Supplementary document for “Incorporating historical control information in ANCOVA models using the meta-analytic-predictive approach”

Hongchao Qi*1, 2, Dimitris Rizopoulos1, 2, and Joost van Rosmalen1, 2

1Department of Biostatistics, Erasmus University Medical Center
2Department of Epidemiology, Erasmus University Medical Center

In this supplementary document, additional results of the simulation study are presented in Section 1. Section 2 provides results of the sensitivity analysis for the motivating example, and Section 3 presents JAGS scripts for the motivating data analysis.

1 Additional results of the simulation study

In this section, the additional results of the simulation, including prior ESS, bias, standard deviation, and root mean squared error are presented in Table S1 to Table S4.

*Correspondence: Hongchao Qi, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. Email: h.qi@erasmusmc.nl. Data used in the study were obtained from the University of California, San Diego Alzheimer’s Disease Cooperative Study, https://www.adcs.org/.
Table S1: The prior ESS of the intercept and the baseline effect for the MAP approaches in scenarios with treatment effect

| Parameter   | J | Method   | J = 3 | J = 5 |
|-------------|---|----------|-------|-------|
|             |   |          | No    | Small | Moderate | Substantial | Large |
| Intercept   | 3 | MMAP+COR | 14 (7, 22) | 11 (4, 20) | 8 (3, 17) | 5 (2, 16) | 5 (2, 19) |
|             |   | MMAP+IND | 16 (7, 25) | 13 (4, 22) | 8 (2, 19) | 5 (2, 16) | 5 (2, 17) |
|             |   | UMAP+COM | 25 (11, 42) | 20 (7, 38) | 14 (5, 34) | 9 (4, 32) | 8 (4, 25) |
|             |   | UMAP+SEP | 10 (5, 15) | 9 (3, 15) | 6 (2, 15) | 5 (2, 15) | 4 (2, 16) |
|Baseline effect | 3 | MMAP+COR | 15 (7, 22) | 12 (5, 20) | 8 (3, 18) | 6 (2, 18) | 5 (2, 17) |
|             |   | MMAP+IND | 16 (8, 25) | 13 (4, 23) | 9 (3, 19) | 6 (2, 18) | 5 (2, 16) |
|             | 5 | MMAP+COR | 61 (24, 102) | 36 (9, 82) | 14 (4, 45) | 6 (3, 19) | 4 (2, 11) |
|             |   | MMAP+IND | 91 (37, 147) | 53 (9, 121) | 19 (4, 62) | 6 (2, 26) | 4 (2, 10) |
|             |   | UMAP+COM | 120 (46, 186) | 74 (22, 159) | 35 (11, 117) | 16 (7, 47) | 11 (6, 28) |
|             |   | UMAP+SEP | 32 (11, 55) | 22 (6, 50) | 11 (3, 38) | 5 (2, 18) | 4 (2, 10) |
|Baseline effect | 5 | MMAP+COR | 61 (23, 104) | 37 (9, 82) | 16 (5, 50) | 7 (3, 26) | 5 (2, 12) |
|             |   | MMAP+IND | 91 (41, 145) | 55 (9, 119) | 22 (4, 76) | 7 (2, 30) | 4 (2, 12) |
Table S2: The bias of the treatment effect estimate for different methods in the simulation

| J | Trt | Method        | Between-study heterogeneity |
|---|-----|---------------|-----------------------------|
|   |     |               | No  | Small | Moderate | Substantial | Large    |
| 3 | No  | No borrowing  | 0.015 | −0.005 | −0.012 | 0.035 | 0.010 |
|   |     | MMAP+COR      | 0.000 | −0.009 | −0.007 | 0.033 | 0.008 |
|   |     | MMAP+IND      | 0.003 | −0.011 | −0.003 | 0.031 | 0.006 |
|   |     | UMAP+COM      | −0.009 | −0.007 | −0.009 | 0.034 | 0.019 |
|   |     | UMAP+SEP      | 0.012 | −0.011 | −0.006 | 0.034 | 0.007 |
|   |     | Pooling       | −0.041 | −0.014 | 0.015 | −0.014 | 0.136 |
|   | Yes | No borrowing  | 0.074 | −0.001 | −0.036 | −0.065 | −0.001 |
|   |     | MMAP+COR      | 0.067 | 0.002 | −0.035 | −0.058 | 0.002 |
|   |     | MMAP+IND      | 0.070 | 0.004 | −0.036 | −0.056 | −0.001 |
|   |     | UMAP+COM      | 0.065 | 0.004 | −0.032 | −0.055 | 0.015 |
|   |     | UMAP+SEP      | 0.076 | 0.005 | −0.035 | −0.060 | −0.002 |
|   |     | Pooling       | 0.044 | −0.001 | −0.059 | −0.053 | −0.137 |
| 5 | No  | No borrowing  | −0.072 | −0.021 | 0.015 | −0.051 | 0.031 |
|   |     | MMAP+COR      | −0.054 | −0.012 | 0.007 | −0.050 | 0.029 |
|   |     | MMAP+IND      | −0.056 | −0.010 | 0.009 | −0.051 | 0.029 |
|   |     | UMAP+COM      | −0.049 | −0.008 | 0.012 | −0.044 | 0.025 |
|   |     | UMAP+SEP      | −0.071 | −0.019 | 0.012 | −0.050 | 0.030 |
|   |     | Pooling       | −0.037 | −0.014 | 0.007 | −0.058 | 0.012 |
|   | Yes | No borrowing  | −0.035 | 0.025 | −0.058 | 0.017 | −0.003 |
|   |     | MMAP+COR      | −0.056 | 0.014 | −0.061 | 0.017 | 0.003 |
|   |     | MMAP+IND      | −0.057 | 0.007 | −0.063 | 0.013 | 0.001 |
|   |     | UMAP+COM      | −0.062 | 0.014 | −0.057 | 0.014 | 0.005 |
|   |     | UMAP+SEP      | −0.042 | 0.011 | −0.062 | 0.014 | 0.001 |
|   |     | Pooling       | −0.069 | 0.004 | −0.049 | 0.039 | −0.066 |
Table S3: The standard deviation of the treatment effect estimate for different methods in simulated scenarios with treatment effect

| J    | Method  | No        | Small | Moderate | Substantial | Large |
|------|---------|-----------|-------|----------|-------------|-------|
|      |         | 1.255     | 1.251 | 1.249    | 1.251       | 1.252 |
|      | MMAP+COR| 1.174     | 1.194 | 1.220    | 1.241       | 1.248 |
|      | MMAP+IND| 1.186     | 1.204 | 1.228    | 1.247       | 1.251 |
|      | UMAP+COM| 1.138     | 1.168 | 1.207    | 1.248       | 1.285 |
|      | UMAP+SEP| 1.233     | 1.234 | 1.239    | 1.248       | 1.251 |
|      | Pooling | 0.984     | 0.992 | 1.021    | 1.123       | 1.440 |
|      |         | 1.251     | 1.254 | 1.251    | 1.252       | 1.252 |
|      | MMAP+COR| 1.121     | 1.168 | 1.211    | 1.238       | 1.248 |
|      | MMAP+IND| 1.132     | 1.178 | 1.224    | 1.247       | 1.250 |
|      | UMAP+COM| 1.083     | 1.142 | 1.202    | 1.247       | 1.283 |
|      | UMAP+SEP| 1.220     | 1.232 | 1.240    | 1.248       | 1.250 |
|      | Pooling | 0.949     | 0.962 | 0.995    | 1.121       | 1.517 |
Table S4: The root mean squared error of the treatment effect estimate for different methods in simulated scenarios with treatment effect

| J  | Method      | Between-study heterogeneity |
|----|-------------|----------------------------|
|    |             | No | Small | Moderate | Substantial | Large |
| No borrowing | 1.264 | 1.250 | 1.219 | 1.208 | 1.235 |
| MMAP+COR | 1.136 | 1.171 | 1.184 | 1.191 | 1.230 |
| MMAP+IND | 1.157 | 1.187 | 1.198 | 1.200 | 1.236 |
| UMAP+COM | 1.095 | 1.146 | 1.177 | 1.198 | 1.270 |
| UMAP+SEP | 1.234 | 1.233 | 1.212 | 1.203 | 1.236 |
| Pooling  | 0.982 | 1.121 | 1.353 | 2.171 | 3.968 |

| No borrowing | 1.215 | 1.252 | 1.211 | 1.247 | 1.318 |
| MMAP+COR | 1.018 | 1.120 | 1.143 | 1.222 | 1.308 |
| MMAP+IND | 1.031 | 1.139 | 1.166 | 1.236 | 1.312 |
| UMAP+COM | 0.980 | 1.100 | 1.131 | 1.235 | 1.335 |
| UMAP+SEP | 1.166 | 1.221 | 1.197 | 1.238 | 1.313 |
| Pooling  | 0.924 | 1.040 | 1.219 | 1.846 | 3.282 |
2 Results of the sensitivity analysis for the motivating data analysis

In the sensitivity analysis, the proposed MAP approach was implemented with different priors for the between-study standard deviations of $\beta_0$ and $\beta_1$ to assess the method’s robustness to different priors of between-study heterogeneity, and the results with different model specifications were also derived.

2.1 Different priors for the between-study standard deviations

In this part of the sensitivity analysis, exponential and uniform priors that assign 5% probability for large between-study heterogeneity were considered. Namely, the exponential priors for $\tau_0$ and $\tau_1$ were $\text{Exp}(0.15)$ and $\text{Exp}(3)$, and the uniform priors for $\tau_0$ and $\tau_1$ were $\text{Uniform}(0, 21.05)$ and $\text{Uniform}(0, 1.05)$, respectively. The above priors along with the half-normal priors used in the main analysis are visualized in Figure SI.

Despite the same probability assigned to large between-study heterogeneity, the exponential prior assigns more probability to small between-study heterogeneity than the half-normal prior, while the uniform prior provides less probability to small between-study heterogeneity. Hence, the exponential prior express more confidence for a small between-study heterogeneity and the uniform prior is the least informative among the three priors.
Figure S1: Different priors for between-study standard deviations of (A) the intercept ($\tau_0$) and (B) the baseline effect ($\tau_1$)

The prior ESS for the intercept was 108, and the prior ESS for the baseline effect was 75 with the exponential priors. While the prior ESS for the intercept and the baseline effect were 72 and 48 respectively based on the uniform priors. The prior ESS for the two parameters based on half-normal priors (79 and 58) were between those with uniform priors and exponential priors. The results were reasonable in that the exponential prior is more informative while the uniform prior is less informative than the half-normal prior. The MAP priors and the prior ESS are shown in Table S5.
Table S5: The MAP priors and prior ESS for the intercept and the baseline effect with exponential and uniform priors for the between-study standard deviations

| Prior     | Parameter | Mean  | SD   | 95% credible interval | ESS |
|-----------|-----------|-------|------|-----------------------|-----|
| Exponential | $\beta_0$ | 5.27  | 1.80 | 1.58 to 8.90          | 108 |
|           | $\beta_1$ | 0.99  | 0.08 | 0.84 to 1.16          | 75  |
| Uniform   | $\beta_0$ | 5.26  | 2.21 | 0.74 to 9.67          | 72  |
|           | $\beta_1$ | 1.00  | 0.10 | 0.80 to 1.20          | 48  |

The parameter estimates based on the exponential and uniform priors are presented in Table S6. The treatment effect estimate with the exponential priors was -1.27 (SD: 1.16), and the treatment effect estimate based on the uniform priors was -1.28 (SD: 1.18). The estimates were similar to that based on the half-normal priors, which indicated the inference of the parameter of interest was robust to differently shaped priors (but same tail probability) for the between-study standard deviations.

Table S6: The estimates of model parameters with exponential and uniform priors for the between-study standard deviations

| Prior     | Parameter | Mean  | SD   | 95% credible interval |
|-----------|-----------|-------|------|-----------------------|
| Exponential | $\beta_0$ | 3.74  | 1.43 | 0.41 to 6.03          |
|           | $\beta_1$ | 1.06  | 0.06 | 0.97 to 1.19          |
|           | $\lambda$ | -1.27 | 1.16 | -3.56 to 1.02         |
| Uniform   | $\beta_0$ | 3.55  | 1.53 | 0.08 to 6.00          |
|           | $\beta_1$ | 1.07  | 0.06 | 0.97 to 1.20          |
|           | $\lambda$ | -1.28 | 1.18 | -3.60 to 1.02         |

2.2 Different MAP approaches

In the simulation study, there were three other MAP approaches, namely MMAP+IND, UMAP+COM, and UMAP+SEP considered. The results of the abovementioned models are also presented in Table S7 and Table S8.

The prior ESS of the intercept and the baseline effect with the MMAP+IND were larger than those in the MMAP+COR. The UMAP+COM yielded the largest prior ESS for the intercept, while the UMAP+SEP led to the smallest. The results were in line
with those in the simulation study.

Table S7: The MAP priors and prior ESS for the intercept and the baseline effect based on different MAP approaches

| Prior      | Parameter | Mean   | SD     | 95% credible interval | ESS |
|------------|-----------|--------|--------|-----------------------|-----|
| MMAP+IND   | \( \beta_0 \) | 5.39   | 1.62   | 2.28 to 8.51          | 133 |
|            | \( \beta_1 \) | 0.99   | 0.07   | 0.86 to 1.13          | 102 |
| UMAP+COM   | \( \beta_0 \) | 5.32   | 1.30   | 2.95 to 7.93          | 207 |
| UMAP+SEP   | \( \beta_0 \) | 5.27   | 3.04   | -1.01 to 11.42        | 38  |

The inference for the treatment effect in the MMAP+IND was similar to that in the MMAP+COR, while the treatment effect estimates of the UMAP+COM and the UMAP+SEP were more deviated from that in the MMAP+COR.

Table S8: The estimates of model parameters based on different MAP approaches

| Model      | Parameter | Mean   | SD     | 95% credible interval   |
|------------|-----------|--------|--------|-------------------------|
| MMAP+IND   | \( \beta_0 \) | 4.48   | 1.03   | 2.10 to 6.29            |
|            | \( \beta_1 \) | 1.03   | 0.04   | 0.96 to 1.13            |
|            | \( \lambda \) | -1.30  | 1.19   | -3.67 to 1.02           |
| UMAP+COM   | \( \beta_0 \) | 4.65   | 0.82   | 3.01 to 6.28            |
|            | \( \beta_1 \) | 1.02   | 0.03   | 0.96 to 1.07            |
|            | \( \lambda \) | -1.06  | 1.07   | -3.16 to 1.03           |
| UMAP+SEP   | \( \beta_0 \) | 2.80   | 1.78   | -0.96 to 5.83           |
|            | \( \beta_1 \) | 1.11   | 0.07   | 0.98 to 1.24            |
|            | \( \lambda \) | -1.46  | 1.36   | -4.12 to 1.21           |

3 JAGS scripts for the motivating data analysis

In this section, JAGS scripts for ‘No borrowing”, “Pooling”, and ‘MMAP+COR” approaches used in the motivating data analysis of Section 5 are presented. “No borrowing” and “Pooling” approaches share the same JAGS scripts, while the “MMAP+COR” approach has its unique JAGS scripts.
3.1 JAGS scripts for “No borrowing” and “Pooling” approaches

In this subsection, JAGS scripts for “No borrowing” and “Pooling” approaches are presented. To implement the two approaches, a single data set is needed (either the new trial data only or the pooled data without study identifier).

```jags
model {
## Priors
## Prior for the intercept and baseline effect, bivariate normal with low precision
beta ~ dmnorm(mean_beta, prec_beta)
## Treatment effect
lambda ~ dnorm(0, 1e-4)
## Error precision
tau ~ dgamma(1e-3, 1e-3)
## Likelihood
for (i in 1:N) {
  response[i] ~ dnorm(mu[i], tau)
  mu[i] <- fixef[i,] %*% c(beta, lambda)
}
}
```

3.2 JAGS scripts for the “MMAP+COR” approach

In this subsection, JAGS scripts for the “MMAP+COR” approach in both design and analysis of the new trial are presented. The scripts for the design phase which only include the historical controls are presented below.

```jags
model {
## Historical likelihood
## Each of H historical studies
for (i in 1:H) {
## Intercept and baseline effect in ith historical study
beta_historical[i,1:num_fixef] ~ dmnorm(beta, Omega_beta)
## Error precision in ith historical study
tau0[i] ~ dgamma(1e-3, 1e-3)
}
```

## Each observation in ith historical study

for (j in studyindex[2*(i-1)+1]: studyindex[2*i]) {
  response_historical[j] ~ dnorm(mu0[j], tau0[i])
  mu0[j] <- fixef_historical[j,] %*% beta_historical[i,1:num_fixef]
}

## Priors

## Overall mean of intercept and baseline effect
beta ~ dmnorm(mean_beta, prec_beta)

## Sigma_beta, between-study covariance matrix
sigma_beta0 ~ dnorm(0, prec_sigma_beta0) T(0,)
sigma_beta1 ~ dnorm(0, prec_sigma_beta1) T(0,)
 rho_cor ~ dunif(-1, 0)
rho <- ifelse(rho_cor > 0, rho_cor, 0)
c <- 1/((1-rho^2)*(sigma_beta0^2*sigma_beta1^2))
Omega_beta[1, 1] <- c*sigma_beta1^2
Omega_beta[2, 2] <- c*sigma_beta0^2
Omega_beta[1, 2] <- -c*rho*sigma_beta0*sigma_beta1
Omega_beta[2, 1] <- Omega_beta[1, 2]

## Predictive distribution for the new intercept and baseline effect
beta_new ~ dmnorm(beta, Omega_beta)
}

In addition, JAGS scripts for the analysis phase are shown as follows:

model {
  ## Historical likelihood
  ## Each of H historical studies
  for (i in 1:H) {
    ## Intercept and baseline effect in ith historical study
    beta_historical[i,1:num_fixef] ~ dmnorm(beta, Omega_beta)
    ## Error precision in ith historical study
    tau0[i] ~ dgamma(1e-3, 1e-3)
    ## Each observation in ith historical study
for (j in studyindex[2*(i-1)+1]: studyindex[2*i]) {
  response_historical[j] ~ dnorm(mu0[j], tau0[i])
  mu0[j] <- fixef_historical[j,] %*% beta_historical[i,1:num_fixef]
}
}

##Priors
##Overall mean of intercept and time effect
beta ~ dmnorm(mean_beta, prec_beta)
##Sigma_beta, between-study covariance matrix
sigma_beta0 ~ dnorm(0, prec_sigma_beta0) T(0,)
sigma_beta1 ~ dnorm(0, prec_sigma_beta1) T(0,)
rho_cor ~ dunif(-1, 0)
rho <- ifelse(cor, rho_cor, 0)
c <- 1/(((1-rho^2)*(sigma_beta0^2*sigma_beta1^2)))
Omega_beta[1, 1] <- c*sigma_beta1^2
Omega_beta[2, 2] <- c*sigma_beta0^2
Omega_beta[1, 2] <- -c*rho*sigma_beta0*sigma_beta1
Omega_beta[2, 1] <- Omega_beta[1, 2]
##Intercept and baseline effect in the new trial
beta_new ~ dmnorm(beta, Omega_beta)
##Treatment effect in the new trial
lambda ~ dnorm(0, 1e-4)
##Error precision in the new trial
tau ~ dgamma(1e-3, 1e-3)
##New trial likelihood
for (i in 1:N) {
  response_new[i] ~ dnorm(mu[i], tau)
  mu[i] <- fixef_new[i,] %*% c(beta_new, lambda)
}
}