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Authors

Yang, Philip

Dickert, Neal

Haczku, Angela

et al.

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BRIEF REPORT

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Trend in Clinical Trial Participation During COVID-19: A Secondary Analysis of the I-SPY COVID Clinical Trial

Philip Yang, MD, MSc[1]
Neal W. Dickert, MD, PhD[2,3]
Angela Haczku, MD, PhD[4]
Christine Spainhour, RN, CCRC[5]
Sara C. Auld, MD, MSc[1,6]
the I-SPY COVID Consortium

OBJECTIVES: To analyze the temporal trend in enrollment rates in a COVID-19 platform trial during the first three waves of the pandemic in the United States.

DESIGN: Secondary analysis of data from the I-SPY COVID randomized controlled trial (RCT).

SETTING: Thirty-one hospitals throughout the United States.

PATIENTS: Patients who were approached, either directly or via a legally authorized representative, for consent and enrollment into the I-SPY COVID RCT.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Among 1,338 patients approached for the I-SPY COVID trial from July 30, 2020, to February 17, 2022, the number of patients who enrolled ($n = 1{,}063$) versus declined participation ($n = 275$) was used to calculate monthly enrollment rates. Overall, demographic and baseline clinical characteristics were similar between those who enrolled versus declined. Enrollment rates fluctuated over the course of the COVID-19 pandemic, but there were no significant trends over time (Mann-Kendall test, $p = 0.21$). Enrollment rates were also comparable between vaccinated and unvaccinated patients. In multivariable logistic regression analysis, age, sex, region of residence, COVID-19 severity of illness, and vaccination status were not significantly associated with the decision to decline consent.

CONCLUSIONS: In this secondary analysis of the I-SPY COVID clinical trial, there was no significant association between the enrollment rate and time period or vaccination status among all eligible patients approached for clinical trial participation. Additional studies are needed to better understand whether the COVID-19 pandemic has altered clinical trial participation and to develop strategies for encouraging participation in future COVID-19 and critical care clinical trials.

KEY WORDS: clinical trial participation; coronavirus; COVID-19; randomized controlled trials

Since the emergence of the COVID-19 pandemic, clinical trials have played a pivotal role in rapidly identifying effective treatments and vaccinations for COVID-19 (1–3). Despite this success, increasing hesitancy toward research and decreased recruitment into randomized controlled trials (RCTs) have been reported (4, 5), potentially adding to challenges inherent in critical care clinical trials such as logistical difficulties in obtaining timely consent, complexities of trial and protocol design, and heterogeneity of patient presentations (6, 7). However, most available reports of decreasing clinical trial recruitment during the COVID-19 pandemic are anecdotal or descriptive. In a review of critical care studies published before the pandemic, consent rates ranged from 72% to 94% (7), but there is a paucity of studies examining how these consent rates may have changed during the COVID-19 pandemic.

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KEY POINTS

Question: Did enrollment rates in the I-SPY COVID platform trial change significantly throughout the course of the COVID-19 pandemic?

Findings: In the secondary analysis of I-SPY-COVID clinical trial, monthly enrollment rates into the clinical trial did not change significantly during the first three waves of the pandemic and were comparable between vaccinated and unvaccinated patients.

Meaning: The enrollment rates in the I-SPY COVID trial did not significantly decrease during the pandemic and were comparable to those of critical care studies pre-pandemic. Further analyses of other clinical trials are needed to understand the global patterns in clinical trial participation.

To better understand the patterns in COVID-19 RCT participation, we performed a secondary analysis of a multicenter RCT to quantitatively analyze temporal trends in enrollment rates during the COVID-19 pandemic. We hypothesized that the enrollment rates in our COVID-19 RCT decreased over time during the pandemic.

MATERIALS AND METHODS

Parent Clinical Trial Information

This secondary analysis used de-identified data from the I-SPY COVID clinical trial (ClinicalTrials.gov identifier: NCT04488081), for which detailed design and methods have been published previously (8, 9). The trial was overseen by a central institutional review board (IRB) at the Wake Forest School of Medicine (IRB00066805, "I-SPY COVID TRIAL: An Adaptive Platform Trial to Reduce Mortality and Ventilator Requirements for Critically Ill Patients," approved on July 9, 2020). This secondary analysis of the RCT data was approved by the Data Access and Publications Committee for the I-SPY COVID trial ("Changes in Consent Rates Over Time for I-SPY-COVID Clinical Trial," approved March 1, 2022). The study was performed in accordance with the ethical standards of the IRB and with the Helsinki Declaration of 1975. Briefly, the I-SPY COVID clinical trial is an ongoing phase 2, multicenter, multiarm, adaptive, open-label, platform RCT that evaluates up to four potential therapeutic agents for COVID-19 at a given time, each on a backbone of remdesivir and steroids, which also serves as the fifth "control" arm of the trial. Patients with confirmed COVID-19 and World Health Organization (WHO) COVID-19 Ordinal Scale level greater than or equal to 5 (defined here as 5 = requiring ≥ 6 L/min of supplemental oxygen, 6 = requiring invasive mechanical ventilation, and 7 = requiring invasive mechanical ventilation plus additional organ support, such as pressors, renal replacement therapy, and/or extracorporeal membrane oxygenation) were eligible (10). The trial employed a unique two-step consent mechanism. First, eligible candidates or their legally authorized representatives (LARs) were approached, given general information about the trial, and assessed for their interest in study participation prior to randomization. Then, interested candidates underwent randomization and were reapproached to discuss information specifically related to their assigned arm before providing written informed consent for enrollment. Candidates who declined participation either before or after randomization entered an observational cohort using an IRB-approved waiver of consent mechanism, in which disease outcomes and other clinical endpoints were tracked without any study intervention. Those who consented but met an agent-specific exclusion criteria for the investigational agent to which they were randomized were moved into the control arm.

Secondary Analysis of Clinical Trial Data

De-identified clinical trial data from July 30, 2020, to February 17, 2022, were reviewed to determine whether eligible candidates had consented and enrolled in the RCT ("enrolled" group), or declined consent and entered the observational cohort ("declined" group). Those who met study exclusion criteria were excluded from this analysis.

The number of eligible candidates who enrolled versus declined were used to calculate enrollment rates (= [*n* enrolled]/[*n* enrolled + *n* declined], where the denominator included all eligible patients approached before randomization) for each month of the trial. Additional clinical information including demographics, comorbidities, region of residence, severity of illness (according to the WHO COVID-19 Ordinal Scale), and COVID-19 vaccination status were

compared between those who enrolled versus declined. Among the subset of patients evaluated beginning March 2021 (when the Electronic Data Capture system was updated to record vaccination status), enrollment rates were further stratified by vaccination status.

Statistical Analysis

Descriptive statistics were used to compare baseline characteristics between those who enrolled versus declined. Trends in enrollment rates throughout the study period were tested using the Mann-Kendall trend test. Multivariable logistic regression analysis was performed to identify potential factors associated with the decision to decline clinical trial participation, with the "declined" group as the outcome of interest and the "enrolled" group as the reference group. Covariates in the model included age, sex, region (Northeast, South, Midwest, or West), severity of illness (WHO COVID-19 Ordinal Scale 5, 6, or 7), and vaccination status. Statistical tests were performed in R v4.2.0 (R Foundation for Statistical Computing, Vienna, Austria), and *p* value of less than 0.05 was used for significance.

RESULTS

Patient Characteristics

Data were available from 1,470 patients who were evaluated for the I-SPY COVID trial between July 30, 2020, and February 17, 2022. After excluding 124 patients who met exclusion criteria and eight additional patients with incomplete or erroneous baseline data, 1,338 patients remained in the final analysis. Of these, 1,063 patients (79.4%) gave consent and enrolled in the RCT ("enrolled" group) and 275 patients (20.6%) declined to participate and entered the observational cohort ("declined" group) (**Supplemental Fig. S1**, http://links.lww.com/CCX/B206).

The "enrolled" and "declined" groups were comparable with regard to demographic characteristics, medical history, region, severity of illness, and vaccination status (**Table 1**). A large majority of patients who declined (n = 220/275) did not provide a specific reason for declining participation; when documented, common reasons included concerns for side effects or complications from the study drugs, personal preferences regarding research, and/or wanting to be in a different arm than the one to which they were randomized.

Enrollment Rates

Enrollment rates for each month of the clinical trial and the number of candidates who enrolled versus declined are shown in **Figure 1*A***. Enrollment rates for each month ranged between 64.5% and 90.3%. Months with the highest enrollment rates were August 2021 and September 2021 (90.3% and 84.7%, respectively) during the delta wave, and July 2020 to August 2020 (85.7%). Months with the lowest enrollment rates were April 2021 and May 2021 (66.7% and 64.5%, respectively) during the lull just prior to the delta wave, and January 2022 to February 2022 (67.0%) during the omicron wave. Monthly enrollment rates did not demonstrate a significant trend over time (Mann-Kendall test tau = –0.216; p = 0.21).

Stratified and Multivariable Analyses

Enrollment rates were stratified by vaccination status beginning in March 2021. Unvaccinated patients comprised the majority of eligible candidates during this period, but neither group had consistently higher enrollment rates (**Fig. 1*B***). In multivariable logistic regression analysis modeling the odds of declining to consent, age, sex, region, COVID-19 severity of illness, or vaccination status were not significantly associated with declining consent.

DISCUSSION

In this secondary analysis of the I-SPY COVID clinical trial, the overall enrollment rates among eligible candidates for the trial did not significantly change over time. Rather, enrollment rates remained between 75% and 85% during most of the study period, and they were comparable between vaccinated and unvaccinated patients. Multivariable analysis did not find any patient-level factors that were associated with declining trial participation.

These results are informative but also raise important questions. First, enrollment rates in the I-SPY COVID trial were comparable to those of critical care clinical studies prior to the pandemic (7) and, contrary to our hypothesis, did not decrease significantly over the course of the trial. Thus, our results provide

TABLE 1.
Baseline Characteristics of Patients Approached for the I-SPY COVID Trial

Characteristic	Total (*n* = 1,338)	Declined (*n* = 275)	Enrolled (*n* = 1,063)	*p*[a]
Age				
n; median (interquartile range)	1,237; 60 (50–70)	191; 58 (47–69)	1,046; 61 (51–71)	0.07
Sex, *n* (%)				
Female	486 (36.3)	103 (37.5)	383 (36.0)	0.71
Male	852 (63.7)	172 (62.6)	680 (64.0)	
Race, *n* (%)				
Asian	44 (3.3)	6 (2.2)	38 (3.6)	0.07
Black	267 (20.0)	58 (21.1)	209 (19.7)	
White/Caucasian	689 (51.5)	126 (45.8)	563 (53.0)	
Unknown	244 (18.2)	64 (23.3)	180 (16.9)	
2+ races or other	94 (7.0)	21 (7.6)	73 (6.9)	
Medical history, *n* (%)				
Cerebrovascular disease	51 (3.8)	6 (2.2)	45 (4.2)	0.16
Myocardial infarction	35 (2.6)	7 (2.6)	28 (2.6)	1.00
Congestive heart failure	78 (5.8)	16 (5.8)	62 (5.8)	1.00
Hypertension	702 (52.5)	142 (51.6)	560 (52.7)	0.79
Peripheral vascular disease	36 (2.7)	6 (2.2)	30 (2.8)	0.68
Pulmonary disease	244 (18.2)	58 (21.1)	186 (17.5)	0.19
Liver disease	33 (2.5)	11 (4.0)	22 (2.1)	0.08
Chronic kidney disease and/or end-stage renal disease	117 (8.7)	17 (6.2)	100 (9.4)	0.09
Diabetes mellitus	446 (33.3)	97 (35.3)	349 (32.8)	0.47
Rheumatologic disease	53 (4.0)	8 (2.9)	45 (4.2)	0.39
Region, *n* (%)				
Northeast	487 (36.4)	90 (32.7)	397 (37.4)	0.18
South	330 (24.7)	63 (22.9)	267 (25.1)	
Midwest	119 (8.9)	25 (9.1)	94 (8.8)	
West	402 (30.0)	97 (35.3)	305 (28.7)	
World Health Organization COVID-19 severity[b], *n* (%)				
5	1,172 (87.6)	239 (86.9)	933 (87.8)	0.87
6	78 (5.8)	16 (5.8)	62 (5.8)	
7	88 (6.6)	20 (7.3)	68 (6.4)	
COVID-19 vaccination[c], *n* (%)				
Vaccinated	131/729 (18.0)	35/167 (21.0)	96/562 (17.1)	0.30
Unvaccinated	598/729 (82.0)	132/167 (79.0)	466/562 (82.9)	

[a]*p* values were derived using χ^2 or Fisher exact test as appropriate, except for age, for which Wilcoxon-Mann-Whitney *U* test was used.
[b]World Health Organization COVID-19 severity levels were defined as follows: 5 = requiring high-flow oxygen (≥ 6 L/min of supplemental oxygen) or noninvasive ventilation, 6 = requiring invasive mechanical ventilation, 7 = requiring invasive mechanical ventilation plus additional organ support, such as pressors, renal replacement therapy, and/or extracorporeal membrane oxygenation.
[c]Numbers shown in the table include candidates evaluated starting March 2021, when the Electronic Data Capture system was updated to include details regarding the vaccination status.

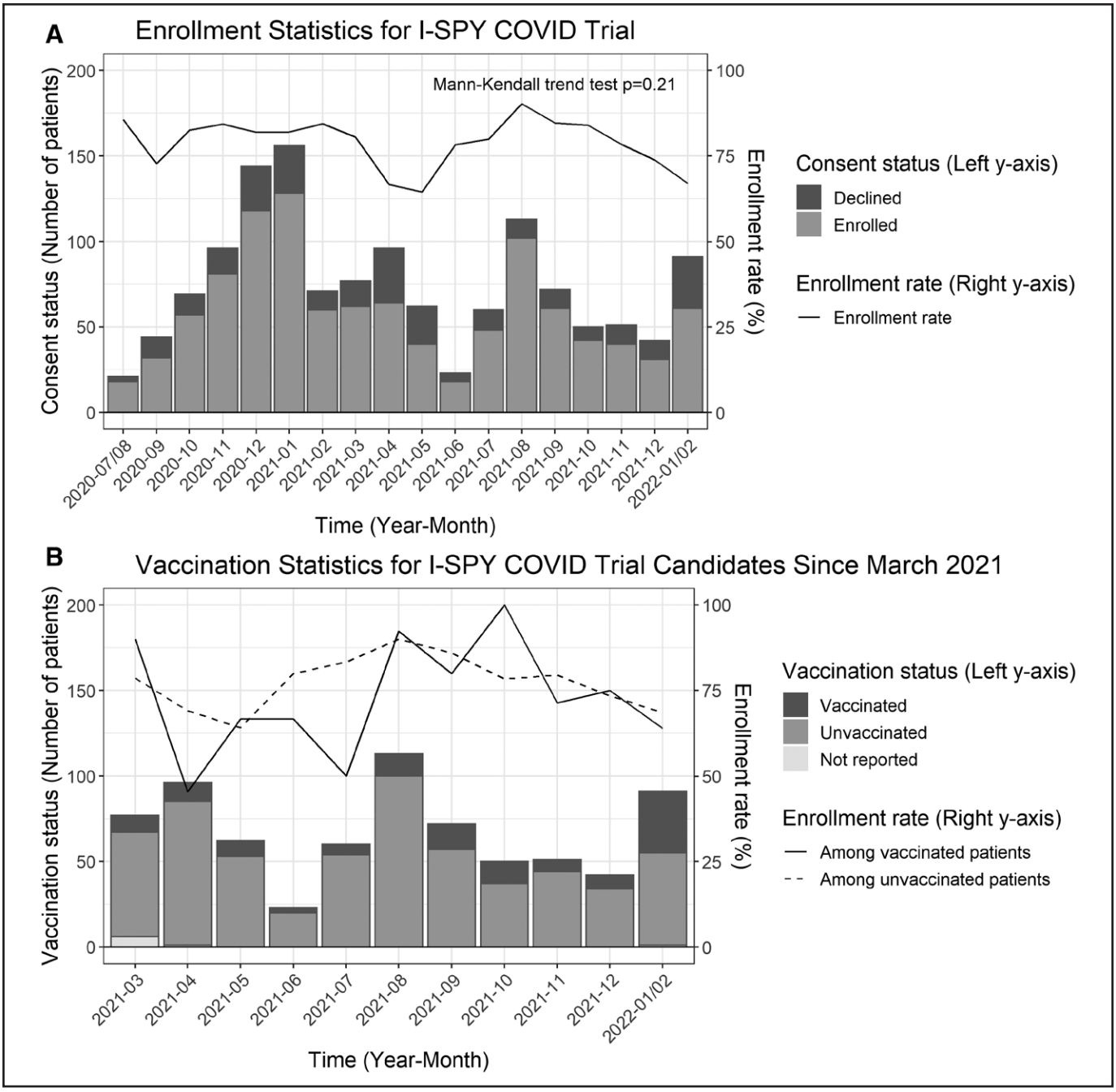

FIGURE 1. Enrollment and vaccination statistics for I-SPY COVID clinical trial. **A**, Number of candidates who declined versus enrolled in the I-SPY COVID trial, as well as the overall enrollment rates for each month. **B**, Number of candidates for the I-SPY COVID trial who were vaccinated versus unvaccinated, as well as the enrollment rates stratified by vaccination status for each month starting March 2021, when COVID-19 vaccines started becoming widely available and the Electronic Data Capture system was updated to include details regarding the vaccination status.

grounds for cautious optimism that the contentious environment surrounding COVID-19 and the perception of increasing scientific skepticism did not significantly reduce clinical trial enrollment. However, our analysis incorporates a single clinical trial, and reduced recruitment has been reported in other COVID-19 clinical trials (4, 5). Continued examination of other COVID-19 and, perhaps more importantly, non-COVID-19 RCTs will shed greater light on global patterns in clinical trial participation and whether those have indeed remained stable in recent years. Second, comparable enrollment rates between vaccinated and unvaccinated patients in this trial suggest that an individual's decisions regarding vaccination and clinical

trial participation may not be the same, although both are frequently discussed together in the broader context of scientific skepticism.

Strengths of this study include the utilization of data from a nationwide, multicenter RCT, and the presence of the observational cohort that allowed for collection of clinical data even for those who declined participation. There are several limitations. First, a small number of potential candidates were not approached about the trial at the request of the treating clinicians due to concerns regarding their clinical status or suitability as a research participant, and we cannot exclude potential selection bias in our cohort. Second, incomplete documentation of the reasons for declining consent limited our ability to gain insight into drivers of nonenrollment decisions; in particular, we could not assess the potential impact of the open-label design and the unique two-step consent process that may have resulted in higher rates of refusal for certain investigational agents and impacted the overall consent rates. Third, our records did not specify whether the patient or LAR was the decision-maker, and we could not assess the concordance of viewpoints on RCT participation or vaccination status between them. Last, due to a temporary suspension of the I-SPY COVID trial between March 2022 and June 2022, we were unable to extend our analysis into the second quarter of 2022, when the clinical trial enrollment decreased more substantially based on anecdotal reports.

CONCLUSIONS

In conclusion, this secondary analysis of the I-SPY COVID clinical trial did not find any significant trend in clinical trial enrollment rates over time during the first three waves of the COVID-19 pandemic. Demographic factors, severity of illness, and vaccination status were not significantly associated with the decision to decline RCT participation. Additional studies are needed to better understand the factors that influence complex decision-making processes for COVID-19 and critical care RCT enrollment and to develop strategies for encouraging participation in future clinical trials.

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1 *Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Emory University, Atlanta, GA.*

2 *Division of Cardiology, Emory University, Atlanta, GA.*

3 *Emory Health Services Research Center, Departments of Medicine & Surgery, Emory University, Atlanta, GA.*

4 *Division of Pulmonary, Critical Care, and Sleep Medicine, University of California Davis, Sacramento, CA.*

5 *Emory Critical Care Center, Department of Surgery, Emory University School of Medicine, Atlanta, GA.*

6 *Departments of Epidemiology and Global Health, Rollins School of Public Health, Emory University, Atlanta, GA.*

Members of the I-SPY COVID Consortium are listed in Appendix 1.

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Drs. Yang, Dickert, and Auld were involved in conceptualization. Drs. Yang and Auld were involved in data curation. Dr. Yang was involved in formal analysis. Drs. Yang, Haczku, and Auld were involved in investigation. Dr. Yang was involved in methodology. Ms. Spainhour was involved in administration. Drs. Yang, Haczku, and Auld were involved in resources. Drs. Dickert, Haczku, and Auld were involved in supervision. Drs. Yang, Dickert, Haczku, and Auld were involved in writing. Drs. Yang, Dickert, and Haczku, Ms. Spainhour, and Dr. Auld were involved in editing.

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For information regarding this article, E-mail: philip.yang@emory.edu

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APPENDIX 1. MEMBERS OF THE I-SPY COVID CONSORTIUM (CONTRIBUTORS)

Writing Committee: Neil R. Aggarwal, MD, MHSc (Department of Medicine, University of Colorado, Aurora, CO); Timothy Albertson, MD (Division of Pulmonary, Critical Care and Sleep Medicine, University of California Davis, Davis, CA); Sara Auld, MD (Department of Medicine, Emory University, Atlanta, GA); Jeremy R. Beitler, MD, MPH (Center for Acute Respiratory Failure, Columbia University, New York, NY); Paul Berger, DO (Department of Critical Care, Sanford Health, Fargo, ND); Ellen L. Burnham, MD (Department of Medicine, University of Colorado, Aurora, CO); Carolyn S. Calfee, MD, MAS (Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, University of California San Francisco, San Francisco, CA); Nathan Cobb, MD (Georgetown University Medical Center, Washington, DC); Alessio Crippa, PhD (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden); Andrea Discacciati, PhD (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden); Martin Eklund, PhD (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden); Laura Esserman, MD, MBA (Department of Surgery and Radiology, University of California San Francisco, San Francisco, CA); D. Clark Files, MD (Department of Internal Medicine, Wake Forest University, Winston-Salem, NC); Eliot Friedman, MD (Department of Medicine, Main Line Health, Springfield, PA); Sheetal Gandotra, MD (Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL); Kashif Khan, MD (Critical Care Medicine, Keck School of Medicine, Los Angeles, CA); Jonathan Koff, MD (Section of Pulmonary, Critical Care, and Sleep Medicine, Yale University, New Haven, CT); Santhi Kumar MD (Division of Pulmonary, Critical Care and Sleep Medicine, Keck School of Medicine at USC, Los Angeles, CA); Kathleen D. Liu, MD, PhD (Divisions of Nephrology and Critical Care Medicine, University of California San Francisco, San Francisco, CA); Thomas R. Martin, MD (Pulmonary, Critical Care and Sleep Medicine, University of Washington, Seattle, WA); Michael A. Matthay, MD (Cardiovacular Research

Institute, University of California San Francisco, San Francisco, CA); Nuala J. Meyer, MD (Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA); Timothy Obermiller, MD, MS (Critical Care Medicine, Logan Health Research Institute, Kalispell, MT and Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA); Philip Robinson, MD (Hoag Memorial Hospital Presbyterian Center for Research and Education, Newport Beach, CA)[j] Derek Russell, MD (Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL and Pulmonary Section, Birmingham Veteran's Affairs Medical Center, Birmingham, AL); Karl Thomas, MD (Department of Internal Medicine, Wake Forest University, Winston-Salem, NC); Se Fum Wong, MD (Critical Care Medicine, Keck School of Medicine, Los Angeles, CA); Richard G. Wunderink, MD (Department of Medicine, Pulmonary and Critical Care Division, Northwestern University Feinberg School of Medicine, Chicago, IL); Mark M. Wurfel, PhD, MD (Pulmonary, Critical Care and Sleep Medicine, University of Washington, Seattle, WA); Albert Yen, MD (Critical Care Medicine, Keck School of Medicine, Los Angeles, CA); and Fady A. Youssef, MD (Department of Internal Medicine, Pulmonary Division, Long Beach Memorial Medical Center, Long Beach, CA).

Site Investigators and Staff: Anita Darmanian, MD (Center for Acute Respiratory Failure, Columbia University, New York, NY); Amy L. Dzierba, PharmD (Center for Acute Respiratory Failure, Columbia University, New York, NY); Ivan Garcia, RRT (Center for Acute Respiratory Failure, Columbia University, New York, NY); Katarzyna Gosek, PharmD (Center for Acute Respiratory Failure, Columbia University, New York, NY); Purnema Madahar, MD, MS (Center for Acute Respiratory Failure, Columbia University, New York, NY); Aaron M. Mittel, MD (Center for Acute Respiratory Failure, Columbia University, New York, NY); Justin Muir, PharmD (Center for Acute Respiratory Failure, Columbia University, New York, NY); Amanda Roden, MD (Center for Acute Respiratory Failure, Columbia University, New York, NY); John Schicchi, MD (Center for Acute Respiratory Failure, Columbia University, New York, NY); Alexis L. Serra, MD, MPH (Center for Acute Respiratory Failure, Columbia University, New York, NY); Romina Wahab, MD (Center for Acute Respiratory Failure, Columbia University, New York, NY); Kevin W. Gibbs, MD (Department of Internal Medicine, Wake Forest University, Winston-Salem, NC); Leigha Landreth, RN (Department of Internal Medicine, Wake Forest University, Winston-Salem, NC); Mary LaRose, RN (Department of Internal Medicine, Wake Forest University, Winston-Salem, NC); Lisa Parks, RN (Department of Internal Medicine, Wake Forest University, Winston-Salem, NC); Adina Wynn, MPH, CCRP (Department of Internal Medicine, Wake Forest University, Winston-Salem, NC); Caroline A. G. Ittner, PhD (Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA); Nilam S. Mangalmurti, MD (Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA)[i] John P. Reilly, MD, MS (Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA); Donna Harris, BSN (Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL); Abhishek Methukupally, MBBS (Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL); Siddharth Patel, MBBS, MPH (Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL); Lindsie Boerger, BA (Section of Pulmonary, Critical Care, and Sleep Medicine, Yale University, New Haven, CT); John Kazianis, MD (Section of Pulmonary, Critical Care, and Sleep Medicine, Yale University, New Haven, CT); Carrie Higgins (Department of Medicine, University of Colorado, Aurora, CO); Jeff McKeehan, MS (Department of Medicine, University of Colorado, Aurora, CO); Brian Daniel, RCP, RRT (Division of Critical Care Medicine, University of California San Francisco, San Francisco, CA); Scott Fields, PharmD (Investigational Drug Service, University of California San Francisco, San Francisco, CA); James Hurst-Hopf, MS (Department of Laboratory Medicine, University of California San Francisco, San Francisco, CA); Alejandra Jauregui, BA (Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, University of California San Francisco, San Francisco, CA); Lamorna Brown Swigart, PhD (Department of Laboratory Medicine, University of California San Francisco, San Francisco, CA); Daniel Belvins, CCRP (Department of Internal Medicine, Pulmonary Division, Long Beach Memorial

Medical Center, Long Beach, CA); Catherine Nguyen, MD (Department of Internal Medicine, Pulmonary Division, Long Beach Memorial Medical Center, Long Beach, CA); Alexis Suarez, MS (Department of Internal Medicine, Pulmonary Division, Long Beach Memorial Medical Center, Long Beach, CA); Maged A. Tanios, MD (Department of Internal Medicine, Pulmonary Division, Long Beach Memorial Medical Center, Long Beach, CA); Farjad Sarafian, MD (Hoag Memorial Hospital Presbyterian Center for Research and Education, Newport Beach, CA); Usman Shah, MD (Hoag Memorial Hospital Presbyterian Center for Research and Education, Newport Beach, CA); Max Adelman MD, MSc (Department of Medicine, Emory University, Atlanta, GA); Christina Creel-Bulos, MD (Department of Anesthesiology, Emory University, Atlanta, GA); Joshua Detelich, MD (Department of Medicine, Emory University, Atlanta, GA); Gavin Harris, MD (Department of Medicine, Emory University, Atlanta, GA); Katherine Nugent, MD (Department of Emergency Medicine, Emory University, Atlanta, GA); Christine Spainhour, RN, CCRC (Department of Emergency Medicine, Emory University, Atlanta, GA); Philip Yang, MD (Department of Medicine, Emory University, Atlanta, GA); Angela Haczku, MD, PhD (Division of Pulmonary, Critical Care and Sleep Medicine, University of California Davis, Davis, CA)[i] Erin Hardy (Division of Pulmonary, Critical Care and Sleep Medicine, University of California Davis, Davis, CA); Richart Harper, MD (Division of Pulmonary, Critical Care and Sleep Medicine, University of California Davis, Davis, CA); Brian Morrissey, MD (Division of Pulmonary, Critical Care and Sleep Medicine, University of California Davis, Davis, CA); Christian Sandrock, MD, MPH (Division of Pulmonary, Critical Care and Sleep Medicine, University of California Davis, Davis, CA); G. R. Scott Budinger, MD (Department of Medicine, Pulmonary and Critical Care Division, Northwestern University Feinberg School of Medicine, Chicago, IL); Helen K. Donnelly, RN, BSN (Department of Medicine, Pulmonary and Critical Care Division, Northwestern University Feinberg School of Medicine, Chicago, IL); Benjamin D. Singer, MD (Department of Medicine, Pulmonary and Critical Care Division, Northwestern University Feinberg School of Medicine, Chicago, IL); and Ari Moskowitz, MD (Division of Critical Care Medicine, Montefiore Medical Center, Bronx, NY).

Safety Working Group Chairs: Melissa Coleman, MD (Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, University of California San Francisco, San Francisco, CA) and Joseph Levitt, MD (Pulmonary, Allergy and Critical Care Medicine, Stanford University, Stanford, CA).

Quantum Leap Healthcare Collaborative Staff: Ruixiao Lu, PhD; Paul Henderson, PhD; Adam Asare, PhD; Imogene Dunn, PhD; and Alejandro Botello Barragan (Quantum Leap Healthcare, San Francisco, CA).