Appendix E1

The cardiac index levels used for this study sample size estimation reflect a 0.5 liters/minute/m^2 difference between the low and high PEEP groups (4.1 versus 3.6). Practically, a change in cardiac index up to 0.5 liters/minute/m^2 may be statistically significant but is not necessarily clinically important. Such a strategy is commonly used in the setting of 'non-inferiority' study designs. Since the hypothesis is lack of association rather than positive association, we chose a clinically insignificant difference to check for a statistically significant difference. Such a strategy also typically requires a larger sample size to prove, which is valid when a clinically insignificant difference is also statistically insignificant. If the approach was to prove an association (i.e., 'superiority' study design), then we would have chosen a clinically significant difference which in our opinion would be at least 1 liter/minute/m^2; such a difference would have required a much smaller sample size.

Sample size calculation was made based on a dichotomous PEEP exposure level (<12 versus $\geq$ 12 cm). Since sample size calculation for a continuous exposure typically requires a smaller sample size than a dichotomous exposure, we present the calculations for the dichotomous variable calculation to ensure that we will have enough power to do the analysis both ways (continuous and dichotomized PEEP variable).

The mean ($\pm$ standard deviation) PEEP for the patients in FACTT that had a PAC was about 8.5 $\pm$ 3.5 cm. So we expected to have more patients in the low PEEP group (< 12 cm) than in the high PEEP group ($\geq$ 12 cm).

Assuming the low PEEP group was 4 times as large as the high PEEP group, and for an 80% power and a 2-sided alpha of 0.05, the total number of observations needed is 587: 118 observations in the high PEEP group and 469 in the low PEEP group. This would have been the estimated sample size if these observations were independent. Because there are up to 3 observations / patient, there may likely be an intra-class (i.e., intra-patient) correlation which would affect the sample size calculations. Assuming an intra-class correlation (ICC) as high as 0.25 and an average number of observations / cluster of 2, the total number of observations needed would be 735 (with a minimum of 368 patients): 148 observations in the high PEEP group and 587 in the low PEEP group (again with 80% power and a 2-sided alpha of 0.05).

There were 1,325 PEEP-cardiac index paired measurements performed on 501 patients in

the PAC arm of the FACTT study during the first 3 days of enrollment (combined mild, moderate, and severe ARDS patients). We expected that about 55% - 60% of these measurements over the 3 day period (about 730 - 800 observations) were in patients with a PF at the time of measurement of $\leq$ 200 (satisfying the clinical diagnosis of moderate to severe ARDS). So we expected the sample size to be able to detect at least a 0.5 liters/minute/m^2 mean difference in cardiac index between PEEP groups, for moderate to severe ARDS' 'observations' based on the above mentioned assumptions if there is indeed an association. Given a smaller ICC, we expected to have an adequate sample to detect even smaller mean differences.

Appendix E2

Final results of the multi-variable regression model:

Cardiac Index	Coefficient	Standard error	p-value
PEEP	+ 0.005	0.013	0.73
APACHE III score	+ 0.003	0.002	0.04
Age	- 0.028	0.003	< 0.01
FACTT fluid arm	+ 0.351	0.090	< 0.01
Sepsis	- 0.095	0.093	0.31
Static Lung Compliance	+ 0.002	0.003	0.43

Appendix E3

Other post-hoc sensitivity analyses done:

1. Including patients beyond the first 3 days of enrollment in the FACTT study:
   There was no association between PEEP and cardiac index in observations included regardless of their time of recruitment into the FACTT study (i.e., not restricted to the first 3 days) when adjusted for age, APACHE score, sepsis, and FACTT fluid study arm. (n= 1,146; p = 0.53).

2. Including patients who were also on vasopressors and / or inotropes:
   There were an additional 315 observations who satisfied the inclusion/exclusion criteria (Fig. 1) except that they were on vasopressors and / or inotropes.
   There was no association between PEEP and cardiac index in observations included within the first 3 days of FACTT recruitment when adjusted for age, APACHE score, sepsis, and FACTT fluid study arm. (n= 1,134; p = 0.40).

3. Including observations who were also on vasopressors and regardless of their time in the FACTT study:
   There was no association between PEEP and cardiac index in observations included when adjusted for age, APACHE score, sepsis, and FACTT fluid study arm. (n= 1,531; p = 0.28).

4. Adjusting for actual net fluids given (net of inputs and outputs within the prior 24 hours), rather than study arm:
   There was no association between PEEP and cardiac index in observations included within the first 3 days of FACTT recruitment when adjusted for age, APACHE score, sepsis, and net of fluids intake / output within the prior 24 hours. (n= 817; p = 0.97).

5. The above sensitivity analyses were done also adjusting for (in addition to the above mentioned variables) static lung compliance. There was no association between PEEP and cardiac index.