

Online Data Supplement

Prospective Assessment of the Feasibility of a Trial of Low Tidal Volume Ventilation for Patients with Acute Respiratory Failure

Michael J. Lanspa MD MS, Michelle Ng Gong, MD, David A. Schoenfeld PhD, Kathleen Tiffany Lee, Colin K. Grissom MD, Peter C. Hou MD, Ary Serpa-Neto MD Msc, Samuel M. Brown MD MS, Theodore J. Iwashyna MD PhD, Donald M. Yealy MD, Catherine L. Hough MD MS, Roy G. Brower MD, Carolyn S. Calfee MD, Robert C. Hyzy, Michael A. Matthay MD, Russell R. Miller III MD MPH, Jay S. Steingrub MD, B. Taylor Thompson MD, Chadwick D. Miller MD, Terry P. Clemmer MD, Gregory W. Hendey MD, David T. Huang MD, Kusum S. Mathews MD MS, Nida Qadir MD, Mark Tidswell MD, and The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung injury (PETAL) Clinical Trials Network

Appendix:

The following persons and institutions participated in the study:

Writing Committee-

Michael J. Lanspa MD MS	Intermountain Medical Center and the University of Utah, Salt Lake City, UT
Michelle Ng Gong, MD	Montefiore Healthcare Center, Albert Einstein College of Medicine, Bronx, NY
David A. Schoenfeld PhD	Massachusetts General Hospital, Harvard T.H. Chan School of Public Health, Boston, MA
Kathleen Tiffany Lee	Massachusetts General Hospital, Harvard T.H. Chan School of Public Health, Boston MA
Colin K. Grissom MD	Intermountain Medical Center and the University of Utah, Salt Lake City, UT
Peter C. Hou MD	Brigham and Women's Hospital, Harvard University, Boston, MA
Ary Serpa-Neto MD Msc	Hospital Israelita Albert Einstein, São Paulo, Brazil
Samuel M. Brown MD MS	Intermountain Medical Center and the University of Utah, Salt Lake City, UT
Theodore J. Iwashyna MD PhD	University of Michigan, Ann Arbor, MI
Donald M. Yealy MD	University of Pittsburgh Medical Center, Pittsburgh, PA
Catherine L. Hough MD MS	University of Washington, Seattle WA
Roy G. Brower MD	Johns Hopkins University School of Medicine, Baltimore, MD
Carolyn S. Calfee MD	University of California San Francisco, San Francisco, CA
Robert C. Hyzy	University of Michigan, Ann Arbor, MI
Michael A. Matthay MD	University of California San Francisco, San Francisco, CA
Russell R. Miller III MD MPH	Intermountain Medical Center and the University of Utah, Salt Lake City, UT
Jay S. Steingrub MD	University of Massachusetts Medical School - Baystate, Springfield, MA
B. Taylor Thompson MD	Massachusetts General Hospital, Harvard University, Boston, MA
Chadwick D. Miller MD	Wakeforest Baptist Health, Winston Salem, NC
Terry P. Clemmer MD	LDS Hospital and the University of Utah, Salt Lake City, UT
Gregory W. Hendey MD	University of California Los Angeles, Los Angeles, CA
David T. Huang MD	University of Pittsburgh Medical Center, Pittsburgh, PA
Kusum S. Mathews MD MS	Icahn School of Medicine at Mount Sinai, New York, NY
Nida Qadir MD	University of California Los Angeles, Los Angeles, CA
Mark Tidswell MD	Baystate Medical Center, Springfield, MA

Clinical Coordinating Center- Nancy Ringwood, Cathryn Oldmixon, Richard E. Morse and Douglas Hayden

Protocol Review Committee- Laurie Morrison, Charles B. Cairns, D. Mark Courtney, Mark N. Gillespie, Damon Scales, Richard J. Kryscio

National Heart, Lung, and Blood Institute- Carol Blaisdell, Andrea Harabin, Lora Reineck, Peyvand Ghofrani, Myron A. Waclawiw, Lauren Kunz

The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network: Massachusetts General Hospital Biostatistics Center (CCC): Douglas Hayden, Richard E Morse, Cathryn F Oldmixon, Nancy J Ringwood **ALIGN Clinical Center:** Baystate Medical Center – Jay S Steingrub*, Leslie De Souza, Cynthia Kardos, Lori Kozikowski, Mark Tidswell Brigham and Women’s Hospital – Peter C Hou*, Imo P Aisiku, Rebecca M Baron, Laura E Fredenburgh, Zach A Gandee, Anthony F Massaro, A Higuera Moreno, Wei Shao, Raghu R Seethala Maine Medical Center – Richard R Riker, Adelene Macleoad Tufts Medical Center – Nicholas S Hill, Veronica Bacong, Haval Chweich, John Devlin, Erik Garpestad **BOSTON Clinical Center:** Beth Israel Deaconess Medical Center - Daniel Talmor*, Nathan Shapiro*, Valerie Banner-Goodspeed, Lihini Keenawinna, Lindsey N Muller, T Pinkhasova Massachusetts General Hospital – Edwin Bajwa, Michael Filbin, Kathryn A Hibbert, Carrie Holland St. Vincent Hospital – Patricia A Arsenault, Pam Sigel University of Mississippi Medical Center - Alan Jones, John R Spurzem, Margaret Cruise **CALIFORNIA Clinical Center:** UCSF San Francisco – Michael A Matthay*, Kathleen D Liu, Annika G Belzer, Carolyn Calfee, Brian M Daniel, Thomas J Deiss, Jeffrey E Gotts Ronald Regan UCLA Medical Center- Gregory W Hendey*, Zafia Anklesaria, Steven Y Chang, Scott Lewis, Ishan Mehta, Nida Qadir, Jamal Sharif Stanford University Medical Center – Joseph Levitt, Rosemary Vojnik UC Davis – Timothy E Albertson, Jason Y Adams, Maya Juarez, Brian Morrissey, Skyler Pearson UCSF Fresno – Eyad Almasri, Janna M Blaauw, **COLORADO Clinical Center:** University of Colorado Hospital – Adit Ginde*, Marc Moss*, Lani Finck, Carrie Higgins, Jeffery McKeehan, Eleanor Mills, Amanda Tompkins, Denver Health Medical Center – Ivor S Douglas, Jason Haukoos, Terra Hiller, Emily Hopkins, Judy L Oaks, Katie Overdier, Meggan Schmidt Medical Center of Aurora – David C Van Pelt, Jonathan S Tashkin National Jewish Health – Saint Joseph’s Hospital James H Finigan, Kenneth Lyn-Kew, Ryan D Paterson Swedish Medical Center- Luciano Lemos-Filho **MICHIGAN Clinical Center:** University of Michigan Medical Center – Pauline K Park*, Tina Chen, Sinan Hanna, Kristine Nelson Henry Ford Medical Center – Bruno DiGiovine, Emanuel P Rivers, Sarah Rubino **MONTEFIORE-SINAI Clinical Center:** Montefiore Moses- Tina Chen, Aluko A Hope, Missiel E Munoz Montefiore North - Swarna Gummadi, Damaris Fuster Montefiore Weiler – Daniel Ceusters, Brenda Lopez, Swarna Gummadi Mt. Sinai Hospital – Lynne D Richardson*, Ezra Fass, Neha N Goel, Lisa Richman, Gabriel Schneider **OHIO Clinical Center:** Cleveland Clinic Foundation – R Duncan Hite*, Abhijit Duggal, Andrei Hastings OSU Wexner Medical Center –

Thomas E Terndrup*, Leesha L Bolton, Matthew C Exline, Emily Robart Summa Akron City Hospital – Jennifer Frey, Kirk Stiffler, Melissa L. Coury University of Cincinnati Medical Center – David Norton, Tammy Roads, Autumn Studer **PITTSBURGH Clinical Center:** UPMC Presbyterian – Derek C Angus*, Donald M Yealy*, Erin G Gilchrist, David T Huang, Michael L Young Penn State Hershey Medical Center - Nancy Campbell, Allison Muller, Susan B Promes **PACIFIC NORTHWEST Clinical Center:** Harborview Medical Center/University of Washington Medical Center – Catherine Hough*, Ellen S Caldwell, Sarah C Katsandres Oregon Health and Science University – Akram Khan, Steve Haberkorn Swedish Hospital – Shane D OMahony, Charlene Boisjolie **SOUTHEAST Clinical Center:** Wake Forest Baptist Health - D Clark Files*, Chadwick D Miller*, Stephanie B Elliott, Lori S Flores, Justin Doroshenko, Wendell Futrell, Erin Harper Moses Cone – Stacey Phelps, Robert Lockwood, Patrick E Wright University of Virginia Medical Center – Lea Becker, Kyle B Enfield, Alex Kadl, Mary H Marshall, Mark R Sochor VCU Medical Center – Marjolein de Wit, Stella Hamman **UTAH:** Intermountain Medical Center – Colin K Grissom*, Todd L Allen*, Samuel M Brown, Michael J Lanspa, Valerie Aston, Juhee Peterson, Russell R Miller III LDS Hospital – Terry P Clemmer McKay Dee Hospital – Stan Pies University of Utah Hospital - Estelle S Harris, Amber Plante Utah Valley Regional Medical Center – Dixie L Harris, David Nielsen, Wayne E Woodward **VANDERBILT Clinical Center:** Vanderbilt University Medical Center – Todd W Rice*, Wesley H Self*, Adrienne H Baughman, Margaret Hayes, Susan Mogan, Matthew W Semler University Medical Center – David R Janz, Paula O Lauto

*Clinical Center Lead Principal investigator

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Development of Inverse Probability Weighted Models of the Association between initial V_T and Mortality

We noted that patients receiving LTVV were more likely to have ARDS, pneumonia, or sepsis, and had higher SOFA scores than patients not receiving LTVV. (Table E2). Patients receiving LTVV also spent more days on mechanical ventilation and had greater mortality than patients not receiving LTVV. Compatible with those preliminary observations, our initial logistic regression model demonstrated higher corrected mortality with lower initial V_T (Table E2).

To account for the possibility that the association between lower initial V_T and higher mortality was driven by confounders, we developed propensity scores for initial V_T using a linear model (See Table E3). The probability of a patient having a specified initial V_T was estimated as a function of relevant covariates. We used the results of that linear propensity model for inverse probability weighting of observations within a final non-linear model of mortality. This allowed us to weight patients based on how likely the observed initial V_T was on the basis of the observed covariates—patients whose initial V_T was likely on the basis of the propensity model were weighted lower than patients whose initial V_T was less likely. In general, such inverse probability weighting yields estimates in the final model that represent the average causal effect of having a given V_T on in-hospital mortality.

The non-linear regression model that used inverse probability weighting resulted in a U-shaped relationship between initial tidal volume and mortality, with a higher mortality with both higher (e.g., >10 ml/kg) and lower (e.g., <5 ml/kg PBW) initial V_T with a nadir around 8 mL/kg PBW and no additional reduction in mortality at 7 or 8 mL/kg PBW when compared to 6 mL/kg PBW.

Table E1: Patient Characteristics and Outcomes by Reason for Intubation

	Acute hypoxemic respiratory failure N=944	Acute hypercapnic respiratory failure N=162	Both hypoxemic and hypercapnic respiratory failure N = 249	Altered mental status N = 805	Metabolic abnormalities N = 29	Emergent surgery N = 376	Others N = 283	Total N = 2848
Age (mean, SD)	57.3 (17)	58.7 (15.6)	59.5 (16.9)	53.6 (18.4)	50.2 (17.6)	57.7 (16.3)	55.6 (17.8)	56.3 (17.4)
Male Gender	548 (58.1%)	95 (58.6%)	146 (58.6%)	495 (61.5%)	20 (69%)	236 (62.8%)	185 (65.4%)	1725 (60.6%)
Race								
American Indian or Alaskan Native	9 (1%)	2 (1.2%)	4 (1.6%)	4 (0.5%)	0 (0%)	3 (0.8%)	3 (1.1%)	25 (0.9%)
Asian	23 (2.4%)	8 (4.9%)	3 (1.2%)	20 (2.5%)	1 (3.4%)	11 (2.9%)	7 (2.5%)	73 (2.6%)
Black or African American	174 (18.4%)	24 (14.8%)	39 (15.7%)	133 (16.5%)	6 (20.7%)	48 (12.8%)	66 (23.3%)	490 (17.1%)
Native Hawaiian or other Pacific Islander	5 (0.5%)	1 (0.6%)	1 (0.4%)	4 (0.5%)	1 (3.4%)	1 (0.3%)	0 (0%)	13 (0.5%)
White	614 (65%)	98 (60.5%)	171 (68.7%)	516 (64.1%)	19 (65.5%)	248 (66%)	154 (54.4%)	1820 (63.6%)
Not reported	126 (13.3%)	30 (18.5%)	32 (12.9%)	132 (16.4%)	2 (6.9%)	65 (17.3%)	54 (19.1%)	441 (15.4%)
Hispanic Ethnicity								
Hispanic or Latino	76 (8.1%)	14 (8.6%)	19 (7.6%)	81 (10.1%)	0 (0%)	43 (11.4%)	22 (7.8%)	255 (9%)
Not Hispanic or Latino	737 (78.1%)	131 (80.9%)	206 (82.7%)	603 (74.9%)	26 (89.7%)	297 (79%)	228 (80.6%)	2228 (78.2%)
Not reported	131 (13.9%)	17 (10.5%)	24 (9.6%)	121 (15%)	3 (10.3%)	36 (9.6%)	33 (11.7%)	365 (12.8%)
Risk Factors for ARDS								
Aspiration	130 (13.8%)	18 (11.1%)	45 (18.1%)	97 (12%)	1 (3.4%)	9 (2.4%)	29 (10.2%)	329 (10.8%)
Pneumonia	235 (24.9%)	34 (21%)	72 (28.9%)	33 (4.1%)	1 (3.4%)	15 (4%)	17 (6%)	407 (13.3%)
Sepsis	272 (28.8%)	42 (25.9%)	60 (24.1%)	93 (11.6%)	7 (24.1%)	56 (14.9%)	32 (11.3%)	562 (18.4%)
Shock	157 (16.6%)	18 (11.1%)	36 (14.5%)	67 (8.3%)	11 (37.9%)	49 (13%)	29 (10.2%)	367 (12%)
Trauma	86 (9.1%)	3 (1.9%)	25 (10%)	143 (17.8%)	0 (0%)	49 (13%)	37 (13.1%)	343 (11.2%)
Location of Intubation								

	Acute hypoxemic respiratory failure N=944	Acute hypercapnic respiratory failure N=162	Both hypoxemic and hypercapnic respiratory failure N = 249	Altered mental status N = 805	Metabolic abnormalities N = 29	Emergent surgery N = 376	Others N = 283	Total N = 2848
Intensive Care Unit (ICU)	403 (42.7%)	79 (48.8%)	94 (37.8%)	154 (19.1%)	19 (65.5%)	32 (8.5%)	66 (23.3%)	847 (29.7%)
Emergency Department	231 (24.5%)	48 (29.6%)	68 (27.3%)	307 (38.1%)	5 (17.2%)	12 (3.2%)	84 (29.7%)	755 (26.5%)
Operating Room	45 (4.8%)	7 (4.3%)	7 (2.8%)	14 (1.7%)	0 (0%)	319 (84.8%)	28 (9.9%)	420 (14.7%)
Referring hospital	131 (13.9%)	8 (4.9%)	40 (16.1%)	162 (20.1%)	3 (10.3%)	12 (3.2%)	44 (15.5%)	400 (14%)
Emergency Medical Services (pre-hospital)	64 (6.8%)	11 (6.8%)	23 (9.2%)	133 (16.5%)	1 (3.4%)	0 (0%)	43 (15.2%)	275 (9.7%)
Hospital Ward	70 (7.4%)	9 (5.6%)	17 (6.8%)	35 (4.3%)	1 (3.4%)	1 (0.3%)	18 (6.4%)	151 (5.3%)
SOFA Score Day 1 ¹	7 (4-10)	5 (3-8)	6 (4-8)	4 (2-7)	8 (6-11)	6 (4-8)	5 (3-8)	6 (3-9)
ICU Length of Stay ²	6 (3-12)	5 (3-12)	5 (3-9)	5 (2-10)	4 (1-7)	5 (3-12)	5 (2-11)	6 (2-11)
Hospital L Length of Stay OS	12 (6-24)	12 (6-25)	10 (5-22)	9 (4-20)	9 (1-28)	13 (8-24)	9 (5-24)	11 (5-23)
Ventilator Free Days ³	19 (0-26)	22.5 (0-27)	21 (0-26)	24 (0-27)	0 (0-25)	26 (21-27)	21 (0-27)	23 (0-27)
Hospital Mortality	324 (34.3%)	45 (27.8%)	76 (30.5%)	208 (25.8%)	12 (41.4%)	42 (11.2%)	86 (30.4%)	793 (27.8%)
ARDS	429 (58.8%)	60 (46.9%)	110 (53.7%)	146 (25.2%)	8 (32%)	75 (24.9%)	67 (32.2%)	895 (31.4%)

¹ Acute hypoxemic resp failure (N=740), acute hypercapnic resp failure (N=130), both hypoxemic and hypercapnic resp failure (N=205), altered mental status (N=591), metabolic abnormalities (N=25), emergent surgery (N=300), other (N=209)

² Acute hypoxemic resp failure (N=740), acute hypercapnic resp failure (N=130), both hypoxemic and hypercapnic resp failure (N=205), altered mental status (N=591), metabolic abnormalities (N=25), emergent surgery (N=300), other (N=209)

³ Acute hypoxemic resp failure (N=906), acute hypercapnic resp failure (N=154), both hypoxemic and hypercapnic resp failure (N=237), altered mental status (N=781), metabolic abnormalities (N=28), emergent surgery (N=367), other (N=271)

Table E2: Comparison of patient characteristics, ventilation practices, and outcomes between patients who received initial set tidal volumes ≤ 6.5 mL/kg and those who received > 6.5 mL/kg

	≤ 6.5 mL/kg N = 839	> 6.5 mL/kg N = 1704	P-value
Age	58 (45-68)	59 (46-69.5)	0.1292
Gender Male	628 (74.9%)	920 (54%)	<0.0001
Reasons for intubation			
Acute hypoxemic	344 (41.0%)	509 (29.9%)	<0.0001
Altered mental status	215 (25.6%)	498 (29.2%)	0.0574
Acute hypoxemic and hypercapnic	83 (9.9%)	140 (8.2%)	0.1598
Emergent surgery	67 (8%)	258 (15.1%)	<0.0001
Acute hypercapnic	50 (6%)	100 (5.9%)	0.9271
Metabolic abnormalities	11 (1.3%)	14 (0.8%)	0.2395
Other/unclear	69 (8.2%)	185 (10.9%)	0.0374
Risk Factor for ARDS			
Aspiration	103 (12.3%)	198 (11.6%)	0.6297
Pneumonia	152 (18.1%)	233 (13.7%)	0.0033
Sepsis	198 (23.6%)	322 (18.9%)	0.0057
Shock	122 (14.5%)	221 (13%)	0.2753
Trauma	95 (11.3%)	193 (11.3%)	0.9980
Location of Intubation			
Intensive Care Unit (ICU)	337 (40.2%)	447 (26.2%)	<0.0001
Emergency Department	212 (25.3%)	472 (27.7%)	0.1936
Operating Room	94 (11.2%)	248 (14.6%)	0.0199
Referring hospital	74 (8.8%)	284 (16.7%)	<0.0001
Emergency Medical Services (pre-hospital)	67 (8%)	165 (9.7%)	0.1622
Hospital Ward	55 (6.6%)	88 (5.2%)	0.1522
Type of ICU			
Medical	443 (52.8%)	710 (41.7%)	<0.0001
Surgical	101 (12%)	223 (13.1%)	0.4558
Medical/Surgical	80 (9.5%)	169 (9.9%)	0.7601
Mixed	75 (8.9%)	85 (5%)	0.0001
Trauma	55 (6.6%)	152 (8.9%)	0.0403

	≤ 6.5 mL/kg N = 839	> 6.5 mL/kg N = 1704	P-value
Cardiothoracic surgical	24 (2.9%)	111 (6.5%)	0.0001
Other	61 (7.3%)	254 (14.9%)	<0.0001
SOFA Score Day 1 ⁴	6 (4-9)	6 (3-8)	0.0031
Height documented at time of intubation	70 (66.9-72)	66 (63-69)	<0.0001
PaO ₂ /FiO ₂ (or SpO ₂ /FiO ₂ , if no arterial blood gas available) on initial intubation ⁵	188.1 (106-296)	194 (117.4-314)	0.0927
Initial Ventilator Mode			0.8860
Volume	481 (57.3%)	982 (57.6%)	
Pressure	358 (42.7%)	722 (42.4%)	
ARDS present at time of intubation ⁶	242 (40.5%)	405 (34.9%)	0.0200
ARDS at any time ⁷	312 (47.2%)	525 (39.8%)	0.0017
Severe ARDS ⁸	119 (38.1%)	172 (32.8%)	0.0023
Moderate ARDS ⁹	151 (48.4%)	251 (47.8%)	0.0337
Mild ARDS ¹⁰	42 (13.5%)	102 (19.4%)	0.3147
ICU LOS	6 (3-13)	5 (3-11)	0.0861
Hospital LOS	12 (6-25)	11 (5-22)	0.0665
Ventilator-Free Days to Day 28	20 (0-26)	24 (0-27)	<0.0001
Hospital Mortality	257 (30.6%)	441 (25.9%)	0.0116

⁴ ≤ 6.5 mL/kg (N=671) and >6.5 mL/kg (N=1330)

⁵ ≤ 6.5 mL/kg (N=597) and >6.5 mL/kg (N=1158)

⁶ ≤ 6.5 mL/kg (N=597) and >6.5 mL/kg (N=1161)

⁷ ≤ 6.5 mL/kg (N=661) and >6.5 mL/kg (N=1319)

⁸ ≤ 6.5 mL/kg (N=312) and >6.5 mL/kg (N=525)

⁹ ≤ 6.5 mL/kg (N=312) and >6.5 mL/kg (N=525)

¹⁰ ≤ 6.5 mL/kg (N=312) and >6.5 mL/kg (N=525)

Table E3: Results of the multivariate linear propensity score model for initial tidal volume after intubation.

	Estimate	Standard Error	P-value
(Intercept)	-0.696	1.332	0.601
Baseline Tidal Volume	-0.149	0.066	0.025
SOFA score	0.251	0.027	0.000
Reason for Intubation			
Hypercapnic respiratory failure	-0.262	0.311	0.400
Both Hypoxemic and Hypercapnic respiratory failure	0.183	0.240	0.444
Altered Mental Status	-0.046	0.216	0.829
Surgery	-1.319	0.416	0.002
Other	0.224	0.267	0.400
PaO₂/FiO₂	0.001	0.001	0.313
ARDS at baseline	-0.048	0.158	0.763
Gender	0.092	0.227	0.686
Sepsis	0.409	0.165	0.013
Pneumonia	-0.019	0.187	0.918
Aspiration	0.097	0.198	0.624
Trauma	0.026	0.274	0.925
Shock	0.330	0.179	0.065
Location			
ED	-0.845	0.290	0.004
Ward	-0.607	0.362	0.093
ICU	-0.713	0.285	0.012
OR	-0.715	0.403	0.076
Referring Hospital	-0.970	0.329	0.003
Predicted Body Weight	-0.011	0.011	0.340

Table E4: Multivariable propensity score regression model

	Estimate	Standard Error	P-value
(Intercept)	13.187	0.451	0.000
SOFA score	0.007	0.012	0.586
Reason for intubation			
Hypercapnic respiratory failure	-0.032	0.141	0.819
Both Hypoxemic and Hypercapnic respiratory failure	0.071	0.114	0.531
Altered Mental Status	0.320	0.099	0.001
Surgery	0.188	0.164	0.251
Other	0.202	0.128	0.115
PaO₂/FiO₂	0.000	0.001	0.460
ARDS at Baseline	-0.001	0.072	0.991
Gender	-0.557	0.102	0.000
Sepsis	-0.127	0.079	0.109
Pneumonia	-0.226	0.087	0.009
Aspiration	-0.039	0.093	0.676
Trauma	-0.112	0.117	0.341
Shock	0.069	0.088	0.434
Location			
Ward	-0.491	0.174	0.005
Intensive Care Unit (ICU)	-0.517	0.135	0.000
Emergency Department	-0.310	0.135	0.021
Operating Room	-0.015	0.186	0.936
Referring hospital	-0.201	0.151	0.182
Predicted Body Weight	-0.078	0.004	0.000

Table E5. Estimated benefit of reducing tidal volume on reducing mortality, based on three models from previously published data.(1, 10) The LOTUS-FRUIT model was a non-linear model derived from inverse probability weighting of the LOTUS-FRUIT data.

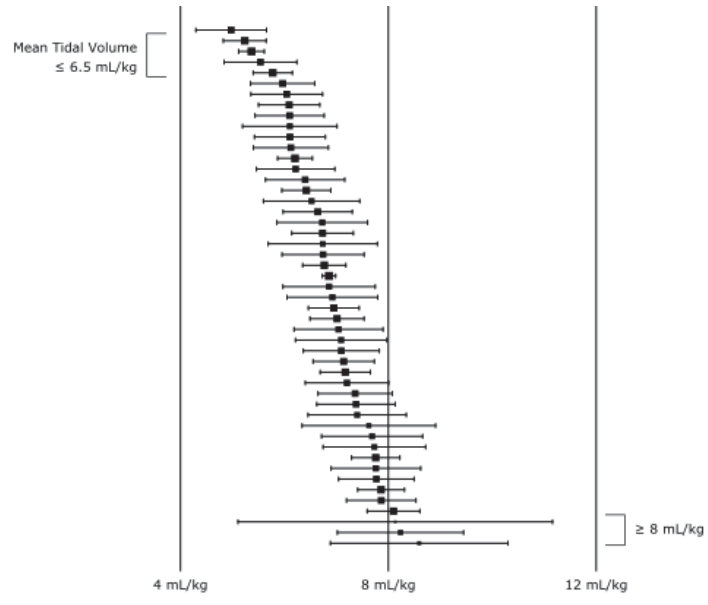
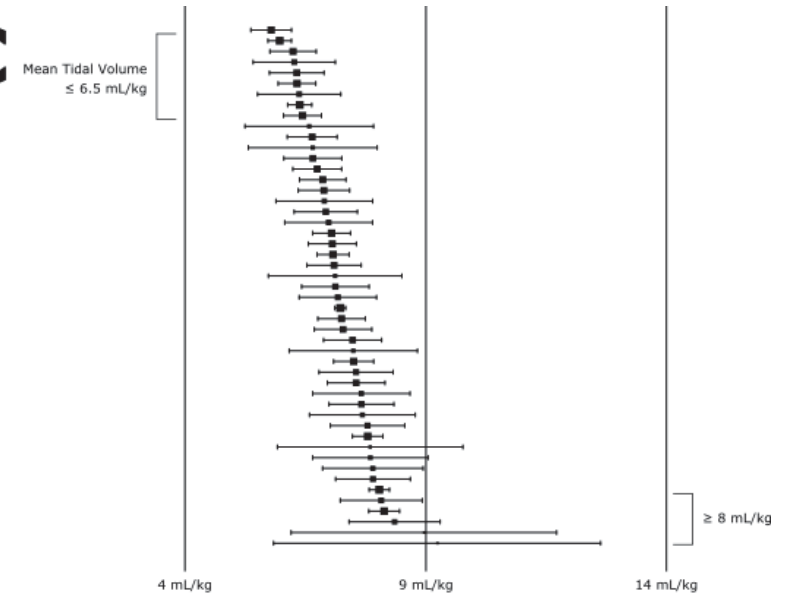
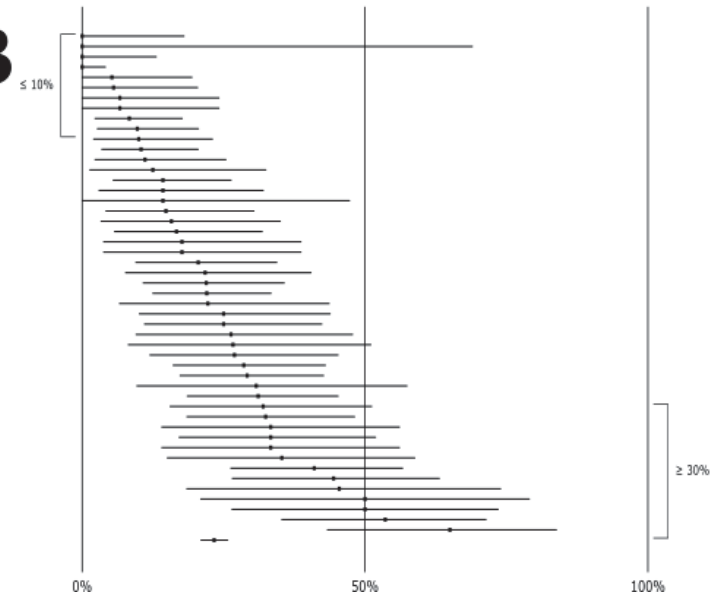
Model	Estimated Mortality Benefit
Neto Linear	0.021
Neto Spline	0.005
Arma Linear	0.015
LOTUS-FRUIT	0.00

Table E6: Random effects estimate and a fixed effects estimate for the 49 hospital clusters. Calculation of Intraclass Correlation for mortality calculated by ANOVA was 2.3%.

Random effects model	Variance	Standard Deviation
(Intercept)	0.037	0.19

Fixed effects Model	Estimate	Standard Error	z- value	P value
(Intercept)	-0.96	0.052	-18.54	< 0.001

Figure E1: Tidal volume practice by hospital in acute respiratory failure (ARF) and acute respiratory distress syndrome (ARDS). **A:** Mean initial tidal volume in ARF, with brackets indicating hospitals with mean tidal volumes ≤ 6.5 or > 8 mL/kg. Mean $V_t = 7.1$ (95% CI 7.1-7.2) mL/kg PBW. **B:** Percent of patients with ARF with initial tidal volume > 8 mL/kg PBW, with brackets indicating hospitals with $\leq 10\%$ or $\geq 30\%$ of patients with initial tidal volume > 8 mL/kg PBW. Mean was 21.8% (95% CI 19.9-23.9%). **C:** Mean initial tidal volume in ARDS. Mean $V_t = 7.2$ (95% CI 7.1-7.3) mL/kg PBW. **D:** Percent of patients with ARDS with initial tidal volume > 8 mL/kg PBW. Mean was 21.0% (95% CI 18.7-23.5%).

A**C****B****D**