomized to the interventional arm will receive equipment (free of charge) and training in provision of LVR. Technique (Appendix 6) will be reviewed by a respiratory therapist or physiotherapist trained to use this equipment, prior to initiation of home use of the device. Positive pressure, via a mouthpiece, will be applied using a resuscitation bag containing a one-way valve. Insufflation volume will be determined by clinical evaluation, consisting of visual inspection of chest wall excursion and patient comfort. The initial positive pressure setting will be titrated individually as tolerated, to a maximum of 40 cmH₂O. Pressures will be measured with a manometer and re-evaluated at each follow-up clinic visit.

Positive pressure breaths will be delivered in coordination with the subject’s own respiration over 2-3 seconds. 3-5 breaths will be delivered in order to achieve MIC, followed by a cough while the subject is at MIC, for a total of 3-5 cycles, as tolerated. Airway suctioning will be performed at the end of each cycle as needed. Twice daily LVR will be performed prior to meals or at least 2 hours after meals to eliminate risk of aspiration of abdominal contents.

Adherence with therapy will be monitored via a data-logging device in-line with the resuscitation bag that records number of compressions of the resuscitation bag along with the time and date (Appendix 7). Data from the device memory will be uploaded by the research assistant at each study visit and sent to the central coordinating centre (CHEO). Since the minimum frequency of LVR use to achieve clinical benefit is unknown, for study purposes, adherence with the study intervention is defined as a participant using LVR for at least 50% of sessions during each year of the study, based on a consensus of investigators (Drs. Katz, Kovesi, Mah, McKim, and MacLusky).

Rescue Treatment: During acute respiratory exacerbations, subjects may use assisted cough techniques, including LVR with or without an abdominal thrust and/or mechanical in-exsufflator, even if they are in the control group, if deemed appropriate by the treating physician. Brief use of such treatment is unlikely to affect the primary outcome, and therefore is not a criterion for withdrawal from the study. Rescue treatment is typically initiated and carried out by clinical care teams during hospitalizations for respiratory exacerbations (Appendix 8).
2. ALLOCATION OF PARTICIPANTS TO TRIAL GROUPS

Along with the study site, use of systemic steroids, baseline FVC (%-predicted), degree of scoliosis, age, and ambulatory status were considered as important prognostic indicators in the design of this study, each believed to influence the primary outcome, FVC (Justification in Appendix 9). Although stratified block randomization is commonly used to ensure balanced prognostic factors in larger trials, the method of minimization is optimal for the number of prognostic factors and study size. The method of “minimization” is described in the CONSORT statement as a methodologically equivalent alternative to randomization. Patients will be allocated to the intervention or control group (1:1 ratio) using a centralized computer algorithm designed by the study statistician and maintained by the Data Management Group of the Ottawa Hospital Research Institute.

3 METHODS FOR PREVENTING BIAS

A. Concealment of allocation. Centralized allocation and random elements in the minimization will ensure participating centres cannot predict the allocation sequence.

B. Masking of intervention from outcome assessor. The study will be single-blinded, where the pulmonary function assessors will not know the participants’ group assignment. Furthermore, the outcomes used are objective tests with defined performance criteria for acceptability.

4. INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria
- Age 6-16 years – This age range was selected as there are accepted normative pulmonary function data and children 6 years of age and older are generally able to reliably perform pulmonary function tests. Children are followed in participating centres until they reach 18 years of age (allowing two years of follow-up).
- Clinical phenotypic features consistent with DMD and confirmed by either: (1) Muscle biopsy showing complete dystrophin deficiency; (2) Genetic test positive for deletion or duplication in the dystrophin gene resulting in an 'out-of-frame' mutation; or (3) Dystrophin gene sequencing showing a mutation associated with DMD.
- FVC ≥ 30% predicted - This range of pulmonary function was selected to exclude those with severe restrictive respiratory impairment, who are less likely to be able to reliably perform pulmonary function testing over a two year period. Ability to perform a single acceptable flow-volume curve meeting criteria for test acceptability as per American Thoracic Society standards is required.
- A caregiver willing to provide the therapy
- Fluency in English or French

Exclusion Criteria
- Unable to perform pulmonary function tests and/or LVR manoeuvre
- Presence of an endotracheal or tracheostomy tube
- Already using LVR and/or the Respironics in-exsufflator between and during respiratory infections
- Known susceptibility to pneumothorax or pneumomediastinum
- Uncontrolled asthma or other obstructive lung disease
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- Symptomatic cardiomyopathy (ejection fraction less than 50%)

5. FREQUENCY AND DURATION OF FOLLOW-UP

Participants will return to clinic 6 months after study initiation and then every 6 months (±2 months) for follow-up, over a 2-year period from time of enrolment. At each visit, pulmonary function testing will be performed (including FVC, MIC, MIP, MEP, PCF, maximum and average pressure achieved during LVR measured, and technique reviewed). Participants will meet with the study assistant by telephone every 3 months (or in clinic), to document courses of oral antibiotics and hospital admissions. LVR use will be recorded using a portable data-logger in-line with the LVR set-up.

6. PRIMARY AND SECONDARY OUTCOME MEASURES

Primary

Relative decline in FVC (%-predicted) over 2 years, measured according to American Thoracic Society (ATS) standards, using the Stanojevic normative equations. Relative decline in FVC (%-predicted) was chosen as the primary outcome as it is a strong predictor of subsequent respiratory failure and mortality. Although survival is not a realistic endpoint for this trial, given expected mortality is less than 5% for the pediatric age group, FVC decline is an appropriate clinical laboratory measure and valid surrogate endpoint to use for this trial.

Secondary

a. Time to FVC decline of 10% of predicted.
b. Total number and duration of outpatient oral antibiotic courses, hospital and ICU admissions for respiratory exacerbations over 2 years.
c. Change in HRQL over 2 years (PedsQL 4.0, Pediatric Quality of Life Inventory and PedsQL DMD 3.0), biannually
d. Change in unassisted PCF, MIC, MIP, MEP, as well as MIC and PCF with LVR

Exploratory

e. Maximal and average pressure achieved with LVR (cmH₂O)
f. Respiratory symptoms, as assessed every 3 months by phone and personnel interview at clinic visits (Appendix 10). A self-report usage diary (Appendix 12) will be given to the participant to record daily activities to help with recall at the telephone follow ups (Appendix 10)
g. Satisfaction with LVR, as assessed every 3 months by phone (Appendix 11)

Spirometry, including FVC, will be performed according to ATS standards. The Stanojevic normative equations will be used to calculate %-predicted values for FVC and FEV₁. Measurements of MIC, MIP, MEP and PCF will be performed according to established protocols. Maximal and average pressure achieved with LVR (cmH₂O) will be measured with a manometer at the time of each pulmonary function test. Adverse events will also be recorded (Appendix 12). Data collection forms are found in Appendix 13.

7. SAMPLE SIZE AND JUSTIFICATION

The consensus from a national survey of Respirologists and Neuromuscular Specialists treating children with neuromuscular disease was that a 30% relative reduction in the average decline in FVC percent predicted would represent the minimal
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clinically important difference (MCID) that would be important to detect in this trial. This magnitude of pulmonary function change has been deemed clinically important in trials of treatment to decrease the decline in lung function in Cystic Fibrosis, another progressive childhood respiratory disease, and should be achievable, based on pilot data in adults with DMD that demonstrated an 89% relative reduction in the rate of decline of FVC after LVR was introduced (Appendix 2).

The following assumptions were used: i) a decline of 12% predicted in FVC over 2 years in the control group (based on an estimate of decline in FVC of 6% predicted per year, being more conservative than the published -8.0% per year decline (range 2-39%) in boys ≥ 10 years old with DMD; ii) an absolute MCID of 3.6% FVC (corresponding to a relative 30% MCID); iii) an estimated standard deviation (SD) of 5.5% in the change of FVC from baseline (the SD of the annual change of FVC was reported to be 4.1%). With a 2-year follow-up, the SD of the change of FVC from baseline is likely to be greater than 4.1%, and is assumed to be 5.5%; iv) two-sided test; v) a power of 80% and a type I error of 5%. With these assumptions, the total sample size needed is 76 participants. We believe the non-adherence rate in the treatment arm will be 10%. We also expect very few individuals to cross-over from control to intervention, barring a few cases of rescue therapy. We have therefore conservatively estimated this at 2%. Accounting for noncompliance, cross-overs, and 10% losses to follow-up, the total sample size will be 110.

8. PLANNED RECRUITMENT RATE
Participants will be recruited from established neuromuscular clinics at the participating centres (chart review has revealed 254 individuals who are eligible for this study, Appendix 4). We conservatively anticipate 60% of eligible patients will agree to participate in the study.

9. ADHERENCE
Adherence to therapy will be monitored using a device in line with the resuscitation bag (Appendix 7), as well as self-report usage diary, (Appendix 12). Given the progressive and eventually fatal nature of the disease, this population is generally highly motivated to pursue treatments. We anticipate a 90% adherence rate, seen in other studies in this and similar populations when non-invasive ventilation was implemented for up to 4 – 7 years.

10. ANALYSIS PLAN

Intention to treat and per protocol analyses
The primary analysis will follow the intention-to-treat principle. A per-protocol secondary analysis will also be performed. Adherence in the intervention group will be defined as using LVR for a minimum of 50% of sessions during each year of the study, based on a consensus of experts. Primary analysis: An analysis of covariance will be conducted for FVC % predicted at 2-years follow-up, adjusting for baseline FVC % predicted, treatment group, centre, use of systemic steroids, presence of scoliosis, age, and ambulatory status. A 2-sided p-value less than 0.05 for treatment group will indicate a statistically significant group effect. Secondary analyses: To account for differences in adherence, the primary analysis will be repeated including the measured level of adherence as an additional covariate.
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The slope of decline in FVC (measured every 6 months) will be plotted for each study group and differences between groups will be assessed using linear mixed effects models for repeated measures, adjusting for patient covariates such as baseline FVC %-predicted, treatment group, centre, use of systemic steroids, presence of scoliosis, age, and ambulatory status. In addition, in each study group, the time for each participant’s FVC %-predicted to decline by an absolute 10% from baseline value will be displayed using Kaplan-Meier curves, and compared between the study groups using a log rank test. Cox proportional hazards models will also be used to adjust survival time for the important prognostic risk factors listed above.

Poisson regression models, allowing for possible over-dispersion, will be fit to assess the differences in a) the number of courses of oral antibiotics for respiratory infections; b) the number of hospitalizations for respiratory exacerbations; c) the number of admissions to the intensive care unit; d) the total number of days requiring intubation and mechanical ventilation over the study period and, e) PedSQL scores.

A comparison will be made of frequencies of the most common adverse events between the two study groups using chi-square or Fisher’s exact test. Sub-group analysis will also be performed to compare the primary outcome between those who are adherent with LVR but experience no improvement in MIC after LVR (i.e. MIC is equal to FVC) and those who experience an increase in MIC after LVR (i.e. MIC is greater than FVC). Given the exploratory nature of this subgroup analysis, we will interpret the results cautiously.

PILOT STUDIES

1. National Practice Survey: We recently published a Canadian survey of Pediatric Respirologists’ and Neuromuscular Specialists’ respiratory management of individuals with neuromuscular disease. This assisted in informing the feasibility of the study and confirmed that while no centres are routinely prescribing LVR for use between respiratory exacerbations, there is strong support for research into LVR therapy, with our proposed intervention selected as most important by respondents (Appendix 3).

2. Evaluation of Adherence Monitoring Device: Drs. McKim and Katz have completed a study evaluating the performance of the in-line data-logging device to monitor adherence to LVR, compared to nursing report, on in-patients with neuromuscular disease. We demonstrated substantial correlation in the number of LVR cycles/session between nurses and the device (Wilcoxon signed rank test, p=0.531, Spearman correlation co-efficient 0.76, Intra-class correlation coefficient 0.59 - Appendix 7).

3. Retrospective Cohort Study of Adults with DMD Using LVR: Drs. McKim and Katz have published a manuscript in Archives of Physical Medicine and Rehabilitation, describing the trajectory of pulmonary function in adults with Duchenne Muscular Dystrophy, in whom LVR has been used for up to 2 years. The difference between the two rates was 4.2 %-predicted/year, demonstrating significant benefit of LVR, with an 89% relative reduction in the rate of decline of FVC per year (p < 0.001) (Appendix 2).
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TIMELINE/MILESTONES

STEERING COMMITTEE AND DATA SAFETY MONITORING BOARD

The study Executive Committee will consist of Dr. Katz (PI), as well as Dr. MacLusky, Pediatric Respirologist and Dr. Barrowman, Statistician. Drs. Katz and MacLusky have collaborated previously on a multi-centre cohort study evaluating the impact of non-invasive ventilation in childhood neuromuscular disease. Dr. Katz is currently running a CIHR-funded multi-centre prospective cohort study evaluating the impact of non-invasive ventilation in obese adolescents. She has formal research training with a Master’s of Science and has completed the Royal College Clinician Investigator Program at the University of Toronto.

The Team will be strengthened by Drs. Momoli (Epidemiologist), Dr. Aaron and Ms. Hoey, a senior research coordinator with the CHEO CRU, who have successfully run CIHR-funded multi-centre studies. Drs. McKim and Kovesi have pioneered the introduction of LVR techniques in Canada. Dr. Mah is a Pediatric Neurologist involved in DMD research, who leads the Canadian Pediatric Neuromuscular Group, who support this project (Appendix 15). A Data Safety Monitoring Committee of experienced clinicians and clinical trialists not involved with the study will examine data annually and advise the Steering Committee.
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DSMB Committee Membership

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<tr>
<th>Committee</th>
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<tr>
<td>Safety Monitoring Committee*</td>
<td>Dr. J. Reisman, Dr. Lee Burkholder, Dr. Andrea Benedetti and Dr. Robert Dales</td>
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<tr>
<td>Executive Committee</td>
<td>Dr. Sherri Katz, Dr. Ian MacLusky and Dr. Nick Barrowman</td>
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<tr>
<td>Steering Committee</td>
<td>Co-applicants and Collaborators</td>
</tr>
<tr>
<td>Study Consultants</td>
<td>Dr. S. Aaron</td>
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* Safety Monitoring Committee will be experienced clinicians and trialists, who will not be involved in the day-to-day running of the study.

Committee Roles

The participating Principal Collaborators and their clinical centre staff are responsible for the conduct of the study at their own institutions. They will interact with the Executive Committee on clinical and practical issues related to the trial. Additional collaborators may be added at each centre at the discretion of the principal investigator. There will be a research nurse coordinator (part-time or full-time) specifically assigned to the study.

The Steering committee will include the Executive Committee, as well as co-applicants and collaborators. It will have responsibility for the design, execution, analysis and publication of Trial results. It will convene monthly by conference call and monthly study bulletins will be sent to each site.

A Data Safety Monitoring Committee of experienced clinicians and clinical trialists not involved with the study will examine data annually and advise the Steering Committee on continuation or early termination of the trial, based on clear guidelines defined at the first meeting.

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ACRONYMS

%-predicted – percent predicted  
ALS – Amyotrophic Lateral Sclerosis  
ATS – American Thoracic Society  
CHEO – Children’s Hospital of Eastern Ontario  
CIHR – Canadian Institutes of Health Research  
cmH2O – centimeters of water  
CRU – Clinical Research Unit  
DMD – Duchenne Muscular Dystrophy  
FVC – forced vital capacity (percent-predicted)  
HRQL – health-related quality of life  
ICU – intensive care unit  
LVR – lung volume recruitment  
MCID – minimum clinically important difference  
MEP – maximum expiratory pressure (cmH2O)  
MIC – maximum insufflation capacity (litres)  
MIP – maximum inspiratory pressure (cmH2O)  
NPPV – noninvasive positive pressure ventilation  
PCF – peak cough flow (litres/minute)  
PedsQL – Pediatric Quality of Life Inventory  
RCT – randomized controlled trial  
SD – standard deviation
Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time (STEADFAST)

Katz Jesse's Journey 2013

ANTICIPATED IMPACT/RELEVANCE TO DUCHENNE MUSCULAR DYSTROPHY

In Duchenne Muscular Dystrophy (DMD), a neuromuscular disease for which there is no cure, progressive respiratory muscle weakness results in decline in pulmonary function, leading to impaired quality of life, enormous costs to families and the health care system, and respiratory failure, which is the cause of death in over 85% of patients with this condition. Our proposed study of Lung Volume Recruitment (LVR) therapy in children and youth with Duchenne Muscular Dystrophy is relevant to Jesse’s Journey Foundation, because the intervention we propose to study has the potential to slow the decline in pulmonary function in this condition, and because the intervention is easily performed, inexpensive, and safe. In small studies, it has been shown to considerably enhance lung volume and cough capacity in adults with DMD. This simple, non-pharmacologic treatment, consisting of stacking breaths to inflate the lungs, has potential to preserve lung function by preventing micro-atelectasis and reducing contractures of the intercostal muscles, preventing restriction of the thoracic cage. It also enhances cough efficacy and airway clearance, which may prevent atelectasis and pneumonia. By preserving lung function, LVR has the potential to decrease mortality and improve quality of life for individuals with DMD. The findings from this study can be directly translated into clinical practice, within 3 years, at the conclusion of the project.

There are no long-term controlled prospective studies evaluating LVR as a treatment in neuromuscular disease. As a result, adoption of LVR has been limited, with several groups worldwide calling for further prospective, controlled studies. Our recent Canadian survey revealed that LVR is not routinely prescribed for regular use at any Canadian Pediatric Centre. The potential of regular LVR to maintain lung function (a measure directly related to respiratory complications and mortality) and alter the clinical practice of respiratory health maintenance in this population, must be investigated in order that this simple therapy becomes widely available to those who will benefit. We therefore believe that a randomized controlled trial is critical to establish the role of LVR in the care of DMD patients to assist in recommendations of standards of care for this population both in Canada and worldwide. Results of this study will also have application in the management of other neuromuscular conditions, making this a study of great clinical relevance with direct impact on patient care.
Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time (STEADFAST)

Katz

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(STEADFAST)

APPENDICES

Appendix 1- LVR SET-UP WITH DATA LOGGER
Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time
(STEADFAST)

APPENDIX 2. LVR PILOT DATA


This retrospective cohort study was conducted by Drs. McKim and Katz, evaluating the impact on the rate of pulmonary function decline, of the introduction of twice daily LVR in 20 adult patients (mean age 19.6 years, SD 2.4) with Duchenne Muscular Dystrophy, over a minimum two year period before and after introduction of LVR. The median duration of follow-up post LVR initiation was 26 months (min 7, max 127).

Trajectory of FVC (percent-predicted) over time, before and after LVR initiation
The thin colored lines represent slopes from individual patients. The two thick black lines are the fitted slopes before and after LVR initiation, estimated from a linear regression model with an interaction term to account for the introduction of LVR. The fitted slope prior to LVR initiation was -4.7 percent-predicted per year (95% CI: -5.3, 4.2). The fitted slope after LVR initiation was -0.5 percent-predicted per year (95% CI: -0.9, -0.1). The difference in the rate of decline of FVC was 4.2 percent-predicted per year, which was statistically significant (p<0.001).
Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time (STEADFAST)


The survey was sent to all 56 practicing Pediatric Respirologists in Canada and to all 24 members of the Pediatric Neuromuscular Interest Group (PNIG) comprised of Pediatric Neurologists and Physiatrists. Responses were received from 38 Pediatric Respirologists (66%) and 17 Pediatric Neuromuscular Specialists (66%). Of 38 Respirologists, 33 see DMD patients under the age of 18. Of these 33, only 6 (18%), practicing at 3 centres, reported using LVR in their patients at least twice daily during clinical stability. On average, these Respirologists reported using LVR on 33% of their patients. Of 17 Neuromuscular Specialists, all of whom see DMD patients under the age of 18, only 2 (12%), practicing at a single centre, reported using LVR in their patients at least twice daily during clinical stability. On average, these Neuromuscular Specialists reported using LVR on 50% of their patients.

Study participants were told that a study was being planned to evaluate a respiratory treatment for patients with DMD. When asked what the intervention should be, the majority of Respirologists (61%) indicated manual LVR between respiratory exacerbations. When asked what outcome they would consider most clinically important, 47% indicated change in FVC decline (% predicted) and 37% indicated quality of life. Among Neuromuscular Specialists, the majority (64%) indicated that the intervention should be manual LVR between respiratory exacerbations. When asked what outcome they would consider most clinically important, 25% indicated change in FVC decline (% predicted) and 67% indicated quality of life. While our main focus is on the physiologic benefit of LVR, because of the interest in quality of life as an outcome, it has been included as a secondary outcome for the proposed study.
**APPENDIX 4. List of Study Sites & Letters of Support**

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<th>Centre number</th>
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<th>Investigator</th>
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<td>14</td>
<td>Stollery Children’s Hospital</td>
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APPENDIX 5: STUDY FLOW DIAGRAM & STUDY ACTIVITIES

Study Flow

Potentially eligible Child identified by Physician, based on neuromuscular disease and pulmonary function

Letter of information sent or given to parent and child. If interested in participating in the study they are asked to contact RA or identify their interest to clinic nurse

Interested - Set up appointment for consent

Not Interested

No further contact

Research Assistant meets with parents and child for consent

Consent signed

Note is written in child’s chart regarding consent process and randomization

Child is randomized to Conventional therapy or Conventional therapy plus lung volume recruitment exercises

Conventional therapy plus lung volume recruitment exercises
- Baseline questionnaire
- Baseline PFT testing
- Lung volume recruitment exercises training & measurement of maximal pressure achieved at participating sites only

Conventional therapy
- Baseline questionnaire
- Baseline PFT Testing
- Lung volume recruitment exercises training & measurement of maximal pressure achieved at participating sites only

Confirm child is eligible for study based on results of Baseline FVC
Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time (STEADFAST)

Clinic Visit
Participants will be seen in clinic at Baseline, 6, 12, 18 and 24 months

Telephone follow-up at months 3, 9, 15 and 21 months

At clinic visits: Conventional therapy plus lung volume recruitment exercises
- pulmonary function testing (including FVC, MIC, MIP, MEP and PCF)
- pressure measurements documented during LVR (at participating sites only)
- LVR technique reviewed
- Upload data from data-logger
- Review of AE’s and Medications
- QOL Questionnaire (baseline and 6 months)

At clinic visits: Conventional therapy
- pulmonary function testing (including FVC, MIC, MIP, MEP and PCF)
- pressure measurements documented during LVR (at participating sites only)
- Review of AE’s and Medications
- QOL Questionnaire (baseline and 6 months)

Protocol Version_ Extension Amendment 3_4 June 2015

**Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time (STEADFAST)**

**Jesse’s Journey 2013**

### Study Activities

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<th>3 Month Telephone Visit</th>
<th>6 Month Clinic Visit</th>
<th>9 Month Telephone Visit</th>
<th>12 Month Clinic Visit</th>
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* only for those randomized to Conventional Therapy plus LVR
APPENDIX 6. LUNG VOLUME RECRUITMENT TECHNIQUE FOR THERAPISTS

Definitions

**LVR**
Lung Volume Recruitment refers to breath stacking techniques, which promote maximum insufflation capacity. This includes the use of a self-inflating resuscitator bag with appropriate one-way valve and a mouthpiece. NEVER use a self-inflating resuscitator bag with one-way valves in place on an intubated patient to perform LVR.

**MIC**
Maximum Insufflation Capacity (MIC) measurement (Litres) is the maximum volume of air that can be stacked within a patient’s lungs beyond spontaneous vital capacity. MIC is attained when the patient takes a deep breath, holds his breath and then breath stacking is applied using a LVR resuscitator bag.

Criteria
Patient must be alert, cooperative with respiratory manoeuvres and able to communicate

Absolute Contraindications
- Presence of hemoptysis, untreated or recent pneumothorax, nausea, asthma and recent lobectomy
- Increased ICP
- Impaired Consciousness
- DO NOT perform LVR with resuscitation bag if endotracheal tube or tracheostomy tube is in place

Relative Contraindications
- Therapy following meals
- History of Pneumothorax
- Pleural Effusion
- Cardiac Instability
- Patients with long standing thoracic cage restriction may have severely reduced thoracic compliance and will require slow incremental insufflations during initial LVR period.
- Bullous emphysema or risk of pneumothorax or pneumomediastinum

Equipment
- Self Inflating Resuscitation Bag, clearly identified NOT for CPR
- 50-100 cc corrugated tubing
- One-way valve closest to bag
- One-way valve with inner silicone piece removed, but inner screen intact, positioned closest to patient (prevents aspiration in case silicone valve becomes dislodged!)
- mouthpiece
- nose clip

Procedure for Therapist to Teach
Assemble necessary equipment
Have patient sit (or lie) as upright as possible on edge of bed or in chair. This technique may be done supine or semi fowlers depending on patient situation. Assess for c-spine stabilization and ensure that head and neck are supported if an assisted cough is to be performed.
Place nose clip
Establish with patient the signal he/she will use to notify you that MIC is reached (blinking for example)
Ask patient to take a breath in and hold and exhale completely before beginning first breath in with self inflating bag.
Ask patient to place lips tightly around mouthpiece
Gently squeeze the resuscitation bag, coordinating with the patient’s inspiration. Assess for leaks throughout the manoeuvre.
Squeeze the bag 2-5 times until you feel that the lungs are full (assess chest expansion etc) or until the patient indicates with a signal that MIC is reached.
Patient may feel a stretch in the chest or slight discomfort
Once the lungs are full, remove mouthpiece and ask the patient to hold the maximum insufflation for 2-5 seconds if possible.
Exhale slowly, preferably through pursed lips, or measure PCF (LVR assisted) and MIC
Repeat steps 5-11 three to five times.
If secretions are present, ask the patient to produce a strong cough from maximum insufflation capacity.

Note:
For very young patients steps 5 and 10 are very difficult. Children will generally wait to take a breath in once the mouth piece is in place. They also tend to exhale as soon as the mouthpiece is removed. As they get older and more used to the technique you can add these steps in. Remember the total respiratory cycle is much shorter than an adult’s, especially for those with compromised lung function who compensate with an increased respiratory rate. A breath hold for a very stiff lung after breath stacking may be too difficult for some children. You will need to modify the cycles and instructions for each child. The most important thing is to achieve MIC at least 3 times per session.

Sessions are usually performed:
With assisted cough BID and prn if secretions are present...a maximum of Q10 minutes (avoid hyperventilation!)
Ideally before meals and at bedtime

References
Carol Leblanc RRT, Lung Volume Recruitment for Paralytic/Restrictive Disorders Ottawa Hospital Respiratory Therapy Policy/Procedure, April 2007
APPENDIX 7. DATA-LOGGER TO MONITOR ADHERENCE

Technology:
The device recording the LVR manoeuvre mechanically will be activated when two pressure switches are closed. One switch will close when a minimum pressure threshold is detected at the mouthpiece; the second switch will close when a minimum pressure threshold is detected at the bag. It is only when both switches are closed, that a count will be recorded. This is so that if there is an inadequate seal at the mouthpiece or the bag is unintentionally squeezed, the device will not count it. The pressure switches chosen for this application are miniature adjustable pressure switches by Dwyer (Model #MDA-111). The recording component of the device will hold in its memory the number of counts until the memory is cleared. The recording device is an event data logger by Omega (Model # OM-CP-EVENT110). This data logger can record and store the date and time for 13,000 counts continuously over an expected battery life of at least three months (maximum 6 months). The device sensitivity will be individually set and confirmed to record accurately when a minimum pressure (5 cm H2O) is achieved in each patient prior to data collection. It was found through preliminary trials that the minimum pressure threshold that generally produced the best results was approximately 5 cmH2O. The data will be downloaded using a USB interface and Windows software designed for this data logger (OM-CP-IFC200).

Study:
Drs. McKim and Katz have recently completed a study investigating the performance of the data-logger measuring frequency of LVR treatment, as compared to records made by the nurses administering the treatment, in adult neuromuscular and spinal cord disease in-patients in the Ottawa Hospital Rehabilitation Centre. The full dataset contains 243 matched pairs of sessions from 19 treatment periods on 125 days from 8 patients.

Analysis of the number of cycles recorded by nurses and by the counters showed agreement in 215 pairs (88.5%). There was not statistically significant evidence of a systematic difference between nurses and counters (Wilcoxon signed-rank test, p=0.531). The Spearman correlation coefficient (0.76) indicated substantial correlation, and the intra-class correlation coefficient (0.59) indicated moderate to substantial agreement.
APPENDIX 8. RESCUE TREATMENT

During acute respiratory exacerbations, subjects may use assisted cough techniques, including LVR with or without an abdominal thrust and/or mechanical in-exsufflator, even if they are in the control population, if deemed appropriate by the treating physician. Brief use of such treatment is unlikely to affect the primary outcome, and therefore is not a criterion for withdrawal from the study. Rescue treatment is typically initiated and carried out by clinical care teams during hospitalizations for respiratory exacerbations (Appendix 4), which are expected to occur less than once per year per patient and last, on average, two weeks. Patients and their families are not taught LVR manoeuvres during a hospitalization; therefore we do not feel that treatment with LVR during an acute hospitalization will contaminate the control group’s treatment regimens once they are discharged from hospital. The use of any rescue medications or treatments will be recorded for both treatment groups.
APPENDIX 9: Justification for co-variates in minimization analytical model

Systemic steroids: It has been documented that boys 10-18 years of age with Duchenne muscular dystrophy (DMD) treated (with deflazacort have significantly better pulmonary function than boys not treated. 1 As this therapy is not uniformly applied in Canada2, often because it has significant side effects associated with it, it was necessary to minimize on steroid use or non-use.

Baseline FVC: Pulmonary function in DMD has been shown in a longitudinal study to have an ascending, plateau, and descending phase during the course of the disease.3 Based on the inclusion criteria of age and range of FVC 30-70% of predicted, we expect that the majority of individuals will be in the descending phase of FVC decline. However, as baseline FVC may predict the expected rate of decline of FVC, it was included in the analytical model.

Scoliosis: As scoliosis can result in significant chest wall restriction and contribute to restrictive lung disease, thereby reducing FVC, this too was included as a co-variate. 4

Age: As pulmonary function decline and muscle weakness progress predictably with age3, this is an important variable in determining expected decline in pulmonary function.

Ambulatory Status: As the progression from ambulation to wheelchair dependency is an important marker of disease progression and muscle weakness, this variable was included in the analytical model.5 Loss of ambulation may also be associated with development of scoliosis.6

References

APPENDIX 10: RESPIRATORY SYMPTOM QUESTIONNAIRE

Respiratory SYMPTOM questionnaire

Administered by Research Assistant at Telephone Visit

The purpose of this questionnaire is to obtain information about your child for the past 3 months. We are asking the same questions of each participant in the study. All the information will be kept confidential.

Subject ID: __________     Date Completed: ______________

PERSON COMPLETING THE QUESTIONNAIRE:
Child’s mother:   Child’s father:   Female guardian   Male guardian

In the past 3 month, has the child had any respiratory problems?

Yes                                     No

If yes did your child have a

1. cold or runny nose
2. cough apart from colds
3. wheezy or whistling sounds in chest when he has a cold
4. wheezy or whistling sounds in chest between colds
5. attack of wheezing or chest congestion that has caused him/her to be short of breath
6. any change in the volume or color of respiratory secretions
7. experienced chest pain during LVR

In the past 3 month, has the child had any cardiac problems?

Yes                                     No

If yes, did your child

1. experienced chest pain at other times than during LVR
2. palpitations(feeling that your heart is skipping beats) during LVR
3. palpitations(feeling that your heart is skipping beats) other than during LVR

In the past 3 month, has the child had any other symptoms?

Yes                                     No

If yes what were the symptoms?
In the past 3 months, has this child needed to visit a physician?

Yes. Number of times ________________       No

If Yes

Why did you visit the physician?

In the past 3 months, has this child been admitted to the hospital?

Yes,                                                                      No

If yes:

What hospital was your child admitted to?

Why was your child admitted?

Was your child in ICU during this visit?

How long was your child in hospital?
APPENDIX 11: LVR SATISFACTION QUESTIONNAIRE

Administered by Research Assistant at Telephone Visit
The purpose of this questionnaire is to obtain information about your child for the past 3 months. We are asking the same questions of each participant in the study. All the information will be kept confidential.

Subject ID_________________  Date completed_____________

Person completing questionnaire : □ Participant    □ Caregiver

Following questions asked only for group randomized to the Conventional Treatment plus LVR

How many minutes does it take you to do your lung volume recruitment (LVR) each session? __________________

How many LVR sessions do you do per day? __________________

Does LVR help you to move / clear chest secretions?  
Yes      No

Can you be flexible in the location where LVR is performed?  
Yes      No

Are you comfortable in performing the LVR technique?  
Yes      No

Are you satisfied with LVR therapy?  
Yes      No

________________________________________________________________________________________

Any other comments __________________________________________________________
_____________________________________________________________________________

## APPENDIX 12 SELF-REPORT USAGE QUESTIONNAIRE

Reviewed in clinic

### February 2015

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Protocol Version_ Extension Amendment 3, 4 June 2015
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- cough / cough / headache / others ___________________________
- cough / cough / headache / others ___________________________
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APPENDIX 13: PedsQL Generic Core

The following Questionnaires will be administered biannually at Clinic Visits. English and French versions will be used where validated questionnaires are available.

PedsQL Generic Core - Version 4.0
- Child Report (ages 8 - 12)
- Parent Report for Children (ages 8 - 12)
- Parent Report for Young Children (ages 5 - 7)
- Teen Report (ages 13 - 18)
- Parent for Teen (ages 13 - 18)

Peds QL Neuromuscular Module - Version 3.0
- Child Report (ages 8 - 12)
- Parent Report for Children (ages 8 - 12)
- Parent Report for Young Children (ages 5 - 7)
- Teen Report (ages 13 - 18)
- Parent for Teen (ages 13 - 18)
APPENDIX 14: ADVERSE EVENT DEFINITIONS

Definitions

The definitions of adverse events (AEs) and serious adverse events (SAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The investigator at each site is responsible for ensuring this.

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical subject administered a treatment, which does not necessarily have to have a causal relationship with the treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (i.e. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or therapy, whether or not considered related to the medicinal product or therapy.

The phrase “responses to a medicinal product or therapy” means that a casual relationship between a medicinal product or therapy and an adverse event is at least a reasonable possibility, (i.e. the relationship cannot be ruled out)
APPENDIX 15: CASE REPORT (DATA COLLECTION) FORM

Baseline Data Collection

Inclusion and Exclusion met
Consent date
Randomization
Demographic data
initials,
DOB,
gender
Vital signs
Height and weight, arm span
Baseline Pulmonary function tests: FVC, MIP, MEP, MIC, PCF, LVR-assisted PCF and MIC
Initial positive pressure setting
Baseline Medical History
Is Scoliosis present? If present: mild (0-10°), moderate (10-20°) severe (> 20°), Cobb angle (if available)
Wheelchair dependent?
Use of NPPV?
If yes record the setting and length of use
Use of In-EX at home?
If yes record the setting and length of use
Concomitant medications
Quality of life Questionnaires

Data Collection during Study – Clinic Visits at 6, 12, 18 and 24 months (4 visits)

Vital Signs
Height and weight
Ambulatory status: Yes/No
Scoliosis (annually) – Presence: Yes/No. If present: mild (0-10°), moderate (10-20°) severe (> 20°), Cobb angle (if available)
Pulmonary function tests: FVC, MIP, MEP, MIC, PCF, LVR-assisted PCF and MIC
Pressure measurement during LVR: maximal pressure achieved with LVR, average pressure achieved with LVR
Number of times per day LVR done (if applicable)
Physiotherapy – Frequency, suctioning required
Re-assess use of LVR – retrain as necessary
Collection of adverse events
Concomitant medications
Respiratory Symptom Review

Quality of life Questionnaires (every 6 months)
Data download from data-logger (for LVR Group)
Symptom and satisfaction questionnaires (every 3 months)
Data collection if ER visit and/or Hospital Admission

Date of visit (admission)
Date of Discharge
Admitting Diagnosis
Discharge diagnosis
Was Lung Volume Recruitment used during this visit/admission?
   If yes – provide details
Was the In-Exsufflator used during this visit/admission?
   If yes – provide details
Medications received during Emergency/Hospital stay
Procedures done
Physio and RT time
Adverse Events
Respiratory Symptoms and exacerbations
Courses of antibiotics for respiratory infections
Hospitalization for respiratory infections
Days in intensive care for respiratory exacerbations
Days intubated and mechanically ventilated for respiratory exacerbations