Model

Here is the model that I am using (as I mentioned, the planned COMPILE analysis will be adjusting for additional baseline characteristics):

$$
\text{logit} \left(P\left(Y_{kis} \ge y\right)\right) = \tau_{yk} + \beta_s + I_{ki} \left(\gamma_{kcs} + \delta_{kc} \right), \; \; y \in \{1, \dots L-1\} \text{ with } L \text{ response levels}
$$

And here are the assumptions for the **prior distributions**:

$$
\begin{aligned}
\tau_{yk} &\sim t_{\text{student}} \left(\text{df=} 3, \mu=0, \sigma = 5 \right), \; \; \text{monotone within } \text{site } k \\
\beta_s &\sim \text{Normal} \left(\mu=0, \sigma = 5 \right), \qquad \; \;s \in \{1,\dots, S \} \text{ for symptom duration strata}, \beta_1 = 0 \\
\gamma_{kcs} &\sim \text{Normal}\left(\gamma_{cs}, 1 \right), \qquad \qquad \;\;\;\;\;\;c \in \{0, 1, 2\} \text{ for control conditions }, \gamma_{kc1} = 0 \text{ for all } k \\
\gamma_{cs} &\sim \text{Normal}\left(\Gamma_s, 0.25 \right), \qquad \qquad \; \; \gamma_{c1} = 0 \text{ for all } c \\
\Gamma_s &\sim t_{\text{student}} \left(3, 0, 1 \right), \qquad \qquad \qquad \Gamma_{1} = 0 \\
\delta_{kc} &\sim \text{Normal}\left(\delta_c, \eta \right)\\
\delta_c &\sim \text{Normal}\left(-\Delta, 0.5 \right) \\
\eta &\sim t_{\text{student}}\left(3, 0, 0.25 \right) \\
-\Delta &\sim t_{\text{student}} \left(3, 0, 2.5 \right)
\end{aligned}
$$

There are K RCTs. The outcome for the ith patient from the kth trial on the L-point scale at day 14 is $Y_{ki}=y$, $y=0,\dots,L-1$ (although the COMPILE study will have $L = 11$ levels, I will be using $L=5$ to speed up estimation times a bit). I_{ki} indicates the treatment assignment for subject i in the kth RCT, $I_{ki} = 0$ if patient i received CP and $I_{ki} = 1$ if the patient was in *any* control arm. There are three control conditions C: standard of care, $C=0$; non-convalescent plasma, $C=1$; saline/LR with coloring, $C=2$; each RCT k is attached to a specific control condition. There are also $S=3$ symptom duration strata: short duration, $s=0$; moderate duration, $s=1$; and long duration, $s=2$. (COMPILE will use five symptom duration strata – again I am simplifying.)

τ_{yk} corresponds to the kth RCT's intercept associated with level y; the τ's represent the cumulative log odds for patients with in symptom duration group $s=0$ and receiving CP treatment. Within a particular RCT, all τ_{yk}'s, satisfy the monotonicity requirements for the intercepts of the proportional odds model. β_s), $s \in {2, 3}$, is the main effect of symptom duration ($\beta_1 = 0$, where $s=1$ is the reference category). γ_{kcs} is the moderating effect of strata s in RCT k; $\gamma_{kc1} = 0$, since $s=1$ is the reference category. δ_{kc} is the RCT-specific control effect, where RCT k is using control condition c.

Each γ_{kcs} is normally distributed around a control type/symptom duration mean γ_{cs}. And each γ_{cs} is centered around a pooled mean Γ_s. The δ_{kc}'s are assumed to be normally distributed around a control-type specific effect δ_c, with variance η that will be estimated; the δ_c's are normally distributed

around $-\Delta$ (we take $-\Delta$ as the mean of the distribution to which δ_c belongs so that $\exp(\Delta)$ will correspond to the cumulative log-odds ratio for CP relative to control, rather than for control relative to CP.). (For an earlier take on these types of models, see here.)

Go or No-go

The focus of a Bayesian analysis is the estimated posterior probability distribution of a parameter or parameters of interest, for example the log-odds ratio from a cumulative proportional odds model. At the end of an analysis, we have credibility intervals, means, medians, quantiles – all concepts associated a probability distribution.

A "Go/No-go" decision process like a hypothesis test is not necessarily baked into the Bayesian method. At some point, however, even if we are using a Bayesian model to inform our thinking, we might want to or have to make a decision. In this case, we might want recommend (or not) the use of CP for patients hospitalized with COVID-19. Rather than use a hypothesis test to reject or fail to reject a null hypothesis of no effect, we can use the posterior probability to create a decision rule. In fact, this is what we have done.

In the proposed design of COMPILE, the CP therapy will be deemed a success if both of these criteria are met:

$$ P \left(\exp\left(-\Delta\right) < 1 \right) = P \left(OR < 1 \right) > 95\%$$

$$P \left(OR < 0.80 \right) > 50\%$$

The first statement ensures that the posterior probability of a good outcome is very high. If we want to be conservative, we can obviously increase the percentage threshold above 95%. The second statement says that the there is decent probability that the treatment effect is clinically meaningful. Again, we can modify the target OR and/or the percentage threshold based on our desired outcome.

Goals of the simulation

Since there are no Type I or Type II errors in the Bayesian framework, the concept of power (which is the probability of rejecting the null hypothesis when it is indeed not true) does not logically flow from a Bayesian analysis. However, if we substitute our decision rules for a hypothesis test, we can estimate the probability (call it Bayesian power, though I imagine some Bayesians would object) that we will make a "Go" decision given a specified treatment effect. (To be truly Bayesian, we should impose some uncertainty on what that specific treatment effect is, and calculate a probability distribution of Bayesian power. But I am keeping things simpler here.)

Hopefully, I have provided sufficient motivation for the need to simulate data and fit multiple Bayesian models. So, let's do that now.

The simulation

I am creating four functions that will form the backbone of this simulation process: `s_define`, `s_generate`, `s_estimate`, and `s_extract`. Repeated calls to each of these functions will provide us with the data that we need to get an estimate of Bayesian power under our (static) data generating assumptions.

Data definitions

The first definition table, `defC1`, sets up the RCTs. Each RCT has specific symptom duration interaction effect a and control treatment effect b. To introduce a little variability in sample

size, 1/3 of the studies will be larger (150 patients), and 2/3 will be smaller (75 patients).

The remaining tables, `defC2`, `defS`, and `defC3`, define patient-level data. `defC2` adds the control group indicator (0 = CP, 1 = standard care, 2 = non-convalescent plasma, 3 = saline) and the symptom duration stratum. `defS` defines the interaction effect conditional on the stratum. `defC3` defines the ordinal categorical outcome.

```
s_define <- function() {

  defC1 <- defDataAdd(varname = "a",formula = 0, variance = .005, dist
= "normal")
  defC1 <- defDataAdd(defC1,varname = "b",formula = 0, variance= .01,
dist = "normal")
  defC1 <- defDataAdd(defC1,varname = "size",formula = "75+75*large",
dist = "nonrandom")

  defC2 <- defDataAdd(varname="C_rv", formula="C * control", dist =
"nonrandom")
  defC2 <- defDataAdd(defC2, varname = "ss", formula = "1/3;1/3;1/3",
                      dist = "categorical")

  defS <- defCondition(
    condition = "ss==1",
    formula = 0,
    dist = "nonrandom")
  defS <- defCondition(defS,
    condition = "ss==2",
    formula = "(0.09 + a) * (C_rv==1) + (0.10 + a) * (C_rv==2) + (0.11
+ a) * (C_rv==3)",
    dist = "nonrandom")
  defS <- defCondition(defS,
    condition = "ss==3",
    formula = "(0.19 + a) * (C_rv==1) + (0.20 + a) * (C_rv==2) + (0.21
+ a) * (C_rv==3)",
    dist = "nonrandom")

  defC3 <- defDataAdd(
    varname = "z",
    formula = "0.1*(ss-1)+z_ss+(0.6+b)*(C_rv==1)+(0.7+b)*
(C_rv==2)+(0.8+b)*(C_rv==3)",
    dist = "nonrandom")

  list(defC1 = defC1, defC2 = defC2, defS = defS, defC3 = defC3)

}
```

Data generation

The data generation process draws on the definition tables to create an instance of an RCT data base. This process includes a function `genBaseProbs` that I described previously.

```
s_generate <- function(deflist, nsites) {
```

```
  genBaseProbs <- function(n, base, similarity, digits = 2) {

    n_levels <- length(base)

    x <- gtools::rdirichlet(n, similarity * base)

    x <- round(floor(x*1e8)/1e8, digits)
    xpart <- x[, 1:(n_levels-1)]
    partsum <- apply(xpart, 1, sum)
    x[, n_levels] <- 1 - partsum

    return(x)
  }

  basestudy <- genBaseProbs(n = nsites,
                            base =  c(.10, .35, .25, .20, .10),
                            similarity = 100)

  dstudy <- genData(nsites, id = "study")
  dstudy <- trtAssign(dstudy, nTrt = 3, grpName = "C")
  dstudy <- trtAssign(dstudy, nTrt = 2, strata = "C", grpName =
"large", ratio = c(2,1))
  dstudy <- addColumns(deflist[['defC1']], dstudy)

  dind <- genCluster(dstudy, "study", numIndsVar = "size", "id")
  dind <- trtAssign(dind, strata="study", grpName = "control")
  dind <- addColumns(deflist[['defC2']], dind)
  dind <- addCondition(deflist[["defS"]], dind, newvar = "z_ss")
  dind <- addColumns(deflist[['defC3']], dind)

  dl <- lapply(1:nsites, function(i) {
    b <- basestudy[i,]
    dx <- dind[study == i]
    genOrdCat(dx, adjVar = "z", b, catVar = "ordY")
  })

  rbindlist(dl)[]
}
```

Model estimation

The estimation involves creating a data set for `Stan` and sampling from the Bayesian model. The `Stan` model is included in the addendum.

```
s_estimate <- function(dd, s_model) {

  N <- nrow(dd)                                ## number of observations
  L <- dd[, length(unique(ordY))]              ## number of levels of
outcome
  K <- dd[, length(unique(study))]             ## number of studies
  y <- as.numeric(dd$ordY)                     ## individual outcome
```

```
  kk <- dd$study                                  ## study for individual
  ctrl <- dd$control                              ## treatment arm for
individual
  cc <- dd[, .N, keyby = .(study, C)]$C           ## specific control arm
for study
  ss <- dd$ss
  x <- model.matrix(ordY ~ factor(ss), data = dd)[, -1]

  studydata <- list(N=N, L= L, K=K, y=y, kk=kk, ctrl=ctrl, cc=cc,
ss=ss, x=x)

  fit <-  sampling(s_model, data=studydata, iter = 4000, warmup = 500,
                   cores = 4L, chains = 4, control = list(adapt_delta =
0.8))
  fit
}
```

Estimate extraction

The last step is the extraction of summary data from the posterior probability distributions. I am collecting quantiles of the key parameters, including Δ and $OR = \exp(-\Delta)$. For the Bayesian power analysis, I am estimating the probability of falling below the two thresholds for each data set. And finally, I want to get a sense of the quality of each estimation process by recovering the number of divergent chains that resulted from the MCMC algorithm (more on that here).

```
s_extract <- function(iternum, mcmc_res) {

  posterior <- as.array(mcmc_res)

  x <- summary(
    mcmc_res,
    pars = c("Delta", "delta", "Gamma", "beta", "alpha", "OR"),
    probs = c(0.025, 0.5, 0.975)
  )

  dpars <- data.table(iternum = iternum, par = rownames(x$summary),
x$summary)

  p.eff <- mean(rstan::extract(mcmc_res, pars = "OR")[[1]] < 1)
  p.clinic <- mean(rstan::extract(mcmc_res, pars = "OR")[[1]] < 0.8)
  dp <- data.table(iternum = iternum, p.eff = p.eff, p.clinic =
p.clinic)

  sparams <- get_sampler_params(mcmc_res, inc_warmup=FALSE)
  n_divergent <- sum(sapply(sparams, function(x) sum(x[,
'divergent__'])))
  ddiv <- data.table(iternum, n_divergent)

  list(ddiv = ddiv, dpars = dpars, dp = dp)
}
```

Replication

Now we want to put all these pieces together and repeatedly execute those four functions and save the results from each. I've described using `lapply` to calculate power in a much more traditional setting. We're going to take the same approach here, except on steroids, replacing `lapply` not with `mclapply`, the parallel version, but with `Slurm_lapply`, which is a function in the `slurmR` package.

Slurm (Simple Linux Utility for Resource Management) is a HPC cluster job scheduler. slurmR is a wrapper that mimics many of the R `parallel` package functions, but in a Slurm environment. The strategy here is to define a meta-function (`iteration`) that itself calls the four functions already described, and then call that function repeatedly. `Slurm_lapply` does that, and rather than allocating the iterations to different *cores* on a computer like `mclapply` does, it allocates the iterations to different *nodes* on the HPC, using what is technically called a *job array*. Each node is essentially its own computer. In addition to that, each node has multiple cores, so we can run the different MCMC chains in parallel within a node; we have parallel processes within a parallel process. I have access to 100 nodes at any one time, though I find I don't get much performance improvement if I go over 90, so that is what I do here. Within each node, I am using 4 cores. I am running 1,980 iterations, so that is 22 iterations per node. As I mentioned earlier, all of this runs in about an hour and a half.

The following code includes the "meta-function" `iteration`, the compilation of the `Stan` model (which only needs to be done once, thankfully), the `Slurm_lapply` call, and the **Slurm** batch code that I need to execute to get the whole process started on the HPC, which is called Big Purple here at NYU. (All of the R code goes into a single `.R` file, the batch code is in a `.slurm` file, and the Stan code is in its own `.stan` file.)

```
iteration <- function(iternum, s_model, nsites) {

    s_defs <- s_define()
    s_dd <- s_generate(s_defs, nsites = nsites)
    s_est <- s_estimate(s_dd, s_model)
    s_res <- s_extract(iternum, s_est)

    return(s_res)

}
library(simstudy)
library(rstan)
library(data.table)
library(slurmR)

rt <- stanc("/.../r/freq_bayes.stan")
sm <- stan_model(stanc_ret = rt, verbose=FALSE)

job <- Slurm_lapply(
  X = 1:1980,
  iteration,
  s_model = sm,
  nsites = 9,
  njobs = 90,
  mc.cores = 4,
```

```
  tmp_path = "/.../scratch",
  overwrite = TRUE,
  job_name = "i_fb",
  sbatch_opt = list(time = "03:00:00", partition = "cpu_short"),
  export = c("s_define", "s_generate", "s_estimate", "s_extract"),
  plan = "wait")

job
res <- Slurm_collect(job)

diverge <- rbindlist(lapply(res, function(l) l[["ddiv"]]))
ests <- rbindlist(lapply(res, function(l) l[["dpars"]]))
probs <- rbindlist(lapply(res, function(l) l[["dp"]]))

save(diverge, ests, probs, file = "/.../data/freq_bayes.rda")
#!/bin/bash
#SBATCH --job-name=fb_parent
#SBATCH --mail-type=END,FAIL                          # send email if the
job end or fail
#SBATCH --mail-user=keith.goldfeld@nyulangone.org
#SBATCH --partition=cpu_short
#SBATCH --time=3:00:00                                # Time limit
hrs:min:sec
#SBATCH --output=fb.out                               # Standard output and
error log

module load r/3.6.3
cd /.../r

Rscript --vanilla fb.R
```

Results

Each of the three extracted data tables are combined across simulations and the results are saved to an `.rda` file, which can be loaded locally in R and summarized. In this case, we are particularly interested in the Bayesian power estimate, which is the proportion of data sets that would results in a “go” decision (a recommendation to strongly consider using the intervention).

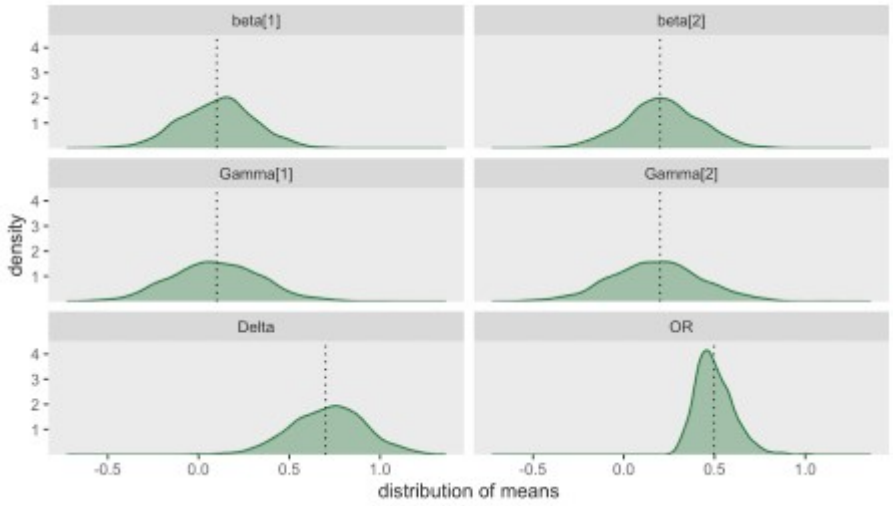
However, before we consider that, we should first get a rough idea about how many replications had divergence issues, which we extracted into the `diverge` data table. For each replication, we used four chains of length 3,500 each (after the 500 warm-up samples), accounting for a total of 14,000 chains. Here are the proportion of replications with at least one divergent chain:

```
load("DataBayesCOMPILE/freq_bayes.rda")
diverge[, mean(n_divergent > 0)]
## [1] 0.102
```

While 10% of replications with at least 1 divergent chain might seem a little high, we can get a little more comfort from the fact that it appears that almost all replications had fewer than 35 (0.25%) divergent chains:

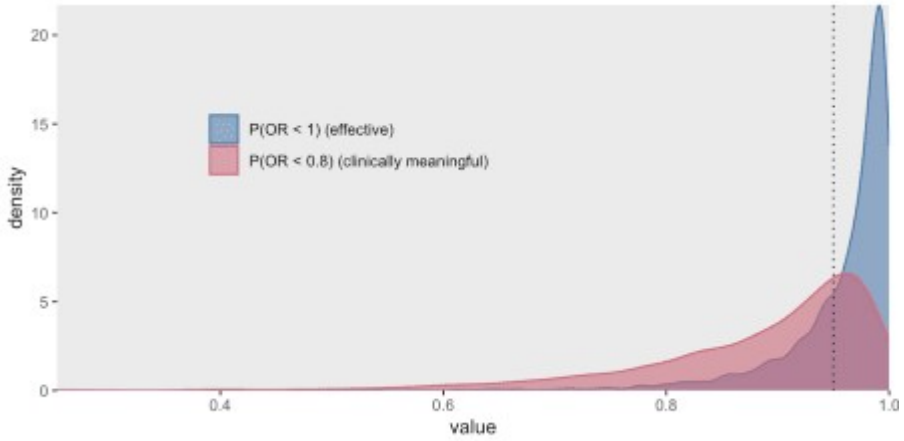
```
diverge[, mean(n_divergent < 35)]
## [1] 0.985
```

To get a general sense of how well our model is working, we can plot the distribution of posterior medians. In particular, this will allow us to assess how well the model is recovering the values used in the data generating process. In this case, I am excluding the 29 replications with 35 or more divergent chains:



Finally, we are ready to report the estimated Bayesian power (again, using the replications with limited number of divergent chains) and show the distribution of probabilities.

```
probs_d <- merge(probs, diverge, by = "iternum")[n_divergent < 35]
probs_d[, mean(p.eff > 0.95 & p.clinic > 0.50)]
## [1] 0.726
```



So, given an actual effect \(OR=\exp(-0.70) = 0.50\), we would conclude with a decision to go ahead with the therapy with 73% probability. However, a single estimate of power based on one effect size is a bit incomplete; it would be preferable to assess power under numerous scenarios of effect sizes and perhaps prior distribution assumptions to get a more complete picture. And if you have access to a HPC, this may actually be something you can do in a realistic period of time.

Addendum

The `stan` model that implements the model described at the outset actually looks a little different than that model in two key ways. First, there is a parameter \(\alpha\) that appears in the outcome model, which represents an overall intercept across all studies. Ideally, we wouldn't need to include this parameter since we want to fix it at zero, but the model behaves very poorly without it. We do include it, but with a highly restrictive prior that will constrain it to be very close

to zero. The second difference is that standard normal priors appear in the model - this is to alleviate issues related to divergent chains, which I described in a previous post.

```
data {
    int N;                // number of observations
    int L;                // number of WHO categories
    int K;                // number of studies
    int y[N];     // vector of categorical outcomes
    int kk[N];    // site for individual
    int ctrl[N];  // treatment or control
    int cc[K];    // specific control for site
    int ss[N];    // strata
    row_vector[2] x[N];            // strata indicators  N x 2 matrix
  }

parameters {

  real Delta;               // overall control effect
  vector[2] Gamma;          // overall strata effect
  real alpha;               // overall intercept for treatment
  ordered[L-1] tau[K];      // cut-points for cumulative odds model (K
X [L-1] matrix)

  real  eta_0;     // sd of delta_k (around delta)

  // non-central parameterization

  vector[K] z_ran_rx;      // site-specific effect
  vector[2] z_phi[K];      // K X 2 matrix
  vector[3] z_delta;
  vector[2] z_beta;
  vector[2] z_gamma[3];    // 3 X 2 matrix
}

transformed parameters{

  vector[3] delta;          // control-specific effect
  vector[K] delta_k;        // site specific treatment effect
  vector[2] gamma[3];       // control-specific duration strata effect
(3 X 2 matrix)
  vector[2] beta;           // covariate estimates of ss
  vector[2] gamma_k[K];     // site-specific duration strata effect (K
X 2 matrix)
  vector[N] yhat;


  delta = 0.5 * z_delta + Delta; // was 0.1
  beta = 5 * z_beta;

  for (c in 1:3)
    gamma[c] = 0.25 * z_gamma[c] + Gamma;
```

```
  for (k in 1:K){
    delta_k[k] = eta_0 * z_ran_rx[k] + delta[cc[k]];
  }

  for (k in 1:K)
    gamma_k[k] = 1 * z_phi[k] + gamma[cc[k]];

  for (i in 1:N)
    yhat[i] = alpha + x[i] * beta + ctrl[i] * (delta_k[kk[i]] +
x[i]*gamma_k[kk[i]]);
}

model {

  // priors

  z_ran_rx ~ std_normal();
  z_delta ~ std_normal();
  z_beta ~ std_normal();

  alpha ~ normal(0, 0.25);
  eta_0 ~ student_t(3, 0, 0.25);

  Delta ~ student_t(3, 0, 2.5);
  Gamma ~ student_t(3, 0, 1);

  for (c in 1:3)
      z_gamma[c] ~ std_normal();

  for (k in 1:K)
      z_phi[k] ~ std_normal();

  for (k in 1:K)
      tau[k] ~ student_t(3, 0, 5);

  // outcome model

  for (i in 1:N)
    y[i] ~ ordered_logistic(yhat[i], tau[kk[i]]);
}

generated quantities {

  real OR;
  OR = exp(-Delta);

}
```