

Appendix 3

R code

```
library(simstudy)
library(cmdstanr)
library(data.table)
library(slurmR)
library(posterior)

mco <- cmdstan_model("./primary_co.stan")

#--- generating the study-specific baseline probabilities for each outcome level---#
genBaseProbs <- function(n, base, similarity, digits = 2) {
  n_levels <- length(base)
  x <- gtools::rdirichlet(n, similarity * base)

  #--- ensure that each vector of probabilities sums exactly to 1

  x <- round(floor(x * 1e+08)/1e+08, digits) # round the generated probabilities
  xpart <- x[, 1:(n_levels - 1)] # delete the base prob of the final level
  partsum <- apply(xpart, 1, sum) # add the values of levels 1 to K-1
  x[, n_levels] <- 1 - partsum # the base prob of the level K = 1 - sum(1:[K-1])

  return(x)
}

nsites <- 9 # assume 9 RCTs in total

basestudy <- genBaseProbs(n = nsites, base = c(0.1, 0.107,
  0.095, 0.085, 0.09, 0.09, 0.108, 0.1, 0.09, 0.075, 0.06),
  similarity = 100)

# More detailed information:
# https://www.rdatagen.net/post/generating-probabilities-for-ordinal-categorical-data/

#--- data definition code ---#

defC <- defDataAdd(varname = "b", formula = 0, variance = 0.01,
  dist = "normal") # RCT specific intercept
defC <- defDataAdd(defC, varname = "size", formula = "75+75*large",
  dist = "nonrandom") # sample size; large=1: 150 patients, large=0: 75 patients
defC2 <- defDataAdd(varname = "C_rv", formula = "C * control",
  dist = "nonrandom") # 0=CP, 1= standard of care, 2=non-CP, 3=saline
defC2 <- defDataAdd(defC2, varname = "sex", formula = 0.5,
  dist = "binary")
defC2 <- defDataAdd(defC2, varname = "who_enroll", formula = "1/3;1/3;1/3",
  dist = "categorical")
defC2 <- defDataAdd(defC2, varname = "age", formula = "0.25;0.25;0.50",
  dist = "categorical")
```

```

defC2 <- defDataAdd(defC2, varname = "ss", formula = "0.2;0.2;0.2;0.2;0.2",
  dist = "categorical")
defC2 <- defDataAdd(defC2, varname = "z", formula = "0.05*(ss-1) + 0.1*sex +
  0.075*(age-1) + 0.06*(who_enroll-1) +
  (0.3 + b ) * (C_rv==1) +
  (0.4 + b ) * (C_rv==2) + (0.5 + b ) * (C_rv==3)",
  dist = "nonrandom")

```

```

iter <- function(iternum, defC, defC2, basestudy, nsites,
  mco) {

  set_cmdstan_path(path = "/gpfs/share/apps/cmdstan/2.25.0")

  #--- data generation ---#

  dstudy <- genData(nsites, id = "study") # 9 RCTs
  dstudy <- trtAssign(dstudy, nTrt = 3, grpName = "C") # allocate 3 control conditions
  dstudy <- trtAssign(dstudy, nTrt = 2, strata = "C",
    grpName = "large", ratio = c(2, 1))
  dstudy <- addColumns(defC, dstudy)

  dind <- genCluster(dstudy, "study", numIndsVar = "size",
    "id")
  dind <- trtAssign(dind, strata = "study", grpName = "control")
  dind <- addColumns(defC2, dind)

  setkey(dind, "id")

  dl <- lapply(1:nsites, function(i) {
    b <- basestudy[i, ]
    dx <- dind[study == i]
    dx <- genOrdCat(dx, adjVar = "z", b, catVar = "ordY")
    dx[, `:=`(ordY, factor(ordY, levels = c(1:11))))]
    dx[]
  })

  dind <- rbindlist(dl)

  #--- model estimation ---#

  N = nrow(dind) # number of observations
  L <- dind[, length(unique(ordY))] # number of levels of outcome
  K <- dind[, length(unique(study))] # number of RCTs
  y <- as.numeric(dind$ordY) # individual outcome
  kk <- dind$study # RCT for each individual
  ctrl <- dind$control # treatment arm for individual
  cc <- dind[, .N, keyby = .(study, C)]$C # specific control arm for RCT
  x <- model.matrix(ordY ~ factor(who_enroll) + factor(age) +
    factor(sex) + factor(ss), data = dind)[, -1]
  D <- ncol(x)
  prior_div <- 8
  prior_Delta_sd <- 0.354
  eta <- 0.1

```

```

prior_eta_0 <- 0.25
prior_beta_sd <- 2.5

studydata <- list(N = N, L = L, K = K, y = y, ctrl = ctrl,
  cc = cc, kk = kk, prior_div = prior_div, prior_Delta_sd = prior_Delta_sd,
  eta = eta, prior_eta_0 = prior_eta_0, x = x, D = D,
  prior_beta_sd = prior_beta_sd)

fit_co <- mco$sample(step_size = 0.1, data = studydata,
  chains = 4L, parallel_chains = 4L, refresh = 500,
  iter_warmup = 500, iter_sampling = 2500, adapt_delta = 0.8)

#--- estimate extraction ---#

diagnostics_df <- as_draws_df(fit_co$sampler_diagnostics())
div_num_co <- sum(diagnostics_df[, "divergent__"])

res_co <- data.table(fit_co$summary(variables = "negDelta"))[,
  .(median)]
res_co$div_co <- div_num_co
data.table(iternum, res_co)
}

```

```

#--- Replication ---#

job <- Slurm_lapply(1:2520, iter, defC = defC, defC2 = defC2,
  basestudy = basestudy, nsites = nsites, mco = mco, njobs = 90,
  mc.cores = 4, tmp_path = "/gpfs/scratch/...", job_name = "sim_1",
  sbatch_opt = list(time = "24:00:00"), plan = "wait",
  overwrite = TRUE)

site_plasma_all <- Slurm_collect(job)
site_plasma <- rbindlist(site_plasma)

date_stamp <- gsub("-", "", Sys.Date())
dir.create(file.path("/gpfs/home/.../r/", date_stamp), showWarnings = FALSE)
save(site_plasma, file = paste0("/gpfs/home/.../r/", date_stamp,
  "/model_co.rda"))

```

Stan code

```
data {
  int<lower=0> N;           // number of observations
  int<lower=2> L;           // number of WHO categories
  int<lower=1> K;           // number of RCTs
  int<lower=1,upper=L> y[N]; // vector of categorical outcomes
  int<lower=1,upper=K> kk[N]; // RCT for individual
  int<lower=0,upper=1> ctrl[N]; // treatment or control
  int<lower=1,upper=3> cc[K]; // specific control for RCT
  int<lower=1> D;           // number of covariates
  row_vector[D] x[N];      // strata indicators  N x D matrix

  real<lower=0> prior_div;  // prior sd of tau
  real<lower=0> prior_Delta_sd; // prior sd of overall control effect
  real<lower=0> eta;        // prior sd of delta
  real<lower=0> prior_beta_sd; // prior sd of beta
  real<lower=0> prior_eta_0; //prior sd of eta_0 (the sd of delta_k)
}

parameters {

  real alpha;              // overall intercept for treatment
  ordered[L-1] tau[K];     // cut-points for cumulative odds model (K X [L-1] matrix)
  real<lower=0> eta_0;      // sd of delta_k (around delta)

  // non-central parameterization

  vector[K] z_ran_rx;
  vector[3] z_delta;
  vector[D] z_beta;
  real z_Delta;
}

transformed parameters{

  vector[3] delta;          // control-specific effect
  vector[K] delta_k;        // RCT-specific treatment effect
  vector[D] beta;           // covariate estimates
  real Delta;               // overall control effect
  vector[N] yhat;

  Delta = prior_Delta_sd * z_Delta;
  delta = eta * z_delta + Delta;
  beta = prior_beta_sd * z_beta;

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

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

```

model {

  // priors
  alpha ~ normal(0,0.1);
  z_ran_rx ~ std_normal();
  z_delta ~ std_normal();
  z_beta ~ std_normal();
  z_Delta ~ std_normal();

  eta_0 ~ student_t(3,0,prior_eta_0);

  for (k in 1:K)
    for (l in 1:(L-1))
      tau[k, l] ~ student_t(3, 0, prior_div);

  // outcome model

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

generated quantities {

  real OR;          // overall CCP effect (odds ratio)
  real negDelta;    // overall CCP effect on log scale

  OR = exp(-Delta);
  negDelta=-1*Delta;

}

```