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CLINICAL INVESTIGATION

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Higher vs Lower Doses of Dexamethasone in Patients with COVID-19 and Severe Hypoxia (COVID STEROID 2) trial: Protocol for a secondary Bayesian analysis

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Abstract

Background: Coronavirus disease 2019 (COVID-19) can lead to severe hypoxic respiratory failure and death. Corticosteroids decrease mortality in severely or critically ill patients with COVID-19. However, the optimal dose remains unresolved. The ongoing randomised COVID STEROID 2 trial investigates the effects of higher vs lower doses of dexamethasone (12 vs 6 mg intravenously daily for up to 10 days) in 1,000 adult patients with COVID-19 and severe hypoxia.

Methods: This protocol outlines the rationale and statistical methods for a secondary, pre-planned Bayesian analysis of the primary outcome (days alive without life support at day 28) and all secondary outcomes registered up to day 90. We will use hurdle-negative binomial models to estimate the mean number of days alive without life support in each group and present results as mean differences and incidence rate ratios with 95% credibility intervals (CrIs). Additional count outcomes will be analysed similarly and binary outcomes will be analysed using logistic regression models with results presented as probabilities, relative risks and risk differences with 95% CrIs. We will present probabilities of any benefit/harm, clinically important benefit/harm and probabilities of effects smaller than pre-defined clinically minimally important differences for all outcomes analysed. Analyses will be adjusted for stratification variables and conducted using weakly informative priors supplemented by sensitivity analyses using sceptic priors.

Discussion: This secondary, pre-planned Bayesian analysis will supplement the primary, conventional analysis and may help clinicians, researchers and policymakers interpret the results of the COVID STEROID 2 trial while avoiding arbitrarily dichotomised interpretations of the results.

Trial registration: ClinicalTrials.gov: NCT04509973; EudraCT: 2020-003363-25.

1 | INTRODUCTION

Severe acute respiratory syndrome corona-virus-2 (SARS-CoV-2) has caused an ongoing pandemic of coronavirus disease 2019 (COVID-19). The manifestations of COVID-19 vary from asymptomatic infections over fever and mild symptoms from the respiratory tract to viral pneumonia and severe acute respiratory distress syndrome (ARDS).[1,2] As of January 24 2021, COVID-19 has caused over 2.1 million deaths worldwide and strained the capacity of hospitals and intensive care units (ICUs) in particular.[1,2]

Preliminary results from the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial demonstrated a 28-day mortality rate ratio of 0.83 (95% confidence interval [CI] 0.75 to 0.93) with 6 mg daily of dexamethasone for up to 10 days compared to usual care in hospitalised patients with suspected or confirmed COVID-19.[3] The results also indicated a possible larger effect in patients on invasive mechanical ventilation.[3] Following this, a World Health Organization (WHO)-initiated prospective meta-analysis summarised the results from all critically ill patients from the RECOVERY trial and 6 other randomised clinical trials (RCTs) comparing corticosteroids to usual care or placebo.[4] This meta-analysis confirmed the findings from the RECOVERY trial with a pooled odds ratio (OR) of 0.66 (95% CI 0.53 to 0.82) for 28-day mortality with corticosteroids.[4] Consequently, corticosteroid therapy has become standard practice in severely and critically ill patients with COVID-19 and added to clinical practice guidelines.[5-7]

The optimal dose of corticosteroids in COVID-19 patients with severe hypoxia remains uncertain, and a recent RCT conducted in non-COVID-19 ARDS patients suggested improved outcomes with a higher dose of dexamethasone compared to control.[8] The Higher vs Lower Doses of Dexamethasone in Patients with COVID-19 and Severe Hypoxia (COVID STEROID 2) trial investigates the effects of 12 vs 6 mg of dexamethasone in adult patients with COVID-19 and severe hypoxia.[9] The trial will primarily be analysed using conventional, frequentist statistical methods.[9] Bayesian statistical methods are increasingly used and recommended in clinical trials in critical care as they may offer advantages or supplementary information in addition to the conventional analyses.[10-16] This protocol and statistical analysis plan outline the rationale and methodology for a secondary, pre-planned Bayesian analysis of the COVID STEROID 2 trial. We hypothesise that a higher dose of dexamethasone will improve outcomes in adult patients with COVID-19 and severe hypoxia, and that Bayesian analyses provide additional information that will help clinicians, researchers and policymakers interpret the findings of the trial.

2 | METHODS

2.1 | Study design and conduct

The COVID STEROID 2 trial is an investigator-initiated, international, parallel-group, blinded, centrally randomised and stratified (for site, use of invasive mechanical ventilation and age <70 years) clinical trial assessing the effects of higher (12 mg) vs lower (6 mg) doses of dexamethasone in adult patients with COVID-19 and severe hypoxia. The design was based on the COVID STEROID trial, which compared low-dose hydrocortisone with placebo in adult COVID-19 patients with severe hypoxia.[17] The COVID STEROID trial was paused following the preliminary results from the RECOVERY trial and afterwards terminated after publication of the WHO meta-analysis.[3,4]

Additional details on the COVID STEROID 2 trial including detailed variable definitions are available in the primary protocol[9] and on the trial website (www.cric.nu/covid-steroid-2).

2.2 | Approvals and reporting

The COVID STEROID 2 trial was approved by the Committee on Health Research Ethics in the Capital Region of Denmark (H-20051056); the Danish Medicines Agency (2020-07-16); the Capital Region Knowledge Centre for Data Compliance in Denmark (P-2020-842); and registered at ClinicalTrials.gov (NCT04509973) and the European Union Drug Regulating Authorities Clinical Trials Database (2020-003363-25). Additional local/national registrations and approvals in other participating countries will be or have been obtained prior to start of enrolment in these countries as required (not listed in this secondary study protocol); informed consent will be obtained for all patients according to applicable local/national laws.

The primary trial protocol[9] was prepared according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[18]; this secondary study protocol was prepared in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement[19] (completed checklist included in the supplement) with the Bayesian analyses specified in accordance with the Reporting Of Bayes Used in clinical STudies (ROBUST) guideline.[20] The primary trial results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement,[21] and the results from this secondary analysis will be reported in accordance with the STROBE statement and the ROBUST guideline regardless of the results.

2.3 | Enrolment criteria

Adult patients aged 18 years or above with documented SARS-CoV-2/COVID-19 requiring hospitalisation *and* receiving at least 10 L/min of supplemental oxygen (regardless of delivery system) *or* mechanical ventilation (ie non-invasive ventilation, continuous use of continuous positive airway pressure or invasive mechanical ventilation) are screened for inclusion. Exclusion criteria are use of systemic corticosteroids for other indications than COVID-19 in doses higher than 6 mg dexamethasone equivalents; use of systemic corticosteroids for COVID-19 for 5 consecutive days or more; invasive fungal invasion; active tuberculosis; fertile woman (below 60 years of age)

with positive urine or plasma human chorionic gonadotropin; known hypersensitivity to dexamethasone; previously randomised in the COVID STEROID 2 trial and informed consent not obtainable. Co-enrolment with other clinical trials is allowed if the interventions or protocols do not collide.[9]

2.4 | Interventions

Patients will be randomised in a 1:1 ratio to either 12 mg (higher dose, intervention group) or 6 mg (lower dose, control group) of dexamethasone intravenously once daily for up to 10 days (until death, hospital discharge or total 10 days of consecutive corticosteroid use, including days with corticosteroid use before inclusion). Shelf medication is used, and betamethasone is allowed if dexamethasone is not available.[9] To ensure blinding of clinicians, participants and outcome assessors, trial medication is prepared by unblinded trial staff not involved in patient care or outcome assessment.[9]

2.5 | Outcomes

This secondary study will assess all outcomes registered within 90 days of randomisation using Bayesian statistical methods; we do not plan to include outcomes registered at 180 days in this secondary analysis. The primary trial outcome is days alive without life support (ie invasive mechanical ventilation, circulatory support or renal replacement therapy, including days in between intermittent renal replacement therapy) from randomisation to day 28. Secondary outcomes assessed in this study include:

- One or more serious adverse reactions from randomisation to day 28, including new episodes of septic shock, invasive fungal invasion, clinically important gastrointestinal bleeding or anaphylactic reaction to intravenous dexamethasone
- All-cause mortality at day 28 and day 90
- Days alive without life support (as defined for the primary outcome) at day 90
- Days alive and out of hospital at day 90

2.6 | Sample size and trial status

Detailed sample size justifications for the conventional, frequentist analyses are available in the primary protocol.[9] At maximum, we plan to randomise 1000 patients and conduct an interim analysis with pre-specified stopping rules after the first 500 participants have been followed for 28 days.[9] Regardless of whether the trial includes the full sample size or is stopped early, this secondary analysis will be conducted including all randomised patients from the intention-to-treat population.

The trial was initiated on August 27 2020 and enrolment is expected to conclude in August 2021. As of January 25 2021, 492/1,000 patients (49.2%) have been enrolled at 27 sites in Denmark, India, Switzerland and Sweden.

2.7 | Statistical analyses

We will conduct analyses using R (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the *Tidyverse*[22] packages and Stan[23] through the *brms* R package.[24] All analyses will include the stratification variables (site, use of invasive mechanical ventilation at baseline and age below 70 years). Models are described below with additional details in the supplement. Baseline data will be presented in the primary trial publication as specified elsewhere.[9]

2.7.1 | Principles of Bayesian analyses

Bayesian analyses differ from their conventional, frequentist counterparts in several aspects. Importantly, Bayesian analyses starts with *prior* beliefs about the effect estimates expressed using probability distributions, which are updated when the data have been collected to *posterior* probability distributions.[12,25,26] The posterior probability distributions can be summarised in multiple ways, including calculation of direct probabilities for any effect size of interest (ie any or clinically important benefit or harm, or no clinically important difference), and calculation of 95% credible intervals (CrIs) that represent the 95% most plausible effect sizes given the prior, the model and the data.[12,25,26]

2.7.2 | Priors

We will use weakly informative priors centred on no difference and including all plausible effect sizes for all parameters in the primary Bayesian analyses, including adjustment (stratification) variables. Weakly informative priors are used as no high-quality direct evidence on the effects of higher vs lower doses of corticosteroids in patients with COVID-19 and severe hypoxia was available at trial initiation.[9] These priors will be overwhelmed by the data and have minimal influence on the results.

Sensitivity analyses will be conducted using *sceptic* priors for the intervention effects, which are sceptic of large effects and *"shrink"* effect estimates towards no difference, as many previous interventions in critical care have shown either small, clinically unimportant or statistically insignificant differences.[27,28] If relevant external evidence of sufficient quality becomes available during the trial, we will consider additional sensitivity analyses incorporating these data in *evidence*-based priors for the intervention effects. The sensitivity analyses will use the same weakly informative priors for all parameters not of primary interest as the primary analyses.

Exact priors and additional prior justifications are presented in the supplement.

2.7.3 | Summarisation and presentation of results

Posteriors will be summarised using median values as point estimates and percentile-based 95% CrIs. Posteriors for the parameters of primary interest will be visualised along with cumulated posterior distributions to present probabilities of all possible effect sizes as outlined in Figure 1.

2.7.4 | Analysis of the primary outcome

We expect the primary outcome (days alive without life support at day 28) to be highly null-inflated and non-normally distributed. Thus,

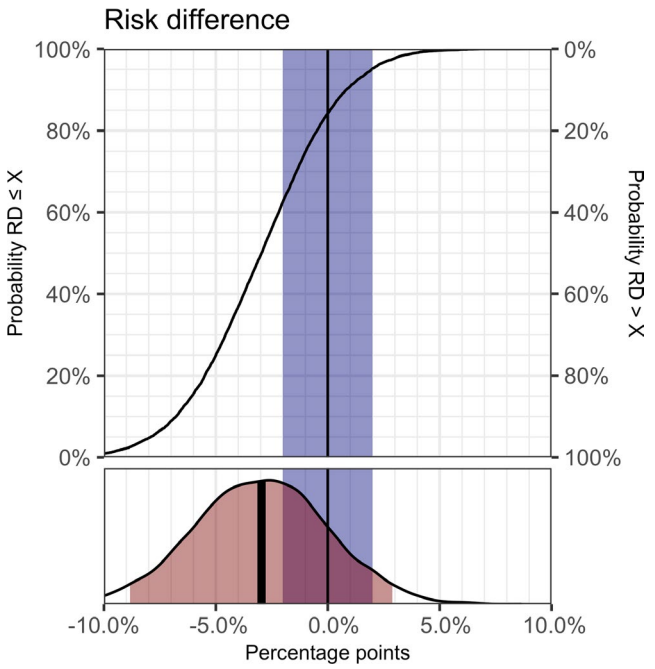

FIGURE 1 Visualisation of results (mock figure). Mock figure illustrating how the posterior distributions for the parameters of primary interest (relative risks, risk differences, incidence rate ratios and mean differences) will be visualised. This example uses randomly generated data from a normal distribution with a mean of −3 and standard deviation of 3, simulating a potential risk difference (RD) in percentage points. In the upper subplot, the cumulative posterior distribution is visualised, corresponding to the probabilities that the RD is less than or equal to (left Y-axis) or greater than (right Y-axis) the effect size on the X-axis. In the lower subplot, the entire posterior distribution is visualised, with the bold, vertical line indicating the point estimate (median value), and the area in red highlighting the percentile-based 95% credible interval. In both subplots, the thin, black, vertical line represents no difference and the area highlighted in blue represents differences smaller than a pre-defined clinically minimally relevant difference of 2 percentage points in either direction [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Effect estimates and probabilities (mock table)

	Effect estimates				Probability of effects				
Outcome	Higher-dose group	Lower-dose group	Relative difference	Absolute difference	Any benefit	Any harm	Clinically important benefit	Clinically important harm	No clinically important difference
Count outcomes—example									
Days alive without life support	Mean: ###.# (##.#% to ##.#%) days	Mean: ###.# (##.#% to ##.#%) days	IRR: ##.# (##.# to ##.#)	MD: ##.# (##.# to ##.#) days	##.#%	##.#%	##.#%	##.#%	##.#%
Binary outcomes—example									
28-day mortality	Prob.: ##.#% (##.#% to ##.#%)	Prob.: ##.#% (##.#% to ##.#%)	RR: ##.# (##.# to ##.#)	RD: ##.#% (##.#% to ##.#%)	##.#%	##.#%	##.#%	##.#%	##.#%

Note: Mock table illustrating how the results from the analyses will be summarised and presented. "#" will be replaced with actual numbers when results are presented.
Effect estimates are presented as median values from the posterior distributions as point estimates with percentile-based 95% credible intervals (CrIs); all effect estimates are adjusted for the stratification variables as outlined in the main text.
Any benefit is the probability of an IRR > 1 / MD > 0 days or a RR < 1 / RD < 0%, while any harm is the probability of an IRR < 1 / MD < 0 days or a RR > 1 / RD > 0%, respectively; no clinically important difference is the probability of a MD >−1 days & MD < 1 days or a RD >−2 & RD < 2 percentage points; clinically important benefit/harm is the probabilities of effects larger than those defined as not being clinically important.
Abbreviations: <1 favours a higher dose); >0 favours a higher dose); IRR: incidence rate ratio (>1 favours a higher dose); MD: mean difference (or difference in means; prob.: probability; RD: risk difference (<0 favours a higher dose); RR: relative risk (or risk ratio.

we will analyse it using a Bayesian hurdle-negative binomial regression model. This model consists of two parts that are simultaneously estimated: 1) a logistic regression model, estimating the probability of having 0 days alive without life support, and 2) a zero-truncated negative binomial model (an over-dispersed count model[29]), which estimates the mean number of days alive without life support for all patients with at least 1 day alive without life support. There may be some inflation of patients with 28 days alive without life support (patients who never received life support and are alive at day 28) due to truncation of follow-up at this time-point; the negative binomial model is able to estimate the mean number of days alive without life support in patients with at least 1 day alive without life support, even if truncation of higher values means that data do not perfectly follow a negative binomial distribution. Of note, the hurdle-negative binomial model has conceptual similarities with the Kryger Jensen and Lange test,[30] which will be used in the primary, frequentist analyses.[9]

We will estimate the adjusted mean number of days alive without life support in each group and estimate differences on the absolute scale using the mean difference (MD) and on the relative scale using the incidence rate ratio (IRR). This will be done by combining both parts of the model comparing the higher vs lower dose with all adjustment variables set to the most common group. In addition, we will calculate probabilities of any benefit/harm, clinically important benefit/harm (defined as a MD ≥ 1 or ≤-1 day) or no clinically important difference. Results from the model will be presented as outlined in Table 1.

2.7.5 | Analysis of the secondary outcomes

Secondary count outcomes (days alive without life support at day 90 and days alive and out of hospital at day 90) will be analysed as the primary outcome and clinically important benefit/harm will be defined similarly.

Secondary binary outcomes will be analysed using Bayesian logistic regression models. Results will be presented as probabilities of the outcome in each group with groups compared using adjusted relative risks (RRs) and adjusted absolute risk differences (RDs). Probabilities, RRs and RDs will be calculated with all adjustment variables set to the most common group as for the primary outcome. In addition, we will calculate probabilities of any benefit/harm, clinically important benefit/harm (defined as a RD of ≥ 2 or ≤-2 percentage points) and no clinically important differences. The results for the binary secondary outcomes will be presented as outlined in Table 1.

2.7.6 | Missing data handling

The amount of missing data will be reported. We expect limited missing data for the outcomes included in this study and for all stratification variables; if ≥5% of patients have missing data for variables included in any of the specified analyses, we will multiply impute missing data using the same strategy as in the primary analyses of the trial.[9,31]

2.7.7 | Model settings and diagnostics

Models will generally be assessed as previously described.[11,15,32] We will use Stan's default dynamic Hamiltonian Monte Carlo sampler with 4 chains with at least 50,000 post–warm-up samples in total, and with bulk/tail effective sample sizes of at least 10,000 for the parameters of interest. We will tune sampler settings to avoid divergent transitions and assess chain convergence by visual inspection of overlain density and trace plots, and by requiring *Rhat* statistics ≤ 1.01 for all parameters.[33,34] We will assess model fit by using graphical posterior predictive checks[25] and Pareto-smoothed importance sampling leave-one-out cross validation.[35,36] If multiple imputation is used, models will be fitted and assessed separately in each imputed dataset before posteriors are pooled, with the requirements for the number of post–warm-up samples and effective sample sizes applying to the pooled samples.

3 | DISCUSSION

The outlined, pre-planned, secondary Bayesian analysis of the COVID STEROID 2 trial will provide additional information on the effects of higher vs lower doses of dexamethasone in adult patients with COVID-19 and severe hypoxia as a supplement to the conventional frequentist analyses. These Bayesian analyses may help clinicians, researchers and policymakers interpret the results and guide care and further research.

In frequentist analyses, *P*-values <.05 are conventionally interpreted as evidence for different intervention effects. This dichotomisation frequently leads to the common misinterpretation that absence of evidence (ie $P \geq .05$) equals evidence of absence (ie no difference),[37,38] although the reason for $P \geq .05$ can be either no difference, random variation, too little accrued data or an effect size smaller than expected when the trial was planned. Moreover, comparable problems exist when interpreting *P*-values < .05 of single trials.[39] As P-values offer no information on the effect size, estimates of effect sizes and associated uncertainty measures are more informative.[40] Frequentist methods assess uncertainty using 95% confidence intervals (CIs); if the study was repeated an indefinite number of times, 95% of these would contain the *true* intervention effect. However, 95% CIs are frequently misinterpreted as the 95% most likely values.[38]

Results from Bayesian analyses may be easier to interpret, as *direct* probabilities of *any* effect size of interest can be calculated, and as 95% CrIs *do* represent the 95% most likely values, given the prior, the data and the model.[12] In addition, the use of Bayesian analyses may help avoid common errors in interpretation and may, as recently recommended,[41] help shift focus away

from dichotomised interpretations of trial results and towards a focus on effect sizes and interpretation of evidence as a continuous measure. Regardless of how the COVID STEROID 2 trial is analysed, some uncertainty is expected to remain even after the results are available. However, as corticosteroids are generally considered safe and are widely used in critically ill patients, the clinical threshold for using a higher dose of corticosteroids in COVID-19 may be different from thresholds for introducing new, potentially expensive and potentially invasive treatments.[42] Given the current pandemic, it may be considered reasonable to act on probabilities in spite of uncertainty, as has recently been argued for other treatment decisions in the critically ill.[42,43]

3.1 | Strengths and limitations

The proposed study has several strengths in addition to the general strengths of the COVID STEROID 2 trial outlined in the primary protocol.[9] The Bayesian approach offers potential advantages when interpreting the results, as outlined above. In addition, we will present results on both the absolute and relative effect scales; while relative effect measures are generally more transportable to other populations and settings, absolute effect measures may be easier to interpret from a clinical point of view.

The study comes with limitations, too. As discussed above, uncertainty may remain after the results are known, and no statistical method will prevent this. Furthermore, the effects of different doses of dexamethasone may differ in patients with different comorbidities or by interacting with other treatments that may not be identified in this study. Moreover, our choice of what constitutes minimally important clinical differences may be challenged, and both smaller and larger effects may be relevant; this limitation, however, is mitigated by graphical presentation of probabilities for all effect sizes.

4 | CONCLUSION

In conclusion, the proposed secondary, pre-planned Bayesian analysis of the COVID STEROID 2 trial will provide additional information on the effects of higher vs lower doses of dexamethasone in adult patients with COVID-19 and severe hypoxia. These results will supplement the conventional, frequentist analyses and may help clinicians, researchers and policymakers interpret the results and guide care and further research while avoiding arbitrary dichotomisations and potentially erroneous claims of *"no difference"* between intervention effects.

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CONFLICTS OF INTEREST

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AUTHORS' CONTRIBUTIONS

AG drafted the first version of this protocol, which was critically revised by all authors. All authors contributed to the design or conduct of the COVID STEROID 2 trial.

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REFERENCES

1. Arabi YM, Murthy S, Webb S. COVID-19: a novel coronavirus and a novel challenge for critical care. *Intensive Care Med*. 2020;46:1087-1088.
2. World Health Organization. Coronavirus disease (COVID-19). Pandemic 2020. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 [Last accessed 24 Jan 2021]
3. The RECOVERY Collaborative Group: Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N Engl J Med*. 2020. https://doi.org/10.1056/NEJMoa2021436
4. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically Ill patients With COVID-19: a meta-analysis. *JAMA*. 2020;324:1330-1341.
5. Siemieniuk R, Rochwerg B, Agoritsas T, et al. A living WHO guideline on drugs for covid-19. *BMJ*. 2020;370:m3379.
6. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis*. 2020; https://doi.org/10.1093/cid/ciaa478
7. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov [Last accessed 29 Oct 2020]
8. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8:267-276.
9. Munch MW, Granholm A, Myatra SN, et al. Higher vs. Lower Doses of Dexamethasone in Patients with COVID-19 and Severe Hypoxia (COVID STEROID 2) trial: protocol and statistical analysis plan. *Acta Anaesthesiol Scand*. 2021; https://doi.org/10.1111/aas.13795
10. Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (randomized embedded multifactorial adaptive platform for community-acquired pneumonia) study: rationale and design. *Ann Am Thorac Soc*. 2020;17:879-891.
11. Granholm A, Marker S, Krag M, et al. Heterogeneity of treatment effect of prophylactic pantoprazole in adult ICU patients: a post hoc analysis of the SUP-ICU trial. *Intensive Care Med*. 2020;46:717-726.
12. Ryan EG, Harrison EM, Pearse RM, Gates S. Perioperative haemodynamic therapy for major gastrointestinal surgery: the effect of a Bayesian approach to interpreting the findings of a randomised controlled trial. *BMJ Open*. 2019;9:e024256.
13. Zampieri FG, Damiani LP, Bakker J, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: a Bayesian reanalysis of the ANDROMEDA-SHOCK Trial. *Am J Respir Crit Care Med*. 2020;201:423-429.
14. 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.
15. Klitgaard TL, Schjørring OL, Lange T, et al. Bayesian and heterogeneity of treatment effect analyses of the HOT-ICU trial – a secondary analysis protocol. *Acta Anaesthesiol Scand*. 2020;64:1376-1381.
16. The Writing Committee for the REMAP-CAP Investigators: Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324:1317-1329.
17. Petersen MW, Meyhoff TS, Helleberg M, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia (COVID STEROID) trial - protocol and statistical analysis plan. *Acta Anaesthesiol Scand*. 2020;64:1365-1375.
18. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158:200-207.
19. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344-349.
20. Sung L, Hayden J, Greenberg ML, Koren G, Feldman BM, Tomlinson GA. Seven items were identified for inclusion when reporting a Bayesian analysis of a clinical study. *J Clin Epidemiol*. 2005;58:261-268.
21. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332. https://doi.org/10.1136/bmj.c332
22. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *J Open Source Softw*. 2019;4:1686.
23. Carpenter B, Guo J, Hoffman MD, et al. Stan: a probabilistic programming language. *J Stat Softw*. 2017;76:https://doi.org/10.18637/jss.v076.i01
24. Bürkner P-C. brms: An R package for Bayesian multilevel models using Stan. *J Stat Softw*. 2017;80. https://doi.org/10.18637/jss.v080.i01
25. Kruschke J. *Doing Bayesian Data Analysis – A Tutorial with R, JAGS, and Stan*, 2nd ed, London, UK: Academic Press; 2014.
26. Bendtsen M. A gentle introduction to the comparison between null hypothesis testing and Bayesian analysis: reanalysis of two randomized controlled trials. *J Med Internet Res*. 2018;20:e10873.
27. Ridgeon EE, Bellomo R, Aberegg SK, et al. Effect sizes in ongoing randomized controlled critical care trials. *Crit Care*. 2017;21:132. https://doi.org/10.1186/s13054-017-1726-x
28. Santacruz CA, Pereira AJ, Celis E, Vincent J-L. Which multicenter randomized controlled trials in critical care medicine have shown reduced mortality? A Systematic Review. *Crit Care Med*. 2019;47:1680-1691.
29. Jakobsen JC, Tamborrino M, Winkel P, et al. Count data analysis in randomised clinical trials. *J Biom Biostat*. 2015;06:227. https://doi.org/10.4172/2155-6180.1000227
30. Jensen AK, Lange T. A novel high-power test for continuous outcomes truncated by death. *arXiv*. 2019:1910.12267 [stat.ME].
31. van Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. *J Stat Software*. 2011;45:https://doi.org/10.18637/jss.v045.i03.
32. Granholm A, Marker S, Krag M, et al. Heterogeneity of treatment effect of stress ulcer prophylaxis in ICU patients: a secondary analysis protocol. *Acta Anaesthesiol Scand*. 2019;63:1251-1256.
33. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. *Bayesian Data Analysis*, 3rd edn. London, UK: Chapman and Hall/CRC; 2013.
34. Vehtari A, Gelman A, Simpson D, Carpenter B, Bürkner P-C. Rank-normalization, folding, and localization: An improved Rhat for assessing convergence of MCMC. *arXiv*. 2020:1903.08008v3 [stat.CO].
35. Vehtari A, Gelman A, Gabry J. Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. *Stat Comput*. 2017;27:1413-1432.
36. Lambert B. *A Student's Guide to Bayesian Statistics*, 1st edn. London, UK: SAGE Publications Ltd; 2018.
37. Altman DG, Bland JM. Statistics notes: absence of evidence is not evidence of absence. *BMJ*. 1995;311:485.
38. Greenland S, Senn SJ, Rothman KJ, et al. Statistical tests, *P* values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol*. 2016;31:337-350.

39. IntHout J, Ioannidis JPA, Borm GF. Obtaining evidence by a single well-powered trial or several modestly powered trials. *Stat Methods Med Res*. 2016;25:538-552.
40. Dunkler D, Haller M, Oberbauer R, Heinze G. To test or to estimate? P-values versus effect sizes. *Transpl Int*. 2020;33:50-55.
41. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature*. 2019;567:305.
42. Young PJ, Nickson CP, Perner A. When should clinicians act on non-statistically significant results from clinical trials? *JAMA*. 2020;323:2256-2257.
43. Harhay MO, Young PJ, Hari MS. Could stress ulcer prophylaxis increase mortality in high - acuity patients? *Intensive Care Med*. 2020;46:793-795.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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