Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
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Bayesian meta-analysis

Our random-effect model is defined as:

\[
\begin{align*}
    y_i & \sim \text{Normal}(\theta_i, \sigma^2_i) \\
    \theta_i & \sim \text{Normal}(\mu, \tau^2) \\
    \mu & = \alpha_{\text{subgroup}[k]}
\end{align*}
\]

where \(y_i\) is the observed mean log odds ratio of tocilizumab versus control and \(\sigma^2_i\) is the known sampling variance in study \(i\). Because this is a random-effect model, each study \(i\) has its own distribution, where \(\theta_i\) represents its mean effect. All \(\theta_i\)'s are drawn from normal distribution where the mean effect is \(\mu\) and the variance \(\tau^2\), which represents the between-study heterogeneity. \(\mu\) is predicted by a no-intercept linear regression, where each subgroup \(k\) (simple oxygen only; noninvasive ventilation; invasive mechanical ventilation) has its own parameter \(\alpha\), representing the effect of each respective subgroup.

In this case, we can assess tocilizumab’s effect in each subgroup while assuming a common between-study heterogeneity:

- Simple oxygen only = \(\alpha_{\text{SOO}}\)
- Noninvasive ventilation = \(\alpha_{\text{NIV}}\)
- Invasive mechanical ventilation = \(\alpha_{\text{IMV}}\)

Weakly informative priors

Because we applied the Bayesian framework, we assigned a prior distribution to each parameter. In our main model, we implemented priors that cover plausible values for all parameters, assigning limited density to impossible values, and thus employed little influence in the results (hereafter, known as weakly informative priors). These are our weakly informative priors:

\[
\begin{align*}
    \alpha & \sim \text{Normal}(0, 0.82^2) \\
    \tau & \sim \text{Half-Normal}(0.5^2)
\end{align*}
\]

Now, we will explain the rationale underlying these distributions.

We find highly unlikely that a pharmacological treatment, such as tocilizumab, will yield a 80% odds reduction in 28-days all-cause mortality regardless of the subgroup of patients, as suggested by empirical evidence. Thus, for \(\alpha\), we set a prior distribution of \(\text{Normal}(0, 0.82)\) in the log odds ratio scale.
To facilitate the understanding of these distributions, here are the corresponding 95% quantile intervals in the linear scale.

| Log scale | Linear scale |
|-----------|--------------|
| Mean      | SD           | Mean | 95% CI |
| 0         | 0.82         | 1    | [0.2, 5] |

Another way to assess the plausibility of the priors is to perform a prior predictive check⁴, which can be visualized below:

Point estimate depicts the median and interval bar depicts the 95% credible (quantile) interval.

As expected, the distribution approximately ranges from 0.2 to 5.0.

Lastly, we will now discuss the weakly informative prior distribution for $\tau$. Because we wanted to perform unconditional inferences beyond the included studies, we fitted a random-effect meta-analysis. In this model, one assumes there is within-study heterogeneity (represented by $\sigma_i^2$, the known sampling variance in study $i$) and the between-study heterogeneity (represented by $\tau$).

Although the definition of small or large between-study heterogeneity is arbitrary, previous work suggests cutoff values (“reasonable” heterogeneity between 0.1 and 0.5, “fairly high” between 0.5 and 1.0, and “fairly extreme” for values larger than 1.0 log odds ratio).²,⁵ We added a category for low heterogeneity (between 0 and 0.1).
The Half-Normal(0.5) distribution yields plausible probabilities in each of these ranges:

Here are the corresponding probabilities within each of the heterogeneity ranges:

| Heterogeneity Range  | Low | Reasonable | Fairly High | Fairly Extreme |
|----------------------|-----|------------|-------------|----------------|
| 16%                  | 52% | 27%        | 5%          |

**Alternative priors**

To check whether the choice of weakly informative priors meaningfully impacted our results or our conclusions, we also fitted models using vague or informative priors.

Vague priors:

\[
\alpha \sim \text{Normal}(0, 4^2) \\
\tau \sim \text{Half-Normal}(4^2)
\]

Informative priors:\(^6\)

\[
\alpha \sim \text{Normal}(0, 0.35^2) \\
\tau \sim \text{Log-Normal}(-1.975, 0.67^2)
\]
Here are graphical representations of these normal distributions (along with the weakly informative mentioned before):

| Log scale | Linear scale |
|-----------|--------------|
| Mean | SD | Mean | 95% CI |
| 0 | 0.35 | 1 | [0.5, 2] |
| 0 | 0.82 | 1 | [0.2, 5] |
| 0 | 4.00 | 1 | [0, 2540.2] |

Here are graphical representations of distributions for the between-study standard deviation ($\tau$) (along with the weakly informative mentioned before):
### Deriving risk difference from odds ratio

We used the odds ratio as our primary estimand.\textsuperscript{11,14} We derived the risk in the tocilizumab group using the following formula:\textsuperscript{11}

\[ R_T = \frac{R_C OR}{R_C (OR - 1) + 1} \]

where \( R_T \) is the mortality risk in the tocilizumab group, \( R_C \) is the mortality risk in the control group and \( OR \) is the odds ratio.

We then calculated the risk difference (RD) with the following formula:\textsuperscript{11}

\[ RD = R_T - R_C \]

We assumed different mortality risks in each subgroup. For the simple oxygen only and noninvasive ventilation subgroups, we used the average mortality risk in each subgroup based on the data included in this reanalysis. In contrast, regarding the invasive mechanical ventilation (IVM) subgroup, we found a striking discrepancy between the control mortality risk in the data included in this reanalysis (52\%) in comparison to another previously published meta-analysis (34\% in patients on IVM and using corticosteroids).\textsuperscript{10} Thus, we have decided to use 43\% (arithmetic mean between 34 and 52) as our reference risk in the IVM subgroup. Recognizing the potential variability of the subgroup baseline risks, we estimated the risk differences with twenty different plausible baseline risks for each subgroup (spanning \( \pm 10\% \) change from the reference risks mentioned above).

| Subgroup                        | Control Risk   |
|--------------------------------|----------------|
| Simple oxygen only             | 20 \( \pm \) 10\% |
| Noninvasive ventilation        | 34 \( \pm \) 10\% |
| Invasive mechanical ventilation| 42 \( \pm \) 10\% |
Predictive analysis to confirm tocilizumab’s association with mortality benefit

In brief, we will update our current evidence (as modeled in our main model) with generated randomized clinical trials (RCTs) of different sample sizes comparing tocilizumab to control on patients on invasive mechanical ventilation.

We will use the estimated marginal posterior mean and standard error on this subgroup to create a prior distribution. Then, we will use normal conjugate analyses to update this prior with new data (likelihood) and form updated posterior distributions.

Prior
As described before, we fitted a Bayesian meta-analysis model, from which we estimated marginal posterior distributions on different subgroups. Once again using a Bayesian approach, we updated our current belief, as expressed by the results of our current Bayesian meta-analysis, and which has now become our new prior, with the results of these new generated RCTs to arrive at revised posterior distributions.

Of note, the only subgroup of interest now is the invasive mechanical ventilation:

*Marginal posterior distribution of the invasive mechanical ventilation subgroup (also depicted in Figure 1A). The interval bar depicts the mean and 95% credible (quantile) interval.*

In the linear scale, the mean of this marginal posterior distribution is 0.89. Because we will use normal conjugate analysis, it is of greater interest to evaluate this distribution on the log scale, which is approximately normally distributed. In this case, the mean is -0.12 and the standard error is 0.17.

Thus, in the following normal conjugate analyses, we will use the following distribution as our prior:

\[
\text{Normal}(-0.12, 0.17^2)
\]

Likelihood
We created six different RCTs and update the prior distribution mentioned above six separate times.

Assuming the prior is normally distributed

\[
N(\theta, \sigma^2)
\]
and so is the data (likelihood).

\[ N(\theta, \sigma^2) \]

The mean and variance of the posterior distributions can be estimated by the following formulas:5

- Mean

\[ \frac{\theta + \hat{\theta}}{\frac{1}{\sigma^2} + \frac{1}{\hat{\sigma}^2}} \]

- Variance

\[ \frac{1}{\frac{1}{\sigma^2} + \frac{1}{\hat{\sigma}^2}} \]

In summary, we can update a normally distributed prior distribution (shown in the Figure above) with normally distributed data to generate a normally distributed posterior distribution. Based on the posterior’s mean and variance, we generated 100,000 random samples (seed number of 123).

Now, we must decide the mean and standard deviation of the likelihood. All RCTs will have a mean of -0.26 (log scale). This value is the equal to 0.77 in the linear scale, which was chosen based on WHO’s meta-analysis (page 14 in their Supplement 2).7 This is the mean odds ratio of tocilizumab vs. control in patients using corticosteroids (overall results). We decided to use this value to reflect a skeptical view to heterogeneity of treatment effect across subgroups,8 and thus the “real” effect in this subgroup would be equal to the largest body of evidence available for tocilizumab in all hospitalized COVID-19 patients on corticosteroids.

Given that all six generated RCTs were set to find the same effect size, the only difference between them was the total number of included patients: 200, 500, 1000, 1500, 2000, or 4000. To calculate the standard deviation of each corresponding prior based on the number of total patients included, one must also assume the proportion of patients included in each treatment arm and the mortality risk in the control arm:

1. We assumed equal allocation in both treatment arms
2. Adapting from the suggestions in the GRADE guidelines,9 we found a striking discrepancy between the control mortality risk in the data included in this reanalysis (52%) in comparison to another previously published meta-analysis (34% in patients on IVM and using corticosteroids).10 Thus, we have decided to use 43% (arithmetic mean between 34 and 52) as our reference risk in the IVM subgroup
3. The mortality risk in the tocilizumab was calculated using the following formula:11

\[ R_T = \frac{R_c \cdot OR}{R_c \cdot (OR - 1) + 1} \]

where \( R_T \) is the mortality risk in the tocilizumab group, \( R_c \) is the mortality risk in the control group and \( OR \) is the odds ratio mentioned above. Thus, the tocilizumab risk is equal to 37%.

In summary, we are generating RCTs with mean OR equal to 0.77, control risk mortality of 43%, and tocilizumab risk of 37%.

Based on these values, we can estimate the standard deviation (SD) with the following formula:12

\[ SD = \sqrt{\frac{1}{a + \frac{1}{2}} + \frac{1}{b + \frac{1}{2}} + \frac{1}{c + \frac{1}{2}} + \frac{1}{d + \frac{1}{2}}} \]

where \( a, b, c \) and \( d \) are number of events and follow this 2x2 table:
| Event  | Tocilizumab | Control |
|--------|-------------|---------|
| Death  | a           | c       |
| No death | b          | d       |

As previous work has shown,\textsuperscript{13} we can estimate these values as:

- \( a = R_T S_S_T \)
- \( b = S_S_T - R_T S_S_T \)
- \( c = R_C S_S_C \)
- \( d = S_S_C - R_C S_S_C \)

where \( S_S_T \) and \( S_S_C \) are the sample sizes in the tocilizumab and control arms, respectively. As mentioned above, we assume equal allocation in both treatment arms, thus \( S_S_T = S_S_C \).

Finally, the SDs based on the 6 different sample sizes mentioned above are:

| Sample size in each treatment arm | Total sample size | SD  |
|-----------------------------------|-------------------|-----|
| 100                               | 200               | 0.29|
| 250                               | 500               | 0.18|
| 500                               | 1,000             | 0.13|
| 750                               | 1,500             | 0.11|
| 1,000                             | 2,000             | 0.09|
| 2,000                             | 4,000             | 0.06|
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**eFigures and eTables**

**eTable 1. Demographic Information and Total Number of Patients in Each Subgroup per Study**

| Study        | Location                  | Age¹  | Male, %¹ | Number of Patients in Each Subgroup | Sum |
|--------------|---------------------------|-------|----------|-------------------------------------|-----|
|              |                           |       |          | Simple oxygen only                  |     |
|              |                           |       |          | Noninvasive ventilation             |     |
|              |                           |       |          | Invasive mechanical ventilation     |     |
| ARCHITECTS  | USA                       | 61.5  | 56.80    | 0                                   | 19  |
| BACC-Bay     | USA                       | 59.0  | 57.50    | 4                                   | 0   |
|              |                           |       |          |                                      | 4   |
| CORIMUNO-    | France                    | 63.7  | 68.00    | 22                                  | 0   |
| TOCI-1       |                           |       |          |                                      | 0   |
|              |                           |       |          |                                      | 22  |
| CORIMUNO-    | France                    | 64.3  | 72.00    | 0                                   | 3   |
| TOCI-ICU     |                           |       |          |                                      | 9   |
|              |                           |       |          |                                      | 12  |
| COV-AID      | Belgium                   | 62.9  | 75.70    | 46                                  | 31  |
|              |                           |       |          |                                      | 11  |
|              |                           |       |          |                                      | 88  |
| COVACTA      | Europe and North America  | 62.3  | 70.00    | 23                                  | 27  |
|              |                           |       |          |                                      | 42  |
|              |                           |       |          |                                      | 92  |
| COVIDOSE2-   | USA                       | 65.0  | 69.30    | 7                                   | 0   |
| SS-A         |                           |       |          |                                      | 0   |
|              |                           |       |          |                                      | 7   |
| EMPACTA      | North and Latin America;  | 56.5  | 58.60    | 200                                 | 94  |
| Kenya        |                           |       |          |                                      | 0   |
|              |                           |       |          |                                      | 294 |
| HMO-020-0224 | Israel                    | 63.8  | 65.90    | 0                                   | 19  |
|              |                           |       |          |                                      | 27  |
|              |                           |       |          |                                      | 46  |
| ImmCOVA      | Sweden                    | 63.0  | 76.00    | 0                                   | 29  |
|              |                           |       |          |                                      | 0   |
|              |                           |       |          |                                      | 29  |
| PreToVid     | Netherlands               | 66.5  | 67.00    | 234                                 | 79  |
|              |                           |       |          |                                      | 0   |
|              |                           |       |          |                                      | 313 |
| RECOVERY     | UK                        | 63.9  | 67.50    | 1531                                | 1444|
|              |                           |       |          |                                      | 405 |
|              |                           |       |          |                                      | 3380|
| REMAP-CAP    | Europe and Oceania; Saudi | 61.0  | 71.90    | 0                                   | 314 |
| Arabia       |                           |       |          |                                      | 115 |
|              |                           |       |          |                                      | 429 |
| REMDACTA     | Spain, USA, Brazil, Russian | 60.0  | 64.05    | 16                                  | 445 |
| Federation   |                           |       |          |                                      | 78  |
|              |                           |       |          |                                      | 539 |
| TOCIBRAS     | Brazil                    | 56.3  | 67.70    | 34                                  | 20  |
|              |                           |       |          |                                      | 11  |
|              |                           |       |          |                                      | 65  |

Of note, age and male proportion were extracted from the WHO REACT Working Group meta-analysis. They regard the whole sample of patients included in the trial, and not only on patients treated with corticosteroids. Thus, cautious interpretation of these characteristics is warranted.

¹ Mean value of both treatment arms
eFigure 1. Posterior Probabilities of Benefit in the Risk Difference Scale

Posterior probabilities of benefit per subgroup in the risk difference scale assuming weakly informative priors. Each line represents the posterior probability of benefit for a specific cutoff, such as risk difference greater than 0% or 1%, across plausible ranges of mortality risk under control treatment. Underlying weakly informative priors are $N(0, 0.82)$ for the coefficients, and $HN(0.5)$ for the between-study standard deviation. $N(\mu, \sigma) = \text{Normal(mean, standard deviation)}$; $HN(\sigma) = \text{Half-Normal(standard deviation)}$.

eFigure 2. Posterior Distributions of Relative Difference Between Subgroups

Posterior distributions for comparisons of effect sizes between subgroups while assuming weakly informative priors. Each distribution represents the ratio of odds ratios of two subgroups. On top of each distribution, there is a percentage representing the posterior probability of a ratio of odds ratios greater than 1.0 (eTable 2). Arrows on the bottom represent - in that comparison - which subgroup benefited to a greater extent tocilizumab's effect on mortality reduction (lower odds ratio [OR]). For example, according to our model, there was an 85% probability that tocilizumab reduces mortality to a greater extent in the simple oxygen subgroup in comparison to noninvasive ventilation. Underlying weakly informative priors are $N(0, 0.82)$ for each coefficient, and $HN(0.5)$ for the between-study standard deviation. $N(\mu, \sigma) = \text{Normal(mean, standard deviation)}$; $HN(\sigma) = \text{Half-Normal(standard deviation)}$. 
### eTable 2. Posterior Distributions and Probabilities of Relative Difference Between Subgroups While Assuming Distinct Prior Beliefs

| Priors<sup>a</sup> / Comparisons | Ratio of Odds Ratios [95% CI] | Pr(> 1.00), % | Pr(> 1.25), % |
|---------------------------------|-------------------------------|---------------|---------------|
| **Weakly informative<sup>a</sup>** |                               |               |               |
| Simple oxygen only vs. Noninvasive ventilation | 1.17 [0.85, 1.52] | 85.3 | 32.3 |
| Simple oxygen only vs. Invasive mechanical ventilation | 1.28 [0.84, 1.84] | 89.7 | 54.4 |
| Noninvasive ventilation vs. Invasive mechanical ventilation | 1.10 [0.75, 1.54] | 68.9 | 23.5 |
| **Vague<sup>a</sup>** |                               |               |               |
| Simple oxygen only vs. Noninvasive ventilation | 1.17 [0.84, 1.53] | 85.2 | 33.1 |
| Simple oxygen only vs. Invasive mechanical ventilation | 1.29 [0.84, 1.82] | 90.0 | 55.7 |
| Noninvasive ventilation vs. Invasive mechanical ventilation | 1.10 [0.72, 1.50] | 69.7 | 23.5 |
| **Informative<sup>a</sup>** |                               |               |               |
| Simple oxygen only vs. Noninvasive ventilation | 1.14 [0.86, 1.49] | 82.3 | 25.9 |
| Simple oxygen only vs. Invasive mechanical ventilation | 1.25 [0.86, 1.78] | 88.9 | 49.9 |
| Noninvasive ventilation vs. Invasive mechanical ventilation | 1.10 [0.75, 1.47] | 70.8 | 21.6 |

*Weakly informative priors: Coefficients N(0, 0.82); Between-study standard deviation HN(0.5) / Vague priors: Coefficients N(0, 4); Between-study standard deviation HN(4) / Informative priors: Coefficients N(0, 0.35); Between-study standard deviation LN(-1.975, 0.67). N(mu, sigma) = Normal(mean, standard deviation); HN(sigma) = Half-Normal(standard deviation); LN(mu, sigma) = Log-Normal(mean, standard deviation)

Abbreviations: CI, Credible interval; Pr, Posterior probability above specific value
Figure 3. Posterior Distributions of the Between-Study Standard Deviation While Assuming Distinct Prior Beliefs

Posterior distributions (log scale) of the between study standard deviation (tau) upon different underlying prior distributions (weakly informative, vague or informative). Tau is a proxy for the between-study heterogeneity in random-effect meta-analyses. Weakly informative priors: Coefficients N(0, 0.82); Between-study standard deviation HN(0.5) / Vague priors: Coefficients N(0, 4); Between-study standard deviation HN(4) / Informative priors: Coefficients N(0, 0.35); Between-study standard deviation LN(-1.975, 0.67). N(mu, sigma) = Normal(mean, standard deviation); HN(sigma) = Half-Normal(standard deviation); LN(mu, sigma) = Log-Normal(mean, standard deviation).

eTable 3. Posterior Distributions and Probabilities of the Between-Study Standard Deviation While Assuming Distinct Prior Beliefs

| Underlying Prior     | Median [95% CI] | Posterior Probability within Heterogeneity Ranges, % |
|----------------------|-----------------|------------------------------------------------------|
|                      |                 | Low | Reasonable | Fairly High |
| Weakly informative   | 0.11 [0, 0.41]  | 46.2 | 51.4 | 2.4 |
| Vague                | 0.12 [0, 0.49]  | 43.4 | 52.1 | 4.3 |
| Informative         | 0.1 [0.02, 0.26]| 45.3 | 54.6 | 0.1 |

Abbreviations: CI, Compatibility (highest density) interval

Although the definition of small or large between-study heterogeneity is arbitrary, previous work suggests cutoff values: “reasonable” heterogeneity between 0.1 and 0.5, “fairly high” between 0.5 and 1.0, and “fairly extreme” for values larger than 1.0 log odds ratio for the between-study standard deviation (tau).23 We added a category for low heterogeneity (between 0 and 0.1). Thus, in this table, we present the posterior probabilities within each one these ranges. Because we fitted three different models using different prior distributions (weakly informative, vague, and informative), here we depict tau posterior distributions/probabilities regarding each model.

Weakly informative priors: Coefficients N(0, 0.82); Between-study standard deviation HN(0.5) / Vague priors: Coefficients N(0, 4); Between-study standard deviation HN(4) / Informative priors: Coefficients N(0, 0.35); Between-study standard deviation LN(-1.975, 0.67). N(mu, sigma) = Normal(mean, standard deviation); HN(sigma) = Half-Normal(standard deviation); LN(mu, sigma) = Log-Normal(mean, standard deviation)
### eTable 4. Predictive Posterior Distributions and Probabilities While Assuming Weakly Informative Priors

| Subgroup                        | Odds Ratio [95% CI] | Pr(< 0.9), % | Pr(< 1.00), % | Pr(> 1.11), % |
|---------------------------------|---------------------|--------------|---------------|---------------|
| Simple oxygen only              | 0.69 [0.40, 1.09]   | 89           | 94            | 3             |
| Noninvasive ventilation         | 0.80 [0.46, 1.25]   | 75           | 88            | 7             |
| Invasive mechanical ventilation | 0.88 [0.47, 1.40]   | 53           | 72            | 15            |

Abbreviations: CI, Compatibility (highest density) interval; Pr, Posterior probability below or above specific odds ratio
Weakly informative priors: Coefficients N(0, 0.82); Between-study standard deviation HN(0.5)

### eTable 5. Description of the Underlying Generated RCTs Used in the Normal Conjugate Analysis (Mean Equal to 0.77)

| Model                        | Generated RCT Characteristics | Number of Patients Included<sup>a</sup> |
|------------------------------|-------------------------------|-----------------------------------------|
| Main Model                   |                               | 717 (Current Evidence)                  |
| Model 2 RCT enrolling 200 patients | 0.77 [0.44, 1.36]              | 717 + 200 = 917                          |
| Model 3 RCT enrolling 500 patients | 0.77 [0.54, 1.1]              | 717 + 500 = 1217                         |
| Model 4 RCT enrolling 1000 patients | 0.77 [0.6, 0.99]             | 717 + 1000 = 1717                       |
| Model 5 RCT enrolling 1500 patients | 0.77 [0.63, 0.95]             | 717 + 1500 = 2217                       |
| Model 6 RCT enrolling 2000 patients | 0.77 [0.64, 0.92]             | 717 + 2000 = 2717                       |
| Model 7 RCT enrolling 4000 patients | 0.77 [0.68, 0.87]             | 717 + 4000 = 4717                       |

<sup>a</sup>Only considering the invasive mechanical ventilation subgroup

Abbreviations: CI, Compatibility (quantile) interval; Pr, Probability of treatment effect; OR, Odds ratio; RCT, Randomized controlled trial
eFigure 4. Prior, Data, and Posterior Distributions in the Normal Conjugate Analysis (Data Mean Equal to 0.77)

Results from the normal conjugate analyses updating current evidence on invasive mechanical ventilation (used as the Prior) with generated RCTs (used as Data, eTable 5). These analyses yield posterior distributions. Each panel represents a different model, in which the prior distribution is centered at 0.77 odds ratio. The label on top of each panel depicts the number of total patients on invasive mechanical ventilation included in each respective model (current plus generated patients). Point estimates depict the median and interval bars represent the 95% credible intervals for both prior, data (likelihood) and posterior distributions.
eTable 6. Description of the Underlying Generated RCT Used in the Normal Conjugate Analysis (Mean Equal to 1.00)

| Model          | Generated RCT Characteristics                  | Number of Patients Included<sup>a</sup> |
|----------------|-----------------------------------------------|----------------------------------------|
| Main Model     |                                               |                                        |
|                | Evidence Equivalence                          | Mean [95% CI]                           |
|                | Pr(OR < 1.0), %                               | Pr(OR < 0.9), %                         |
| Model 2        | RCT enrolling 200 patients                    | 1 [0.57, 1.75]                          |
| Model 3        | RCT enrolling 500 patients                    | 1 [0.7, 1.42]                           |
| Model 4        | RCT enrolling 1000 patients                   | 1 [0.78, 1.28]                          |
| Model 5        | RCT enrolling 1500 patients                   | 1 [0.81, 1.23]                          |
| Model 6        | RCT enrolling 2000 patients                   | 1 [0.84, 1.19]                          |
| Model 7        | RCT enrolling 4000 patients                   | 1 [0.88, 1.13]                          |

Abbreviations: CI, Compatibility (quantile) interval; Pr, Probability of treatment effect; OR, Odds ratio; RCT, Randomized controlled trial

<sup>a</sup>Only considering the invasive mechanical ventilation subgroup
Results from the normal conjugate analyses updating current evidence on invasive mechanical ventilation (used as the Prior) with generated RCTs (used as Data, eTable 6). These analyses yield posterior distributions as depicted on Panel A. In contrast to the results shown in eFigure4, the generated RCTs in these analyses are centered at 1.0 odds ratio. Panel A: Each panel represents a different model. The label on top of each panel depicts the number of total patients on invasive mechanical ventilation included in each respective model (current plus generated patients). Point estimates depict the median and interval bars represent the 95% credible intervals for both prior, data (likelihood) and posterior distributions. Panel B shows the posterior probability of benefit for different thresholds (OR < 1.0 and < 0.9).