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

Katz

Jesse's Journey 2013

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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). 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. 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. There is no definitive treatment for the underlying condition. Mortality increases substantially in early adulthood, with a median life expectancy of 25-35 years. Respiratory complications are the primary cause of morbidity and mortality, as progressive inspiratory and expiratory respiratory muscle weakness leads to hypoventilation and/or recurrent pneumonia secondary to decreased cough efficacy. 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. Ultimately, 24-hour ventilatory support is required, necessitating continuous caregiver support, and significant healthcare costs. 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.

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. 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.

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).\textsuperscript{30} 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.\textsuperscript{19,21,31} 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.\textsuperscript{14} 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.\textsuperscript{32} 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.\textsuperscript{19,33-36} 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.\textsuperscript{37} It is difficult to determine however, whether the improved outcomes in these studies were due to NPPV or the mechanical in-sufflator.

A single cohort study of adults and children using mechanical in-sufflation twice daily (as per self-report) demonstrated improvement in MIC and PCF over time.\textsuperscript{23} 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.\textsuperscript{38} 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,\textsuperscript{39} 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.\textsuperscript{40} 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.\textsuperscript{14,19,29,33,41,42} The paucity of long-term clinical studies to demonstrate its efficacy has left questions, with several groups worldwide calling for further prospective, controlled studies.\textsuperscript{21,38,43–46} It was listed as a top research priority in recent British Thoracic Society Guidelines on “Respiratory Management of Children with Neuromuscular Weakness”.\textsuperscript{47} 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.\textsuperscript{48}

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 month 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**

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

**Exploratory**

- Maximal and average pressure achieved with LVR (cmH₂O)
- 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)
- 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.\(^\text{48}\)

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,\(^\text{62}\) 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;\(^\text{56,63}\) 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%\(^\text{63}\)). 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.\(^\text{64,65}\)

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.\(^\text{66,67}\)

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.\(^\text{68}\)

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

Katz

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

Katz Jesse's Journey 2013

DSMB
Committee Membership

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<tr>
<td>Safety Monitoring Committee*</td>
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<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.
Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time (STEADFAST)

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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)

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REFERENCES

References


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61. Suarez AA, Pessolano FA, Monteiro SG, Ferreyra G, Capria ME, Mesa L, Dubrovsky A, De Vito EL. Peak flow and peak cough flow in the evaluation of expiratory muscle weakness and bulbar impairment in patients with...
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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).

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

Katz Jesse's Journey 2013

APPENDIX 4. List of Study Sites & Letters of Support

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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

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

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

Katz

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)

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

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Study Activities

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* only for those randomized to Conventional Therapy plus LVR

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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?
APPE NDX 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

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February 2015
*Sick
  - cough / cough / headache / others ___________________________
  - cough / cough / headache / others ___________________________
  - cough / cough / headache / others ___________________________
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)

PedsQL 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 causal 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 (0-10o), moderate (10-20o) severe (> 20o), 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 (0-10o), moderate (10-20o) severe (> 20o), 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