APPENDIX I - MEDLINE Search Strategy

The term Amyotrophic Lateral Sclerosis was combined with one other term (e.g. ALS AND Cough Augmentation) for multiple searches to retrieve titles. One combination of 3 search terms was included, ALS AND Physical Therapy AND Respiratory Failure.

Search Terms: Amyotrophic Lateral Sclerosis, Respiratory Insufficiency/Failure, Respiratory Therapy/Exercise, Physical Therapy/Interventions, Lung Volume Recruitment/Manual Breath Stacking/Lung Inflation Training, Coughing, Cough Augmentation, Inspiratory Muscle Training, Diaphragmatic Breathing/Diaphragm Training, Percussion and Vibration/Chest Physical Therapy

Search Limits: English language

APPENDIX II - Study Intervention & Results

Author: Cheah, 2009
Experiment Design: Double Blind RCT
Intervention Duration: 12 Weeks
Intervention:

- ***Experiment Design:*** Group Introduction: 1-4visits. Home Instruction: IMT for 10 minutes, 3 times per day, 7 days per week for 12 weeks. Intensity initially set to 15% of SnP, progressing to 30%-45%-60%. Also training diaries were used.
- ***Control Design:*** Sham IMT Treatment (spring-loaded valve removed, no resistance). Home Instruction: 10 minutes, 3 times per day, 7 days per week for 12 weeks.

Outcome Measures: ALSFRS-R, Vital Capacity, FVC, MIP, TLC, SnP, 6MWT
Results: Results reported in Percentage Mean Difference (SD); CI, statistical significance p
FVC: Mean difference 4.59(3.02); CI 1.85 - 11.02; p = 0.15
VC: Between group difference 1.44(no SD); CI 4.24 - 7.13; p = 0.60
TLC: Between group mean difference 7.939(4.66); CI 2.07-17.93; p = 0.11
MIP: Between group mean difference 6.10(6.93); CI 8.58 - 20.79; p = 0.39
ALSFRS-R: Between group mean difference 0.049(0.73); CI 1.51-1.60; p = 0.95
6MWT: Between group mean difference in the distance walked, 6.00(3.61); CI 1.80 -13.80; p = 0.12

Post-Cessation: IMT Strength declined post-cessation for both groups (SnP: 6.55(1.88); CI 2.55 -10.54; p </= 0.05; MIP: 4.53(2.15); CI 0.03 - 9.08, p </= 0.05). Max Expiratory pressure remained constant (1.139 (3.33); CI 6.07 - 8.34; p = 0.74) throughout training, however as expected it declined with cessation (4.309 (1.52); CI 1.02 - 7.59; p < 0.05).

No Significant differences in blood gases. ALSFRS-R declined over the study. Percentage-mean difference for VC was higher in the experiment group versus control. Little change in Experiment Group TLC over intervention. TLC declined progressively in the control group throughout the study period. MIP was found to be greater in experimental group versus control group. 6MWT declined over study, but Exp walked further 5th/6th visits. Inspiratory muscle training may potentially strengthen the Inspiratory muscles and slow the decline in respiratory function in patients with ALS/MND

Author: Cleary, 2012
Experiment Design: Repeated measures, Cross-Over Design

Intervention Duration: 2 Days
Intervention:

- ***Experiment Design:*** LVR Treatment: 5 Maximal Insufflations, with 2 trials of Augmented Cough
- ***Control Design:*** Same as intervention, subjects served as their own control.

Outcome Measures: FVC, SnP, PCEF
Results: Results reported as Mean (SD)

FVC	PCEF
Experiment Baseline: 2.23 (.93)	Experiment Baseline: 251.35 (118.55)
Control Baseline: 2.11 (.86)	Control Baseline: 263.08 (130.24)
Experiment 15 Minutes post intervention: 2.30 (.92)	Experiment 15 minutes post intervention: 305.00 (140.70)
Control 15 Minutes post intervention: 2.11 (.83)	Control 15 minute post intervention: 255.19 (120.90)
Experiment 30 minutes post intervention: 2.25 (.95)	Experiment 30 minutes post intervention: 295.38 (122.99)
Control 30 minutes post intervention: 2.14 (.82)	Control 30 minutes post intervention: 259.62 (122.25)

RM-ANOVA revealed a significant interaction effect between treatment condition and time for effects of LVR on FVC.

Mean FVC was significantly higher at 15 minutes post-intervention in the Experiment Group (2.30 +/- 0.92) versus at 15 minutes post-intervention in the Control Group (2.11 +/- 0.83).

There were no statistically significant differences for SnP as a result of treatment condition or time.
Participants had significantly higher PCEF rates in the treatment condition (15 minutes: 305.00 +/- 140.70; 30 minutes: 295.38 +/- 122.99) versus the control (15 minutes: 255.19 +/- 120.90; 30 minutes: 259.62 +/- 122.25) at 15 minutes and 30 minutes.

Within the treatment condition, participants had significantly higher PCEF rates immediately post, and at 30 minutes post treatment compared to baseline. No significant decreased in PCEF was noted over the 30 minutes interval between times 2 (15 minutes) and 3 (30 minutes).

Additional Comments: Each participant completed one treatment session and one control session, separated by a minimum of 24 h and a maximum of seven days

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Author: Mustfa, 2003
Experiment Design: Repeated Measures Design
Intervention Duration: 1 Day
Intervention:

- ***Experiment Design:*** Subjects coughed into a tight fitting full face mask. 5 coughs performed:

1) Maximal unaided cough
2) Maximal Aided Cough with PT provided abdominal thrust
3) Exsufflation Only on Cough Assist
4) Insufflation Only on cough assist

5) Combined in/exsufflation on cough assist.
6) Each cough performed in random order to avoid bias.

- ***Control Design:*** Same as intervention, 10 healthy controls used to examine difference.

Outcome Measures: PCEF

Results: Results reported as Mean Difference (SD); % Increase in PCEF; statistical significance p

Bulbar Patients	Non-Bulbar Patients
Unassisted 178 (61); 0%; --	Unassisted 217 (84); 0%; --
Manual Assist 197 (63); 11%; p<0.01	Manual Assist 244 (83); 13%; p<0.001
Exsufflation 225 (76); 26%; p<0.001	Exsufflation 279 (87); 28%; p<0.001
Insufflation 188 (64); 6%; --	Insufflation 226 (86); 4%; --
Insufflation-Exsufflation 212 (75); 19%; p<0.05	Insufflation-Exsufflation 264 (73); 21%; p<0.001

Manual assistance increased flow 11% in bulbar (p<0.01), and 13% in non-bulbar (p<0.001) patients. Mechanical Insufflation-Exsufflation increased flow 17% in healthy subjects (p<0.05), 26% in bulbar (p<0.001), and 28% in non-bulbar (p<0.001) patients. The greatest improvements were noted in those with the weakest coughs.

Author: Nardin, 2008

Experiment Design: Repeated Measures Pilot Study

Intervention Duration: 3 Sessions

Intervention:

- ***Experiment Design:*** Patients instructed on Diaphragmatic Breathing: Inhalation count of 3, Exhalation count of 5 for 5 cycles. Progress to inhale count of 3, exhale count 10 for 5 cycles. Progress to inhale count 3, exhale count 15 for 5 cycles. Repeated for 10 minutes. Home Instruction was 5x10 minutes per day. Practice Logs provided.
- ***Control Design:*** Same as intervention, subjects served as their own control.

Outcome Measures: FVC

Results: Results reported as Mean (SD)

FVC
Baseline: 69.5 (14.56)
6 weeks post Intervention: 64.875 (22.25)
12 weeks post Intervention: 64 (20.16)

No significant improvement in the proposed outcome measures post instituting diaphragmatic training.

There was a non-significant trend towards a slower rate of decline in respiratory function in those who mastered the technique, however it should be noted that only 50% of participants were able to successfully change their pattern of breathing.

Author: Pinto, 2012

Experiment Design: Parallel Control Group, Delayed Start Design
Intervention Duration: 8 months
Intervention:

- ***Experiment Design:*** Active IMT Training Protocol:2x/day for 8 months. Each subject practiced for 10 minutes, with intensity set at 30-40% MIP, twice/day.
- ***Control Design:*** Placebo IMT Training Protocol for first 4 months, then progress to Active IMT Training Protocol for last 4 months. During placebo period, subjects would breath into the respiratory device at the lowest possible load for the same set parameters.

Outcome Measures: ALSFRS, R of ALSFRS-R, FVC, PCEF (L/min), MIP/MEP, MVV, SnP, Phrenic Nerve Amplitude (mV), Fatigue, QofL
Results: All Results reported as Between Group Mean Difference (SD), CI, statiscal significance p

ALSFRS 0-4 Months: 0.846 (1.455), CI −2.157 to 3.849, p = 0.566 4-8 Months: 2.333 (2.64), CI −3.141 to 7.808, p = 0.386 0-8 Months: 2.051 (2.625), CI −3.463 to 7.564, p = 0.445	R of ALSFRS-R 0-4 Months: 0.077 (0.16), CI −0.254 to 0.407, p = 0.635 4-8 Months: 0.167 (0.297), CI −0.45 to 0.783, p = 0.581 0-8 Months:−0.03 (0.375), CI −0.819 to 0.758, p = 0.937
FVC (sit) 0-4 Months: 10.86 (7.324), CI −4.254 to 25.978, p = 0.151 4-8 Months; 20.71 (9.996), CI −0.073 to 41.502, p = 0.051 0-8 Months: 5.91 (8.642), CI −12.323 to 24.143, p = 0.503 PCEF (sit) 0-4 Months: −5.446 (9.742), CI −25.552 to 14.66, p = 0.581 4-8 Months: 18.801 (14.4), CI −11.154 to 48.755, p = 0.206 0-8 Months: 6.671 (11.99), CI −18.63 to 31.972, p = 0.585	FVC (lay) 0-4 Months: 6.4 (8.434), CI −11.006 to 23.806, p = 0.455 4-8 Months: 14.575 (8.8), CI −3.908 to 33.058, p = 0.115 0-8 Months: 9.433 (8.628), CI −8.857 to 27.724, p = 0.29 PCEF (lay) 0-4 Months: −5.769 (10.94), CI −28.338 to 16.799, p = 0.603 4-8 Months: 9.366 (13.59), CI −19.186 to 37.917, p = 0.5 0-8 Months: 10.367 (10.3), CI −11.466 to 32.199, p = 0.329
MIP (sit) 0-4 Months: −8.154 (10.51), CI −29.85 to 13.538, p = 0.445 4-8 Months: 7.22 (11.157), CI −15.983 to 30.423, p = 0.525 0-8 Months: −13.9 (11.67), CI −38.417 to 10.619, p = 0.249	MIP (lay) 0-4 Months: −8.846 (10.50), CI −30.521 to 12.829, p = 0.408 4-8 Months: −1.864 (11), CI −24.73 to 21.003, p = 0.867 0-8 Months: −8.22 (12.894), CI −35.557 to 19.112, p = 0.533
MEP (sit) 0-4 Months: −7.615 (11.84), CI −32.06 to 16.827, p = 0.526 4-8 Months: −5.485 (12.94), CI −32.399 to 21.429, p = 0.676 0-8 Months: −11.19 (15.73), CI −44.241 to 21.857, p = 0.486	MEP (lay) 0-4 Months: −5.385 (12.94), CI −32.093 to 21.324, p = 0.681 4-8 Months: −3.265 (12.77), CI −29.814 to 23.284, p = 0.801 0-8 Months: −3.222 (15.59), CI −36.261 to 29.816, p = 0.839
MVV (sit) 0-4 Months: −2.508 (10.22), CI −23.597 to 18.582, p = 0.808 4-8 Months: 25.17 (12.94), CI −1.729 to 52.073, p = 0.065 0-8 Months: −0.961 (11.76), CI −25.778 to 23.856, p = 0.936	MVV (lay) 0-4 Months: −0.015 (10.53), CI −21.738 to 21.707, p = 0.999 4-8 Months: 21.743 (12.31), CI −3.852 to 47.338, p = 0.092 0-8 Months: 2.1 (11.023), CI −21.269 to 25.469, p = 0.851
SnP (sit) 0-4 Months: −10.385 (9.72), CI −30.442 to 9.673, p = 0.296 4-8 Months: −6.583 (12.06), CI −31.666 to 18.5, p = 0.591 0-8 Months: −18.63 (12.57), CI −45.146 to 7.891, p = 0.157	SnP (lay) 0-4 Months: −16.62 (10.47), CI −38.214 to 4.983, p = 0.125 4-8 Months: −6.34 (11.434), CI −30.12 to 17.438, p = 0.585 0-8 Months: −22.035 (12.8), CI −49.286 to 5.216, p = 0.105

SpO2
0-4 Months: 0.915 (0.435), CI 0.018 to 1.812, p = 0.046
4-8 Months: 1.055 (0.615), CI −0.228 to 2.337, p = 0.102
0-8 Months: 0.394 (0.61), CI −0.899 to 1.688, p = 0.5267

No significant differences between the two patient groups. Within group analyses demonstrated Inspiratory exercise promotes a transient improvement in the respiratory sub-score on the ALSFRS and in maximal voluntary ventilation, peak expiratory flow, and SnP.
Additional Comments: Results reported as between group mean difference and associated (standard deviation), followed by CI, and p. Respiratory Function tests were taking in various positions such as laying, sitting.

Author: Pinto, 2013
Experiment Design: Follow-Up Comparison to Historical Control
Intervention Duration: From 8-32 months
Intervention:

- ***Experiment Group:*** Active IMT Training Protocol: 2x/day for 8 months. Each subject practiced for 10 minutes, with intensity set at 30-40% MIP, twice/day.
- ***Control Group:*** Active IMT Training Protocol: 2x/day for 8 months. Each subject practiced for 10 minutes, with intensity set at 30-40% MIP, twice/day.

Outcome Measures: ALSFRS-R, R of ALSFRS-R, FVC (% predicted), Total Survival Time (months), Phrenic Nerve Amplitude (mV)
Results:

	Respiratory exercise	Gender	Diagnostic delay (months)	ALSFRS	RofALSFRS-R	FVC (% predicted)	Mean PhrenAmpl (mV)
Kaplan Meier Analysis (χ^2 ; p)	5.217; 0.022 □	3.302; 0.069	3.781; 0.052	0.874; 0.35	0.016; 0.9	5.671; 0.017 □	1.619; 0.203
Cox proportional hazards model (HR (95% CI); p)	2.284 (1.08 – 4.85); 0.032 □ (no exercise)	4.145 (1.57 – 10.96); 0.004 □ □ (males)	-	-	-	-	3.038 (1.25 – 7.42); 0.015 □ (low PhrenAmpl)
Total Population (n=34)							

Participants involved in the experimental group survived longer than those in the historical control group (36.99+/-13.1 months versus 24.06+/-11 months respectively p<0.001).
FVC was a significant prognostic factor for the experiment group while Diagnostic Delay was a significant prognostic factor for the Historical Control.

Patients in the Historical Control group had an increased hazard of 2.284-fold (HR = 2.284, 95% CI 1.075-4.85;0.32). Values of PhrenAmp </= 0.70 mV increased hazard by 3.038-fold compared to those >0.70 mV (HR 3.038, 95% CI 1.245-7.415;0.015). Male Gender increased hazard by 4.145 (HR 4.145, 95% CI 1.567-10.962; 0.004).

Additional Comments:
This is a continuation of the previous PINTO 2012 Study, comparing subjects (combination of previous experiment and control groups) to historical controls.

Author: Senent, 2011
Experiment Design: Repeated Measures Design
Intervention Duration: 1 Day
Intervention:

- ***Experiment Design:*** 3 MAC Techniques:
- All maneuvers performed on the same day with 10-15 minutes interval breaks between segments.1 hour rest between manual versus instrumental.

1) Unassisted cough
2) Coached unassisted cough
3) Cough with abdominal thrust.
4) 4 Instrumental techniques:
5) abdominal thrust with air stacking
6) abdominal thrusts and BiPAP
7) abdominal thrusts plus IPAP 30 cm H20
8) cough assist via in/exsuffalator.

- ***Control Design:*** Same as intervention, subjects served as their own control.

Outcome Measures: PCEF
Results: PCEF
Results reported as Median (25^{th} percentile – 75^{th} percentile)

Baseline Bulbar: 42 (35–130) Non-Bulbar: 89 (40–106)	
Coached Unassisted Cough Bulbar: 67 (37–112) Non-Bulbar: 124 (35–165) Manually Assisted Cough (abdominal thrust) Bulbar: 103 (99–146) Non-Bulbar: 105 (31–134) Manually Assisted Cough (abdominal thrust with air stacking) Bulbar: 298 (263–352) Non-Bulbar: 148 (113–354)	Machine Assist (abdominal thrust, with patients BiPAP) Bulbar: 133 (88–564) Non-Bulbar: 241 (113–697) Machine Assist (abdominal thrust, with patient ventilator IPAP of 30 cm H2O) Bulbar: 107 (93–289) Non-Bulbar: 255 (224–428) Machine Assist (in/exsufflator (CoughAssist®) Bulbar: 436 (244–630) Non-Bulbar: 491 (192–580)

Conclusions: No statistically significant difference between the bulbar and the non-bulbar groups. PCEF values were statistically better with instrumental techniques versus manual techniques (p<.0001). There was no difference between the three manual techniques, nor was there any difference between the instrumental techniques.The in/exsuffulator was not always the best tool for cough augmentation.

Abbreviations: * Statistically Significant, CI – 95% Confidence Interval , SD – Standard Deviation, FVC – Forced Vital Capacity, PCEF – Peak Cough Expiratory Flow, SnP – Sniff nasal Pressure, MIP – Maximal Inspiratory Pressure, MEP – Maximal Expiratory Pressure, ALSFRS – Amyotrophic Lateral Sclerosis Functional Rating Scale

APPENDIX III - Individual Study Risk of Bias Assessment

Cheah, 2009

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low Risk	After baseline measurement, participants were allocated to either experimental (IMT) or control (sham IMT) groups using permutated block randomization process.
Allocation concealment (selection bias)	Low Risk	Consecutively numbered opaque envelopes were prepared and sealed containing group allocation. Physical Therapists not linked to the study delivered envelopes with appropriate IMT device to the participants.
Blinding of participants and personnel (performance bias)	Low Risk	Investigators and participants were both blinded.
Blinding of outcome assessment (detection bias)	Low Risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low Risk	Experiment Group 1 patient lost to follow up (due to patient death) Control Group 0 patients lost to follow up
Selective reporting (reporting bias)	High Risk	No reporting of individual group mean and standard deviations post-interventions. Only group difference.
Other bias	Low Risk	--

Cleary, 2013

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	High Risk	Subjects were counterbalanced to receive intervention, versus no intervention (control condition).
Allocation concealment (selection bias)	Low Risk	Not Described. This study used participants as their own control.

Blinding of participants and personnel (performance bias)	High Risk	All subjects underwent the same experimental design.
Blinding of outcome assessment (detection bias)	Unclear Risk	Not described.
Incomplete outcome data (attrition bias)	Low Risk	No attrition noted. All participants were tested within a 1 week span.
Selective reporting (reporting bias)	Low Risk	As far as it is possible to tell.
Other bias	Unclear Risk	Potential publication bias noted. The author first used this experiment in a dissertation at the University of Alberta, and results from this document were being implemented at the ALS/MND Clinic from which the subject pool was derived. Additionally, subjects were already well versed within the training regiment. This article was used to demonstrate the effectiveness of such a program within this population.

Mustfa, 2003

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	High Risk	This study used 10 healthy controls, versus 47 patients with ALS.
Allocation concealment (selection bias)	High Risk	Both the experiment and control group underwent the same intervention.
Blinding of participants and personnel (performance bias)	High Risk	Both the experiment and control group underwent the same intervention. Both the researcher and the participant were asked to rank which interventions were more effective at the end of the study.
Blinding of outcome assessment (detection bias)	Unclear Risk	Not Described.
Incomplete outcome data (attrition bias)	Low Risk	No attrition noted. All participants were tested on the same day.
Selective reporting (reporting bias)	Low Risk	As far as it is possible to tell.
Other bias	Unclear Risk	Summation Effect - Since all of the interventions were completed in the same order, on the same day, there may be an inherent effect of summation secondary to lack of randomization pertaining to the order of intervention. Manual interventions always preceded mechanical interventions, however, as reported by the author interventions each subset (manual versus mechanical) the interventions were randomized. The lack of order randomization may have allowed the mechanical device to demonstrate a significant.

Nardin, 2008

Bias	Authors' judgment	Support for judgment
Random sequence generation	High Risk	Not Described. This study used participants as their own control.

(selection bias)		
Allocation concealment (selection bias)	High Risk	Not Described. This study used participants as their own control.
Blinding of participants and personnel (performance bias)	High Risk	All subjects underwent the same experimental design.
Blinding of outcome assessment (detection bias)	Unclear Risk	Not described.
Incomplete outcome data (attrition bias)	High Risk	Attrition 20% 2/10 participants did not complete the study.
Selective reporting (reporting bias)	Low Risk	As far as it is possible to tell.
Other bias	Low Risk	--

Pinto, 2012

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low Risk	Randomization via permuted block design.
Allocation concealment (selection bias)	Unclear Risk	Not described.
Blinding of participants and personnel (performance bias)	Low Risk	Participants and personnel both blinded.
Blinding of outcome assessment (detection bias)	Low Risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias)	High Risk	Experiment Group 11/13 (1 participant unable to cope, 1 withdrawn from study secondary to fast progression), Attrition Rate 15% Control Group 9/13 (1 participant lost after entry, 3 withdrawn from study secondary to fast progression), Attrition Rate 31%
Selective reporting (reporting bias)	High Risk	No reporting of individual group mean and standard deviations post-interventions. Only group difference.
Other bias	Low Risk	

Pinto, 2013

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	High Risk	versus Historical Control Group.
Allocation concealment (selection bias)	High Risk	control group was already formed, no allocation described.
Blinding of participants and	Unclear Risk	Not described.

personnel (performance bias)		
Blinding of outcome assessment (detection bias)	Unclear Risk	Not described.
Incomplete outcome data (attrition bias)	Unclear Risk	Not described.
Selective reporting (reporting bias)	Low Risk	As far as it is possible to tell.
Other bias	Low Risk	

Senent, 2011

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	High Risk	Not Described. This study used participants as their own control.
Allocation concealment (selection bias)	High Risk	Not Described. This study used participants as their own control.
Blinding of participants and personnel (performance bias)	High Risk	All subjects underwent the same experimental design.
Blinding of outcome assessment (detection bias)	Low Risk	Patients and Administrators were blinded to the results of peak cough flow measurements.
Incomplete outcome data (attrition bias)	Low Risk	No attrition noted. All patients were tested in 1 day.
Selective reporting (reporting bias)	High Risk	Results were reported in median.
Other bias	Unclear Risk	Summation Effect - Since all of the interventions were completed in the same order, on the same day, there may be an inherent effect of summation secondary to lack of randomization pertaining to the order of intervention. Manual interventions always preceded mechanical interventions, however, as reported by the author interventions each subset (manual versus mechanical) the interventions were randomized. The lack of order randomization may have allowed the mechanical device to demonstrate a significant.