Systematic Review of the “Pragmatism” of Pragmatic Critical Care Trials

OBJECTIVES: To assess the pragmatism of published critical care randomized controlled trials self-described as pragmatic using a validated tool.

DATA SOURCES: Medical Literature Analysis and Retrieval Online database and PubMed interface from inception to November 1, 2021.

STUDY SELECTION: We performed a systematic search of randomized controlled trials evaluating interventions for critically ill adults that self-identified as pragmatic in title or abstract.

DATA EXTRACTION: Reviewers independently performed study selection and data extraction in duplicate; discrepancies were resolved by consensus. Pragmatism was assessed independently in duplicate by trained reviewers using the Pragmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2), a validated tool designed to represent how explanatory/pragmatic a trial is on the pragmatic to explanatory continuum. Trials were scored in nine domains on a 5-point continuum (from 1 = very explanatory to 5 = very pragmatic). Discrepancies of greater than 2 points were adjudicated by consensus discussion.

DATA SYNTHESIS: The search resulted in 284 studies; 56 met eligibility criteria. Forty-one of the trials had a discrepancy in at least one domain that required consensus discussion, most commonly in domains of eligibility and follow-up. Twelve studies (21.4%) were scored as “overall pragmatic,” defined as score of greater than 4 in five domains provided the scores in the remaining domains were three. The overall PRECIS-2 score of self-identified pragmatic studies increased from 1995 to 2021 suggesting increasing pragmatism over time. Pragmatic trials were more likely to have a waiver of informed consent (p = 0.05).

CONCLUSIONS: The number and pragmatism of self-identified pragmatic trials have increased, particularly in the past decade. However, less than one-quarter of these trials that use the term pragmatic in title or abstract were retrospectively rated as pragmatic. Our results support the concept that trials are designed on a spectrum of pragmatic to explanatory. Advances in the design and reporting of critical care trials are needed to ensure their real-world applicability.

KEY WORDS: critical illness; pragmatic clinical trial; randomized controlled trial

Critical care medicine is increasingly complex, with intensivists making over 100 decisions per day (1). These decisions are guided by the results of clinical trials when available—however, the unique practice context of critical care invokes challenges for trials such as problems of patient selection and recruitment as well as heterogeneity in treatment and care delivery (2). For example, participants may be required to meet strict enrollment criteria and intervention protocols may be impractical to implement in the general critical care community. Pragmatic trials use a research design that may overcome some of these barriers and increase the applicability of trial results when applied outside the typical research setting. Experts have called for increased adoption of pragmatic trial methodology in the field of critical care (3, 4).
Schwartz and Lellouch (5) first coined the terms “pragmatic” and “explanatory” as terms to describe the focus of clinical trials in 1967. Explanatory trials are optimized to determine the efficacy of an intervention, confirming a clinical or physiologic hypothesis. Explanatory trials seek to answer the question, “Does this intervention work in ideal conditions?” Pragmatic clinical trials are designed to provide evidence of the real-world effectiveness of an intervention in a broad patient group and therefore inform a clinical or policy decision (6). Pragmatic trials focus on the question, “Does this intervention work under usual conditions?” In practice, most trials exist across a continuum of explanatory to pragmatic (7).

The original Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) tool, published in 2009, attempted to clarify the concept of pragmatism and provided a scoring system across various trial design features for use by researchers at the design phase of a clinical trial (7). This tool was subsequently adapted into PRECIS-2, a validated tool that focuses on trial design choices, which determine the applicability of a trial (8).

Pragmatic trials have their own complexities and, in many cases, may not meet the criteria to constitute a true pragmatic trial (9). We conducted a systematic review of randomized controlled trials (RCTs) that evaluated interventions for critically ill adults and used the term pragmatic in title or abstract. Our study had the following objectives: 1) Quantify the number of critical care trials self-identified as pragmatic and assess the change in prevalence over time of self-described pragmatic critical care intervention trials and 2) Assess the degree of pragmatism for these across different domains of trial design using the PRECIS-2 tool (10).

**Materials and Methods**

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines as detailed in Appendix A (http://links.lww.com/CCX/B41) (11). The protocol was registered in the International Prospective Register for Systematic Reviews (registration CRD42021282329). The study did not meet criteria for human subjects research and was exempt from review by the Institutional Review Board at our institution.

**Search Strategy**

We searched the literature from inception up to November 1, 2021, using the Medical Literature Analysis and Retrieval Online database and the PubMed interface. The search strategy was determined a priori. We identified RCTs evaluating interventions for critically ill adults that included the word pragmatic in title or abstract. Our complete search strategy is listed in Appendix B (http://links.lww.com/CCX/B41).

**Study Selection and Data Extraction**

Two reviewers (J.A.P., S.P.T.) independently screened titles and abstracts for prespecified eligibility criteria. Articles were included for full-text review if the following eligibility criteria were met 1) RCT study design, 2) enrolled critically ill adults, and 3) used the term pragmatic in title or abstract. Discrepancies on eligibility criteria were resolved by consensus. Four trained physician reviewers assessed pragmatism using the PRECIS-2.

**Outcome and Scoring Process**

We scored all articles selected for review using the PRECIS-2 tool (10). The PRECIS-2 rating system has been recommended as a tool to plan pragmatic trials and has also been used to categorize published trial designs (8, 12, 13). PRECIS-2 is represented as a nine-spoked “wheel” with the following individual domains: 1) eligibility criteria; 2) recruitment; 3) setting; 4) organization; 5) flexibility delivery; 6) flexibility adherence; 7) follow-up; 8) primary outcome; and 9) primary analysis (8). Each domain can be scored using a 5-point Likert scale in which 1 means very explanatory, 2 rather explanatory, 3 equally pragmatic and explanatory, 4 rather pragmatic, and 5 very pragmatic. All four physician reviewers involved in this study underwent training on use of the PRECIS-2 trial prior to study initiation. Training included viewing the National Institutes of Health Health Care Systems Research Collaboratory webinar (available at www.nihcollaboratory.org/Pages/Grand-Rounds-01-22-16.aspx), rating two RCTs excluded from the initial search using the PRECIS-2 criteria, and participating in a consensus discussion on the rating.

All articles selected for review were rated independently across all nine domains of the PRECIS-2 tool by
two physician reviewers. Any domain with a discrepancy of greater than 2 in scoring on the Likert scale was discussed with all four physician reviewers until a consensus was reached. For example, if one reviewer scored a study across a particular domain as 2, rather explanatory, and a second reviewer scored the domain as 4, rather pragmatic, the study and domain were discussed among all four reviewers until a consensus was reached on the score. For domains with only 1 point difference, we used the average of the two scores as the domain score included in our analyses. Although there is no standardized cutoff score for when a trial is considered pragmatic enough to be labeled as pragmatic, for this review, we defined a PRECIS-2 summary score as pragmatic after consensus review if scores were 4 or greater in five domains provided the scores in the remaining domains are three as previously described (14).

We also collected data on reporting practices in the selected trials. We recorded whether studies included their own PRECIS-2 wheel, as has been recommended. Because pragmatic trials often involve complex interventions, we also recorded whether authors included a Template for Intervention Description and Replication (TIDieR) checklist, which provides key features of an intervention such as duration, dose or intensity, mode of delivery, essential processes, and monitoring in sufficient detail that the intervention can be understood and replicated (15). We assessed risk of bias using Version 2 of the Cochrane risk-of-bias tool for randomized controlled trials (RoB 2) (16).

### Statistical Analyses

Study characteristics are reported as number (%) for categorical data and median (interquartile range [IQR]) for continuous data. PRECIS-2 scores across individual domains were summarized with descriptive statistics. We used parametric tests (mean) and nonparametric tests (median) given lack of consensus about most appropriate measure of central tendency when reporting results of Likert scale and prior published results using PRECIS-2 (17–19). Differences between PRECIS-2 summary score across key study characteristics were evaluated using Fisher exact tests given small number of pragmatic score trials. Linear regression was used to evaluate for change in mean pragmatic scores over time. All p value reported are for two-sided alpha of less than 0.05. All statistical analyses were conducted using Stata statistical software Version 17.0 (StataCorp, College Station, TX).

### RESULTS

#### Characteristics of Included Studies

After excluding duplicates, our search retrieved 284 articles of which 56 met criteria for full-text review (Fig. 1). The citations for the articles included in this review are included in Appendix C (http://links.lww.com/CCX/B41). Characteristics of included studies are shown in Table 1. The pragmatic trials were published in 28 distinct journals, the median impact factor of which (in March 2022) was 5.70 (IQR, 3.17–17.66). The majority of studies (n = 45, 80.3%) were conducted in North America or Europe and were multicenter (n = 39, 69.6%). Most (n = 51, 91.1%) had an intention-to-treat primary analysis and 18 of the trials (32%) reported the studied intervention improved the primary outcome (positive trial). Two studies (4%) reported a PRECIS wheel; one of these also reported a TIDieR checklist. One additional study reported a TIDieR checklist. Thirty-five studies (63%) were determined to be at low risk of bias. We had some concerns of bias in 18 studies (32%) and 3 (5%) were deemed to be at high risk using the RoB 2 tool.

#### Scoring Across PRECIS-2 Domains

After independent review by two reviewers, 41 of the 56 trials reviewed had a discrepancy of greater than 2 in at least one domain and required consensus discussion. The most common discordance between reviewers was on the domains of “eligibility” and “follow-up”; 14 of the 56 trials required a consensus discussion in these domains. Reviewers most frequently agreed on scoring the domain of “primary analysis” where only four trials required a consensus discussion. After discussion, the mean and median scores for each domain are listed in Table 2. Trials were most pragmatic in “primary analysis” (mean score, 4.25; sd, 0.83) and least pragmatic in “primary outcome” (mean score, 3.49; sd, 1.33). The mean PRECIS-2 score across all nine domains in the 56 trials was 3.81 (sd, 0.63) and median 3.86 (IQR, 3.4–4.3). A total of 12 studies (21.4%) scored 3 or greater across all domains. Using our predetermined cutoff (scores ≥ 4 in five domains provided the scores in the
remaining domains are three as previously described), these 12 self-identified pragmatic trials were labeled as pragmatic after consensus review.

### Association of Trial Characteristics With Pragmatism

There has been an increase in the mean PRECIS-2 scores over time (Fig. 2) with a weak correlation between year ($R^2 = 0.15; p = 0.002$). All of the 12 studies scored as pragmatic after consensus review were published after 2011; nine of the 12 were published between 2018 and 2021. The majority of the pragmatic studies were funded by governmental funds and included individual level randomization; 6 (50%) were cluster randomized trials (Table 2). Nine of the pragmatic trials (75.0%) required individual level informed consent versus 18 (40.9%) of nonpragmatic scored trials ($p = 0.05$). Compared with trials with a nonpragmatic summary score, trials with a pragmatic summary score after consensus review were more likely to have a waiver of individual consent. There were no differences in primary outcome results (positive or negative trial), funding source, unit of analysis, or cluster versus individual level randomization (Table 3). Six of the trials (50%) scored as pragmatic after consensus review were deemed low risk of bias and six (50%) were deemed to have some concerns for bias. Trials with a pragmatic summary score after review were not more likely to have bias concerns compared with trials with a nonpragmatic summary score ($p = 0.32$).

### DISCUSSION

Our study confirms an increase in the number of self-described pragmatic trials of critical care interventions, particularly in the past decade. Although studies’ average PRECIS-2 score indicated slightly increasing overall pragmatism, 79% of self-identified pragmatic trials did not meet our proposed definition of pragmatic after consensus review.

Pragmatism in trial design arose from concerns that result of trials optimized to demonstrate efficacy may not apply to real-world settings (6). In reality, it may not be feasible or appropriate to be pragmatic in all domains and most trials exist along a continuum of pragmatic to explanatory (10, 14). We found self-identified pragmatic trials also existed along this continuum. Trials were most pragmatic in the domain of “primary analysis” (“to what extent are all data included?”) (10). For this domain, a score of 5 (very pragmatic) reflects an intention-to-treat analysis with all available data, whereas a score of 1 (very explanatory) may be given for a primary analysis that included only those participants that followed treatment protocol. We found the majority of self-identified pragmatic trials (> 90%) used an intention-to-treat primary analysis with all available data, now widely considered to be the
gold standard for assessing superiority of an intervention (20, 21). In general, study authors were clear in reporting the primary analysis performed, and there was high agreement among reviewers in scoring this domain (only four required consensus discussion).

We found self-identified pragmatic trials were least pragmatic in the PRECIS-2 domains of “setting” (“how different is the setting of the trial than usual care?”) and “primary outcome” (“to what extent is the outcome relevant to participants?”). Consistent with prior reports, we found the “setting” domain difficult to rate relative to usual care as centers able to conduct complex critical care interventions (even if quality improvement focused) are often relatively well-resourced in terms of organization and resources (19). Furthermore, 30% of self-identified pragmatic critical care trials were single-center studies, a more explanatory and less generalizable approach to trial design. Although this may be necessary in some cases, the implications of single-center designs on pragmatism should be clearly acknowledged by the study authors. The domain “primary outcome,” scored by the extent to which the outcome selected was relevant to participants, also required discussion in our review, partly because much is still unknown about how patients value particular outcomes (22). We categorized 32% of study primary outcomes (from 18 studies) as explanatory (score of < 3), consistent with other reports that remarkably few critical care RCTs select patient-important outcomes as primary outcomes (23). To improve the real-world applicability of critical care research, continued efforts are needed to identify key patient-important outcomes along with efficient methods for their measurement and analysis (22, 24, 25).

Retrospectively scored pragmatic trials were more likely to be conducted with a waiver of individual consent, likely related to the higher frequency of cluster randomization (26). The role of individual level informed consent in cluster RCTs is debated, with arguments for adhering strictly to ethical principles countered by the limitations individual consent pose to the scientific validity of the study (27, 28). Reporting around individual consent for cluster RCTs is poor (26, 29), and we urge trialists to explicitly report their decision to seek or waive informed consent along with ethics committee approval.

Although we were able to reach consensus scores for all studies, the disagreement in independent reviewer

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**TABLE 1.**

| Characteristic                              | n (%) |
|--------------------------------------------|-------|
| Publication period                         |       |
| Prior to 2010                               | 3 (5.4) |
| 2011–2015                                  | 17 (30.4) |
| 2016–2020                                  | 30 (53.6) |
| 2021 to present                            | 6 (10.7) |
| Geographic location                        |       |
| North America                              | 22 (39.3) |
| Europe                                     | 23 (41.1) |
| Asia and Middle East                       | 2 (3.6) |
| Australia                                  | 3 (5.4) |
| Other                                      | 6 (10.7) |
| Study type                                 |       |
| Individual level randomization             | 39 (69.6) |
| Cluster RCT, parallel design               | 4 (7.1) |
| Cluster RCT, crossover (includes stepped-wedge) | 13 (23.2) |
| Multicenter study (vs single-center)       | 39 (69.6) |
| Unit of analysis                           |       |
| Individual patient                         | 47 (83.9) |
| ICU or ward                                | 6 (10.7) |
| Other                                      | 3 (5.4) |
| Type of intervention studied               |       |
| Drug or medication                         | 14 (25.4) |
| Device                                     | 10 (18.2) |
| Patient-level care intervention            | 25 (44.6) |
| Ward-level intervention                    | 4 (7.3) |
| Postdischarge intervention                 | 3 (5.5) |
| Informed consent                           |       |
| Consent prior to randomization             | 24 (42.9) |
| Delayed consent                            | 5 (8.9) |
| No individual level informed consent       | 27 (48.2) |
| Funding source                             |       |
| Federal                                    | 31 (55.4) |
| Industry                                   | 12 (21.4) |
| Departmental or internal                   | 11 (19.6) |
| Other                                      | 2 (3.6) |
| Primary analysis                           |       |
| Intention to treat                         | 51 (91.1) |
| Per protocol                               | 5 (8.9) |
| Primary result, intervention improved outcome | 18 (32) |

RCT = randomized controlled trial.
scores (41/56 studies required discussion) underscores both the subjectivity in rating domains as well as lack of adequate reporting of study elements related to pragmatism. Only two of the trials in this review included a PRECIS-2 wheel in their publication (30, 31). In those two trials, our retrospective ratings were very similar to the authors’ prospective ratings (within 1 point for all domains). Whether factors related to pragmatism were considered prior to study start (as recommended) is unknown (14). Although the PRECIS-2 tool has been used retrospectively to assess the degree of pragmatism, the findings may not be reliable unless clear information is available in each of the nine domains (10, 19). We recommend that journals encourage authors of pragmatic RCTs to include their preregistered PRECIS-2 tool assessment, allowing for reviewers and readers to appraise the degree of pragmatism of the RCT (14). Additionally, despite increasing focus on studying complex health

### TABLE 2.
Pragmatic-Explanatory Continuum Indicator Summary 2 Domain Scores and Consensus Review

| Pragmatic-Explanatory Continuum Indicator Summary 2 Domain | Median Score (IQR) | Mean (sd) | Consensus Review, n (%)a |
|----------------------------------------------------------|-------------------|-----------|--------------------------|
| Eligibility                                              | 4 (4–4.5)         | 3.85 (1.03) | 14 (25.0)               |
| Recruitment                                              | 4 (2.4–5)         | 3.81 (1.22) | 9 (16.07)               |
| Setting                                                  | 4 (2.25–4.5)      | 3.64 (1.20) | 6 (10.71)               |
| Organization                                             | 4 (3.5–4.5)       | 3.88 (0.96) | 10 (17.86)              |
| Flexibility—delivery                                     | 4 (3.25–4.5)      | 3.79 (1.07) | 12 (21.43)              |
| Flexibility—adherence                                    | 4 (3.5–4.75)      | 3.95 (1.00) | 8 (14.29)               |
| Follow-up                                                | 4 (2–4.75)        | 3.49 (1.33) | 14 (25.0)               |
| Primary outcome                                          | 4 (2.5–4.5)       | 3.61 (1.25) | 6 (10.71)               |
| Primary analysis                                         | 4.5 (4–5)         | 4.24 (0.83) | 4 (7.14)                |

IQR = interquartile range.

*Number of studies that required consensus discussion for ≥ 2 point difference in Pragmatic-Explanatory Continuum Indicator Summary 2 score on individual review.

Figure 2. Mean Pragmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) scores of included studies over time. Linear regression line represents best fit; 95% CIs are represented by gray shading.
interventions, only two studies included an explicit intervention description such as the TIDieR checklist (15, 30, 33). The lack of clear intervention reporting made it challenging to retrospectively discern whether certain trial processes were organizational elements of the trial or part of the intervention itself, leading to discrepant scoring for the organization domain.

Our study has several strengths. We conducted this systematic review of pragmatic RCTs using strategies to minimize bias, with a comprehensive search for trials and independent duplicate data abstraction. All reviewers were trained in the use of the PRECIS-2 study wheel, and our design allowed for discussion and consensus to be reached on all disagreements. Our study also has several limitations. We only reviewed RCTs self-identified as pragmatic in title or abstract, and there may be pragmatic trials that were not captured by this search. As we describe, the use of the PRECIS-2 tool to determine pragmatism based on reviewing the publication retrospectively was challenging in many cases. We acknowledge that another group of experienced reviewers or those involved in the design of the individual studies may score pragmatism differently. Finally, we chose a cutoff for pragmatism as described in prior work; we acknowledge that other definitions of pragmatism may be appropriate and provide a different perspective to the relationship of pragmatism with clinical trial characteristics. Most trials exist on a continuum of explanatory to pragmatic across individual domains; however, we feel it is important for study authors to explicitly discuss in what aspects a trial labeled as pragmatic may or may not be pragmatic.

CONCLUSIONS

The number of critical care trials that included the word pragmatic in title or abstract has increased over time; however, the majority of these trials had one or more features of an explanatory trial. Advances in the design, conduct, and reporting of pragmatic critical care trials are needed to ensure real-world applicability.

### TABLE 3.
Differences in Study Characteristics Between Pragmatic and Nonpragmatic Overall Pragmatic-Explanatory Continuum Indicator Summary 2 Scores

| Study Characteristic                        | Pragmatic PRECIS-2 Summary Scorea (n = 12) | Nonpragmatic PRECIS-2 Summary Score (n = 44) | p   |
|---------------------------------------------|--------------------------------------------|---------------------------------------------|-----|
| Intervention improved primary outcome (yes) | 7 (58.3%)                                  | 31 (70.5%)                                  | 0.43|
| Federal funding                            | 10 (83.3%)                                 | 37 (84.1%)                                  | 0.63|
| Unit of analysis at individual level        | 10 (83.0%)                                 | 37 (84.1%)                                  | 0.63|
| Waiver of individual level of consent      | 9 (75%)                                    | 18 (50.9%)                                  | 0.05|
| Cluster randomized study design             | 6 (50%)                                    | 11 (25%)                                    | 0.15|

PRECIS-2 = Pragmatic-Explanatory Continuum Indicator Summary 2.

*Pragmatic PRECIS-2 summary score is defined as a consensus score of ≥ 4 in five domains provided the scores in the remaining domains are three or greater.

1. McKenzie MS, Auriemma CL, Olenik J, et al: An observational study of decision making by medical intensivists. Crit Care Med 2015; 43:1660–1668

REFERENCES
2. Sevransky JE, Checkley W, Martin GS: Critical care trial design and interpretation: A primer. *Crit Care Med* 2010; 38:1882–1889

3. Harhay MO, Casey JD, Clement M, et al: Contemporary strategies to improve clinical trial design for critical care research: Insights from the First Critical Care Clinical Trialists Workshop. *Intensive Care Med* 2020; 46:930–942

4. Bellomo R, Landoni G, Young P: Improved survival in critically ill patients: Are large RCTs more useful than personalized medicine? Yes. *Intensive Care Med* 2016; 42:1775–1777

5. Schwartz D, Lellouch J: Explanatory and pragmatic attitudes in therapeutic trials. *J Chronic Dis* 1967; 20:637–648

6. Ford I, Norrie J: Pragmatic trials. *N Engl J Med* 2016; 375:454–463

7. Thorpe KE, Zwarenstein M, Oxman AD, et al: A Pragmatic-Explanatory Continuum Indicator Summary (PRECIS): A tool to help trial designers. *CMAJ* 2009; 180:E47–E57

8. Loudon K, Zwarenstein M, Sullivan F, et al: Making clinical trials more relevant: Improving and validating the PRECIS tool for matching trial design decisions to trial purpose. *Trials* 2013; 14:115

9. Levy C, Zimmerman S, Mor V, et al: Pragmatic trials in long-term care: Implementation and dissemination challenges and opportunities. *J Am Geriatr Soc* 2022; 70:709–717

10. Loudon K, Treweek S, Sullivan F, et al: The PRECIS-2 tool: Designing trials that are fit for purpose. *BMJ* 2015; 350:h2147

11. Page MJ, McKenzie JE, Bossuyt PM, et al: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; 372:e71

12. Gaglio B, Phillips SM, Heurtin-Roberts S, et al: How pragmatic is it? Lessons learned using PRECIS and RE-AIM for determining pragmatic characteristics of research. *Implement Sci* 2014; 9:96

13. Glasgow RE, Gurfinkel D, Waxmonsky J, et al: Protocol refinement for a diabetes pragmatic trial using the PRECIS-2 framework. *BMJ Health Serv Res* 2021; 21:1039

14. Dal-Ré R, Janiaud P, Ioannidis JPA: Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? *BMC Med* 2018; 16:49

15. Hoffmann TC, Glasiou PP, Boutron I, et al: Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014; 348:g1687

16. Higgins JP, Altman DG, Gotzsche PC, et al: Cochrane Bias Methods Group; Cochrane Statistical Methods Group: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928

17. Sullivan GM, Artino AR Jr: Analyzing and interpreting data from likert-type scales. *J Grad Med Educ* 2013; 5: 541–542

18. Norman G: Likert scales, levels of measurement and the ‘laws’ of statistics. *Adv Health Sci Educ Theory Pract* 2010; 15:625–632

19. Johnson KE, Neta G, Dember LM, et al: Use of PRECIS ratings in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory. *Trials* 2016; 17:32

20. Fergusson D, Aaron SD, Guyatt G, et al: Post-randomisation exclusions: The intention to treat principle and excluding patients from analysis. *BMJ* 2002; 325:652–654

21. Moher D, Hopewell S, Schulz EF, et al: Consolidated Standards of Reporting Trials Group: CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010; 63:e1–e37

22. Auriemma CL, Harhay MO, Haines KJ, et al: What matters to patients and their families during and after critical illness: A qualitative study. *Am J Crit Care Med* 2021; 30:11–20

23. Gaudry S, Messika J, Ricard JD, et al: Patient-important outcomes in randomized controlled trials in critically ill patients: A systematic review. *Ann Intensive Care* 2017; 7:28

24. Spragg RG, Bernard GR, Checkley W, et al: Beyond mortality: Future clinical research in acute lung injury. *Am J Respir Crit Care Med* 2010; 181:1121–1127

25. Auriemma CL, Taylor SP, Harhay MO, et al: Hospital-free days: A pragmatic and patient-centered outcome for trials among critically and seriously ill patients. *Am J Respir Crit Care Med* 2021; 204:902–909

26. Giraudet B, Caille A, Le Gouge C, et al: Participant informed consent in cluster randomized trials: Review. *PLoS One* 2012; 7:e40436

27. Hutton JL: Are distinctive ethical principles required for cluster randomized controlled trials? *Stat Med* 2001; 20:473–488

28. Edwards SJ, Braunholtz DA, Lilford RJ, et al: Ethical issues in the design and conduct of cluster randomised controlled trials. *BMJ* 1999; 318:1407–1409

29. Taljaard M, McAree AD, Weijer C, et al: Inadequate reporting of research ethics review and informed consent in cluster randomised trials: Review of random sample of published trials. *BMJ* 2011; 342:d2496

30. Taylor SP, Murphy S, Rios A, et al: Effect of a multicomponent sepsis transition and recovery program on mortality and readmissions after sepsis: The improving morbidity during post-acute care transitions for sepsis randomized clinical trial. *Crit Care Med* 2022; 50:469–479

31. Wang HE, Schmicker RH, Daya MR, et al: Effect of a strategy of initial laryngeal tube insertion vs endotracheal intubation on 72-hour survival in adults with out-of-hospital cardiac arrest: A randomized clinical trial. *JAMA* 2018; 320:769–778

32. Casey JD, Janz DR, Russell DW, et al: PreVent Investigators and the Pragmatic Critical Care Research Group: Bag-mask ventilation during tracheal intubation of critically ill adults. *N Engl J Med* 2019; 380:811–821

33. McNamee JJ, Gillies MA, Barrett NA, et al: REST Investigators: Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure: The REST randomized clinical trial. *JAMA* 2021; 326:1013–1023