Significant Variability in Surrogate Informed Consent Rates in ARDS and Prevention and Early Treatment of Acute Lung Injury Network Multicenter Trials

To the Editor:

The COVID-19 pandemic magnifies the need for well-conducted clinical trials to identify novel and targeted therapies for critically ill patients. For critical care research, the informed consent process has distinctive challenges that often delay the completion of clinical trials. Most critically ill patients do not have capacity to consent for research participation, given their acute illness and the use of sedative medications, and thus depend on a surrogate for informed consent. Consequently, improving the process of surrogate informed consent for critical care research has been identified as an area of focus to enhance the conduct of clinical trials.[1] Though variability in surrogate informed consent rates in ICU trials has been reported, the extent of the variability within and between multiple large multicenter trials is relatively unknown.[2] Therefore, we sought to determine surrogate informed consent rates at both the center and site level from recent multicenter ICU trials and to determine the extent to which consent rates varied between the different trials. Further understanding of surrogate informed consent rates and variability may enable researchers to improve the surrogate informed consent process.

Methods

We analyzed four National Heart, Lung, and Blood Institute ARDS Network trials: Albuterol for the Treatment of Acute Lung Injury (ALTA), Early vs Delayed Enteral Nutrition in Acute Lung Injury (EDEN), Omega Nutrtion Supplement Trial in Acute Lung Injury (OMEGA), and Statins for Acutely Injured Lungs from Sepsis (SAILS) and one Prevention and Early Treatment of Acute Lung Injury (PETAL) Network trial: Reevaluation of Systemic Early Neuromuscular Blockade (ROSE).[3,4] The trials we analyzed consisted of three pharmaceutical studies (ALTA, OMEGA, SAILS), one study that assessed feeding strategies (EDEN), and one study that assessed neuromuscular blockade (ROSE) in patients with ARDS. Deidentified consent data were obtained from the PETAL Network clinical coordinating center. Because of study network policies, the study centers and sites referenced are anonymous. The ARDS and PETAL Networks each consisted of 12 centers in the United States with $>$ 40 participating hospitals. The ARDS Network trials allowed comparisons of study centers, whereas the ROSE trial allowed comparisons between study centers and different hospitals (referenced as sites).[4]

The primary outcome was surrogate informed consent. For the ARDS Network trials, we performed multivariable logistic analysis that compared odds of consent across trials and Fisher Exact tests to assess within-center variation of consent rates across trials. We were unable to compare the ROSE trial with the ARDS Network trials, given differing study centers. For the ROSE trial, we used a series of binomial logit-link generalized linear mixed models (GLMMs) to model these binary correlated data. We fit four GLMMs, each with no fixed effects and varying levels of random effects: (1) none (null model), (2) center-level, (3) site-level, and (4) center and nested site-level. For each GLMM, we produced a deviance-based measure of the conditional R-squared that approximates the variation in consent explained by each model, conditional on all random effects.[5] We performed likelihood ratio tests to assess whether the site-only or the center-only models exhibit lack of fit compared with the full model (model 4). Analyses were performed in R (version 4.0.2).[6]

Results

In the ALTA, OMEGA, EDEN, and SAILS clinical trials, overall 79% (2,299/2,908) of surrogates consented. The study-specific surrogate consent rates for the ALTA, OMEGA, EDEN, and SAILS trials were 77% (282/364 surrogates), 76% (272/359 surrogates), 85% (1,000/1,182 surrogates), and 74% (745/1,003 surrogates), respectively. Using the SAILS trial as the reference because it had the lowest study-specific consent rate of 74%, there was no significant overall difference in ALTA or OMEGA consent rates, whereas EDEN had higher consent rates with an OR of 1.9 (95% CI, 1.5 to 2.4; $P <$ .001). We found strong evidence that the consent rates varied across trials within centers, with eight of 12 centers exhibiting at least moderately significant differences ($P < .05$) (Table 1).

In the ROSE trial, there were 1,400 total subjects, of whom 1,006 (71.9%) surrogates consented to participate. Subjects were recruited from a total of 51 sites (44 with $\geq$ 5 subjects) and 12 centers. Consent

TABLE 1] Center-Specific Surrogate Consent Rates for Previous ARDS Network Trials

Trial	Study Center[a]											
	1	2	3	4	5	6	7	8	9	10	11	12
Albuterol for the Treatment of Acute Lung Injury	15/40 (38)	19/22 (86)	16/27 (59)	35/42 (83)	15/21 (71)	29/36 (81)	27/28 (96)	34/37 (92)	25/38 (66)	20/22 (91)	30/33 (91)	17/18 (94)
OMEGA	15/24 (62)	26/38 (68)	18/30 (60)	26/34 (76)	26/33 (79)	31/39 (79)	23/36 (64)	31/37 (84)	18/22 (82)	9/10 (90)	33/40 (82)	16/16 (100)
EDEN	67/10 (63)	116/147 (79)	78/96 (81)	101/118 (86)	69/79 (87)	115/130 (88)	66/84 (79)	122/136 (90)	54/62 (87)	49/50 (98)	109/119 (92)	54/55 (98)
Sustained Aeration of Infant Lungs	42/59 (71)	75/126 (60)	41/59 (69)	119/161 (74)	46/51 (90)	83/111 (75)	91/109 (83)	80/116 (69)	46/50 (92)	23/40 (58)	74/92 (80)	25/29 (86)
Total	139/229 (61)	236/333 (71)	153/212 (72)	281/355 (79)	156/184 (85)	258/316 (82)	207/257 (81)	267/326 (82)	143/172 (83)	101/122 (83)	246/284 (87)	112/118 (95)
P value[b]	.008	.002	.031	.10	.16	.046	.008	<.001	.012	<.001	.082	.087

EDEN = Early vs Delayed Enteral Nutrition in Acute Lung Injury; OMEGA = Omega Nutrition Supplement Trial in Acute Lung Injury.
[a]Composed of multiple hospitals (anonymous) with informed consent raw proportions. Data are presented as number consented/number approached for consent (%) tabulated by individual trials and in total.
[b]Consent rate differences were tested via Fisher Exact tests.

rates varied considerably across site (mean, 70.4%; SD, 17.4%) and center (mean, 71.9%; SD, 12.4%) (Figure 1). We observed a statistically significant contribution to the variation in consent rates attributable to both site ($P < .001$) and center ($P = .019$). The center at which a subject presented can explain 6.2% of the variability in consent; a subject's site and center together can explain 9.4% of this variability.

Discussion

The goal of research recruitment is to balance timely enrollment while ensuring an ethical process whereby the patient or surrogate is fully informed and understands both the rationale and risks of engaging in a clinical trial. Our analysis of multicenter critical care trials revealed significant variability in surrogate informed consent rates at the level of study centers and between individual study sites (hospitals). We observed a significant difference in consent rates between studies, specifically comparing EDEN and SAILS, which evaluated feeding strategies and statin therapy, respectively. We suspect the feeding strategy trial (EDEN) was viewed as less risky than the statin therapy trial (SAILS), thereby contributing to this difference. This hypothesis is supported by prior work that showed that surrogates are less willing to consent for research as risk associated with a study increases.[7] The cause of site- and center-specific consent rate variability is unclear, given our limited data. Potential contributors include geographic variation, demographic differences, different recruitment practices that include varying levels of involvement of the treating team, and a myriad of other possibilities.

The studies included in our analyses had strikingly high consent rates (> 70%). For example, a recent ICU study that evaluated the impact of behavioral nudges on study recruitment demonstrated enrollment rates of only 29% and 34% in their intervention and control groups, respectively.[8] One explanation for the high consent rates in ARDS and PETAL Network studies may be due to the extensive experience of the research coordinators and investigators with the informed consent process and their ability to generate trust.[9] In contrast, higher consent rates may be related to the presence of therapeutic misperception on the part of the surrogates. Further studies are necessary to delineate provider, study, and surrogate characteristics that are associated with informed consent rates.

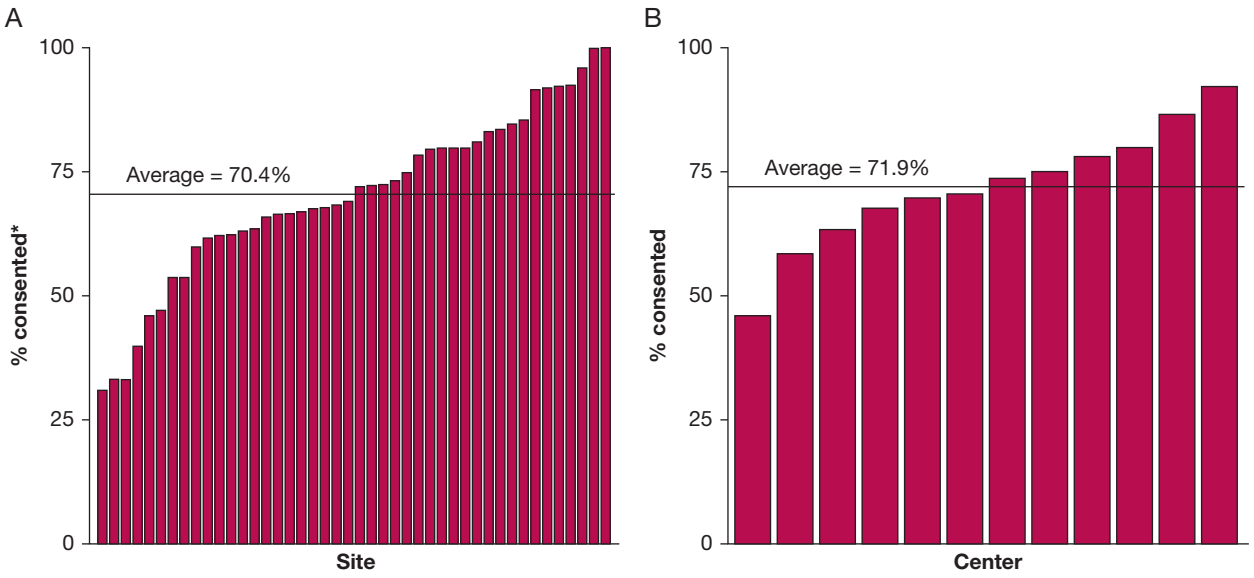

Figure 1 – *A and B, Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial surrogate informed consent rates across A, sites (n = 44) and B, centers (n = 12) are listed anonymously. The asterisk (A) indicates that sites with fewer than five subjects were excluded from the plot across the sites (A). These sites were included in the plot across centers B).*

Our study was limited by the paucity of data collected during the informed consent process to explain this variability. It would have been insightful to have known demographics, who performed consent (ie, research coordinator, research assistant, principal investigator), rationale for surrogate declining consent, adjunctive materials used to facilitate consent discussion, documentation of initial telephone consent, and time from when the surrogates were approached to when they agreed or disagreed to consent.

Despite advances in the conduct of critical care trials, there has been a dearth of research to guide the surrogate informed consent process.[10] In future studies, we suggest that multicenter critical care trial groups should collect the aforementioned information to enhance the conduct of the surrogate informed consent process.

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