# Supplemental Material*

Reis G, dos Santos Moreira Silva EA, Medeiros Silva DC, et al. Oral fluvoxamine with inhaled budesonide for treatment of early-onset COVID-19. A randomized platform trial. Ann Intern Med. 2023. [Epub ahead of print]. doi:10.7326/M22-3305

## Contents



* This supplemental material was provided by the authors to give readers further details on their article. The material was not copyedited.

## Trial Infrastructure and the Extended TOGETHER Investigators

The COVID-19 TOGETHER Trial initiative was designed to evaluate repurposed treatments for COVID-19 disease through an adaptive trial design in two arms being conducted in Brazil and Canada. The trial is supported by a network of primary care research centers located in the state of Minas Gerais, Brazil and several sites in Toronto, Canada, devoted to a comprehensive evaluation and treatment of patients with COVID-19. The trial was fully integrated with local public health authorities (Brazilian Unified Health System – SUS) as part of coping strategy for COVID-19 pandemic. Namely, the main institutions involved were: Cardresearch – Cardiologia Assistencial e de Pesquisa and Toronto Centre for Liver Disease, University Health Network, Michael Garron Hospital, Sunnybrook Health Science Centre, Trillium Health Partners, Women's College Hospital. This initiative is funded by FastGrants, The Rainwater Foundation, Eiger Biopharmaceuticals and the FTX Foundation.

The TOGETHER Trial consortium is a partnership between academics and clinicians at McMaster University in Ontario, Canada, and Pontificia Universidade Catolica de Minas Gerais, Claros State University, University of Ouro Preto in Minas Gerais, Brazil and University Health Network in Ontario, Canada. Other partners include Cytel, Platform Life Sciences, MMS Holdings, WHO Therapeutic Guidelines Committee, and the Society for Clinical Trials.

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Included below are representatives from the enrolling centres at participating cities that enrolled at least 1 patient. Centres are listed in order of enrolment contribution. All study
sites were located in the State of Minas Gerais, Brazil or Ontario, Canada.

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**Women's College Hospital**
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## Description of Statistical Methods

All analyses involving dichotomous outcomes, including the primary outcome, were performed using the Bayesian beta-binomial model with uniform prior distributions for the individual arm event rates. Relative risks and posterior efficacy were evaluated based on size $10^6$ Monte Carlo samples from the resultant Beta posterior distributions. The choice of prior distribution was a Beta distribution because it is a conjugate prior for a Binomial likelihood. This was critical to allowing for interim analyses updates to be made using analyses that reflected prior interim analyses and allowing for simulations that allowed to control for multiplicity. The posterior distribution is then solved for using a closed-form equation based on its relationship to priors and posteriors. Summaries were derived using Monte Carlo samples from the posterior distributions of the two arms. The choice of uniform priors was, in part, made to minimize the impact of prior information, or lack thereof, on the statistical inference. However, given the study size, no major impact of said choice was expected on the estimation, while interim analysis decision boundaries were calibrated to meet frequentist criteria of power and type I error rate. See the statistical analysis plan for more detail.

Time-to-event analyses that were not adjusted for competing risks, and numeric secondary outcomes, were performed using the default Bayesian implementation of the Cox proportional hazards model in the *brms* R library[2] with four independent Markov Chain Monte Carlo (MCMC) chains of size 4,000 each and a flat prior distribution assigned to the treatment assignment coefficient. The likelihood is a function of the hazard rate, cumulative hazard and survival probability as described here (https://arxiv.org/pdf/2002.09633.pdf). The prior and posterior distributions for each of the parameters were Normally distributed. Posterior distributions were estimated using the Hamiltonian Monte Carlo, which is a form of Markov Chain Monte Carlo in which information about the gradient of the log posterior is used to more efficiently sample from the posterior space. This was implemented in Stan using the No-U-Turn Sampler (NUTS).

# Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) in Randomized Controlled Trials (Version 1.0)

### Quick instructions

- Synonyms for effect modification include subgroup effect, interaction, and moderation
- The instrument applies to a single proposed effect modification at a time; complete one form per each outcome, time-point, effect measure, and effect modifier
- Response options on the left indicate definitely or probably reduced, response options on the right probably or definitely increased credibility
- Completely unclear goes under probably reduced credibility
- It is helpful to provide a supporting comment or quotation under each question
- Whether an effect modification is patient-important is not part of the credibility assessment
- The manual provides more detailed instructions and examples

### Preliminary considerations

Study reference(s): NCT04727424

If available, protocol reference(s): NCT04727424

State a single outcome and, if applicable, time-point of interest (e.g., mortality at 1 year follow-up): primary outcome, 28 days

State a single effect measure of interest (e.g., relative or absolute risk difference): Risk ratio

State a single potential effect modifier of interest (e.g., age or comorbidity): days since symptom onset, or vaccination status

Was the potential effect modifier measured before or at randomization? [ **X** ] yes, continue [ ] no, stop here, refer to manual for further instructions

### Credibility assessment

**1: Was the direction of the effect modification correctly hypothesized a priori?**

| [ ] Definitely no | [ ] Probably no or unclear | [ ] Probably yes | [ **X** ] Definitely yes |
|---|---|---|---|
| *Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible* | *Vague hypothesis or hypothesized direction unclear* | *No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification* | *Prior protocol available and includes correct specification of direction of effect modification, e.g., based on a biologic rationale* |

Comment:

**2: Was the effect modification supported by prior evidence?**

| [ ] Inconsistent with prior evidence | [ ] Little or no support or unclear | [ ] Some support | [x ] Strong support |
|---|---|---|---|
| *Prior evidence suggested a different direction of effect modification* | *No prior evidence or consistent with weak or very indirect prior evidence (e.g., animal study at high risk of bias) or unclear* | *Consistent with more limited or indirect prior evidence (e.g., large observational study, non-significant effect modification in prior RCT, or different population)* | *Consistent with strong prior evidence directly applicable to the clinical scenario (e.g., significant effect modification in related RCT)* |

Comment:

**3: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?** (consider irrespective of number of effect modifiers) find strongest

| [x ] Chance a very likely explanation | [ ] Chance a likely explanation or unclear | [ ] Chance may not explain | [ ] Chance an unlikely explanation |
|---|---|---|---|
| *Interaction p-value >0.05* | *Interaction p-value ≤0.05 and >0.01, or no test of interaction reported and not computable* | *Interaction p-value ≤0.01 and >0.005* | *Interaction p-value ≤0.005* |

Comment:

**4: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?**

| [ ] Definitely no | [ ] Probably no or unclear | [ ] Probably yes | [ X] Definitely yes |
|---|---|---|---|
| *Explicitly exploratory analysis or large number of effect modifiers tested (e.g., greater than 10) and multiplicity not considered in analysis* | *No mention of number or 4-10 effect modifiers tested and number not considered in analysis* | *No protocol available but unequivocal statement of 3 or fewer effect modifiers tested* | *Protocol available and 3 or fewer effect modifiers tested or number considered in analysis* |

Comment:

**5: If the effect modifier is a continuous variable, were arbitrary cut points avoided?** [ X ] not applicable: not continuous

| [ ] Definitely no | [ ] Probably no or unclear | [ ] Probably yes | [ ] Definitely yes |
|---|---|---|---|
| *Analysis based on exploratory cut point (e.g., picking cut point associated with highest interaction p-value)* | *Analysis based on cut point(s) of unclear origin* | *Analysis based on pre-specified cut points, e.g., suggested by prior RCT* | *Analysis based on the full continuum, e.g., assuming a linear or logarithmic relationship* |

Comment:

**6 Optional: Are there any additional considerations that may increase or decrease credibility?** (manual section 2.6)

[ ] Yes, probably decrease [ ] Yes, probably increase

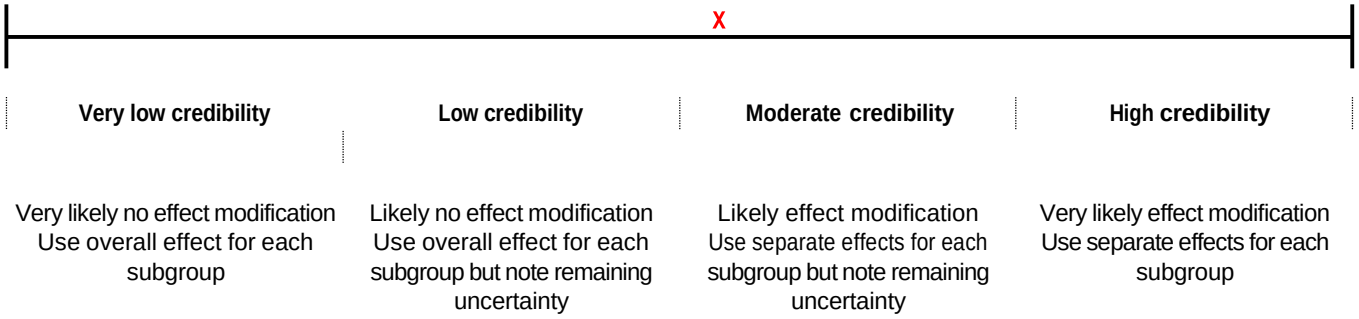
Comment:

**7: How would you rate the overall credibility of the proposed effect modification?**

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:

- All responses definitely or probably reduced credibility or unclear ➔ very low
- Two or more responses definitely reduced credibility ➔ maximum usually low even if all other responses satisfy credibility criteria
- One response definitely reduced credibility ➔ maximum usually moderate even if all other responses satisfy credibility criteria
- **Two responses probably reduced credibility ➔ maximum usually moderate even if all other responses satisfy credibility criteria**
- No response options definitely or probably reduced credibility ➔ high very likely

Place a mark on the continuous line (or type "x" in electronic version)




Comment:

The trial did not hypothesize any subgroup effects and no effect modification was found.

# GRADE Analysis

**Author(s):** Reis et. al
**Question:** Fluvoxamine plus budesonide compared to placebo for COVID-19
**Setting:** Outpatient, high risk
**Bibliography:**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | fluvoxamine plus budesonide | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Primary Outcome (follow-up: 28 days)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | not serious | | 14/743 (1.9%) | 30/740 (4.1%) | **RR 0.48** (0.25 to 0.86) | **21 fewer per 1,000** (from 30 fewer to 6 fewer) | - | CRITICAL |
| **Hospitalization or Death due to COVID-19** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | not serious | | 7/743 (0.9%) | 9/740 (1.2%) | **RR 0.77** (0.29 to 2.06) | **3 fewer per 1,000** (from 9 fewer to 13 more) | - | CRITICAL |
| **Death due to COVID-19 (follow-up: 28 days)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | not serious | | 1/743 (0.1%) | 0/740 (0.0%) | **RR 2.98** (0.12 to 73.23) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | - | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

# Bayesian Analysis Code

## 1.Bayesian analysis of dichotomous outcomes
### Function arguments:

1. **Data**: study data
2. **var**: specify the *column name* from **data** which contains variable to analyze
3. **interim_id_N/interim_id_r**: sample size and N events at each interim analysis
4. **Treatment**: specify the *column name* from **data** which contains the name of the study arms
5. **parameters**: specify parameters to be calculated
6. **code_location**: path where model text file is stored
7. **seed**: set random seed (numeric)
8. **outloc**: specify the directory location where outputs will be saved
9. **density**: Return density. Default FALSE.

```
  run_dichotomous= function(data, var, interim_id_n = NULL, interim_id_r = NULL, Treatment, parameters = c("p_int"
, "p_ctrl", "pval", "RRR", "RR"),code_location = codeloc,  outloc,   seed, density=FALSE){

  ################## #
  # 1. A few basic set-up configurations

  MODELFILE = paste0(code_location, "modelfile.txt")

  # Verify that data is a data.frame
  data = as.data.frame((data))

  if(plots){
    # Set-up the figures folder
    dir.create(file.path(outloc, "Figures"), showWarnings = FALSE)
    dir.create(file.path(outloc, "Figures/Convergence plots"), showWarnings = FALSE)
    figureloc = paste0(outloc, "/Figures/")
    convergefigloc = paste0(outloc, "/Figures/Convergence plots/")
  }
  Treatments = names(summary(as.factor(data[,Treatment])))
  data$intervention = rep(1, length(data[,Treatment]))
  placebo = Treatments[grepl( "placebo", tolower(Treatments), fixed = TRUE)]
  data$intervention[data[,Treatment] == placebo] = 0

  data$temp<-(data[[var]])
  passed=FALSE

  # 2 Data prep
  if(is.null(interim_id_n)){
    datause <- list (N = 1,
                     r_int = sum(data$temp[data$intervention == 1], na.rm=T),
                     r_ctrl = sum(data$temp[data$intervention == 0], na.rm = T),
                     n_int = sum(data$intervention),
                     n_ctrl = sum(data$intervention == 0))
  }else{
    interim_n = data[, names(data) == interim_id_n]
    interim_r = data[, names(data) == interim_id_r]
    interim_tags = names(summary(as.factor(interim_n)))
    N = length(interim_tags)
    r_int = r_ctrl = n_int = n_ctrl = rep(0, N)
    for(i in 1:N){
      r_int[i] = sum(data$temp[(data$intervention == 1) & (interim_r == interim_tags[i])])
      r_ctrl[i] = sum(data$temp[(data$intervention == 0) & (interim_r == interim_tags[i])])
      n_int[i] = sum(data$intervention[interim_n == interim_tags[i]])
      n_ctrl[i] = sum((data$intervention == 0) & (interim_n == interim_tags[i]))
    }
    datause <- list (N = N,
                     r_int = r_int,
                     r_ctrl = r_ctrl,
                     n_int = n_int,
                     n_ctrl = n_ctrl)
  }

  ################ #
```

```
  # 3 Run JAGS
  NBURNIN = 25000
  NITER= 100000
  NTHIN=2

  print('data prep complete')

  # RUN JAGS
  print ("begin jags")
  jags1 <- (jags.model(  file = MODELFILE, data = datause,  n.chains = 2, n.adapt = NBURNIN, inits = list(.RNG.name
="base::Super-Duper",.RNG.seed=seed))   )
  print("part 1 jags.model with 50,000 iterations complete")

  update(jags1,NBURNIN)
  print('part 2 update complete')

  monitorparms = parameters
  jags.out <- coda.samples(jags1, monitorparms, n.iter = NITER, thin = NTHIN)
  print("part 3 coda.samples collecting results/coda complete.")

  # DIC ..........................................................................
  DIC = dic.samples(jags1, NITER, type= "pD")
  print('part 4 dic.samples(jags1, NITER, type= "pD") complete')

  pD_ = round(sum(DIC$penalty,na.rm=TRUE),3)
  deviance_ = round(sum(DIC$deviance,na.rm=TRUE),3)
  dic_ = pD_ + deviance_
  results2 = data.frame(Dbar=deviance_, pD=pD_, DIC=dic_)

  tempR = summary(jags.out)

  ############### #
  # 4 Prep the outputs
  results = data.frame((tempR$statistics)[,c(1,2)],tempR$quantiles, tempR$start, tempR$end)

  ## Save convergence plots
  temp = jags.out
  cnames = colnames(temp[[1]])
  temp[[1]] = (temp[[1]])[,cnames == "RR"]
  temp[[2]] = (temp[[2]])[,cnames == "RR"]
  #png(paste(convergefigloc, "/Gelman plot - ", ,  ".png", sep=""))
  #gelman.plot(temp,autoburnin = FALSE)
  #dev.off()
  if(plots){
    png(paste(convergefigloc, "Density plot ", var,  ".png", sep=""))
    plot(temp)
    dev.off()
  }

  posterior <- as.array(jags.out)
  post <- as_data_frame(posterior)

  estimate=paste0(format(round(results$X50.[1], 2),nsmall=2), " (",
                  format(round(results$X2.5.[1],2),nsmall=2), ", ",
                  format(round(results$X97.5.[1], 2),nsmall=2), ")" )
  prob=format(round(results$Mean[5], 3),nsmall=3)

  if(density){
    return(list(estimate, prob, results2, post))
  }else{
    return(list(estimate,prob, results2))
  }
}
```

**Contents of modelfile.txt**

```
model{
        for(j in 1:N){ # N is the number of interim analyses
                r_int[j] ~ dbin(p_int, n_int[j])
                r_ctrl[j] ~ dbin(p_ctrl, n_ctrl[j])
        }
```

```
        p_int ~ dbeta(1, 1)
        p_ctrl ~ dbeta(1,1)
        # Output
        pval = step(p_ctrl - p_int)
        RRR = 1 - p_int/p_ctrl
        RR = p_int/p_ctrl
}
```

## 2. Bayesian analysis of time-to-event outcomes

**Function arguments:**

1. **data**: data
2. **event**: specify the *column name* from **data** which contains events (0 or 1)
3. **event_date**: specify the *column name* from **data** which contains event dates
4. **rand_date**: specify the *column name* from **data** which contains the date of randomization
5. **lastFU_date**: specify the *column name* from **data** which contains the date of last follow-up
6. **Treatment**: specify the *column name* from **data** which contains the name of the study arms
7. **outloc**: specify the directory location where outputs will be saved
8. **iteration**: specify the number of iterations.

```
tte_bayes <- function(data, event, event_date, rand_date, lastFU_date, Treatment, outloc, iteration=2000)
{
  dir.create(file.path(outloc, "Figures"), showWarnings = FALSE)
  dir.create(file.path(outloc, "Figures/Convergeplot"), showWarnings = FALSE)

  figureloc <- paste0(outloc, "Figures")
  convergefigloc <- paste0(outloc, "Figures/Convergeplot")

  # Data prep
  eval(parse(text=paste0("data$Status = data$", event_response)))
  eval(parse(text=paste0("data$event_date = data$", event_date)))
  eval(parse(text=paste0("data$studyend = data$", studyenddate)))
  eval(parse(text=paste0("data$studystart = data$",rand_date)))
  eval(parse(text=paste0("data$Treatment = data$",Treatment)))

  data$followup<-difftime(data$lastFU_date, data$RANDDAT, units=c("days"))
  data$enddat<-if_else(data$Status==1, data$Outcome_dat, data$lastFU_date)
  data$status<-if_else(data$Status==1, "Met outcome", "Did not meet outcome")
  data$followuptime<-as.numeric(difftime(data$enddat, data$RANDDAT, units=c("days")))
  data$Status[data$followuptime>28] = 0
  data$Time<-if_else(data$followuptime>=28, 28, data$followuptime)
  data$Time[data$Time == 0] = 1

  treatment_name <- names(table(data$Treatment))
  intervention <- treatment_name[treatment_name!="Placebo"]
  data$treat <- if_else(data$Treatment==intervention, 1, 0)

  # Run model
  res <- brm(time|cens(1-Status)~treat, data=data, family = brmsfamily("cox"), sample_prior = "no", save_pars = sav
e_pars(all=TRUE), seed=553, iter = iteration)
  res_mcmc <- as.mcmc(res)
  bayes_probability <- mean(c(sum((res_mcmc[[1]])[,2]<0)/length((res_mcmc[[1]])[,2]), sum((res_mcmc[[2]])[,2]<0)/le
ngth((res_mcmc[[2]])[,2]), sum((res_mcmc[[3]])[,2]<0)/length((res_mcmc[[3]])[,2]), sum((res_mcmc[[4]])[,2]<0)/lengt
h((res_mcmc[[4]])[,2])))

  s_res <- summary(res)
  s_res_HR <- (s_res$fixed$Estimate)[2]
  s_res_lc <- (s_res$fixed$`l-95% CI`)[2]
  s_res_uc <- (s_res$fixed$`u-95% CI`)[2]
  bayesian_Hr <- paste(formatC(round(exp(s_res_HR),2), format='f', digit=2), " (", formatC(round(exp(s_res_lc),2),
format='f', digit=2), ",",
                       formatC(round(exp(s_res_uc),2), format='f', digit=2), " )")

  # Return all of the results
  return(list(bayesian_Hr = bayesian_Hr, bayes_probability = bayes_probability, s_res_HR = s_res_HR, s_res_lc =s_re
s_lc, s_res_uc  = s_res_uc,  model=res))

}
```