Supplementary material

1. **Example R code and BUGs models**

*R code to fit the three alternatives*

**# 1. Loading relevant R commands ####**

library(metafor) # use for meta-analysis

library(BRugs) # use for Bayesian models

**# 2. Fitting model to Trials data only ####**

meta\_trials <- rma.uni(yi=D\_rct, sei=SE\_rct, data=rct\_data)

# Note: the rma.uni command fits a meta-analysis to the RCT data assuming that results from individual trials have been organised into a data frame called rct\_data with effect estimates in a column called D\_rct and standard errors in a column called SE\_rct

ARE\_trial <- as.numeric(meta\_trials[1]) # trials only ARE estimator

SE\_trial <- as.numeric(meta\_trials[2]) # SE of trials only ARE estimator

**# 3. Fitting model to cohort data only ####**

**# 3.1 Identifying cohort data ####**

id <- obs\_data[,1] # patient identifier, one per patient

vt <- obs\_data[,2] # times of outcome measurement (measured from treatment offer)

mmse <- obs\_data[,3] # outcomes measured

POINTS <- nrow(obs\_data) # number of data points in model

PEOPLE <- length(unique(id)) # number of patients in model

 **# 3.2 Prior distributions ####**

mu.BF<-c(0,0,0,0) # mean of prior distribution

tau.BF<-matrix(c( 0.0001,0,0,0,

0,0.0001,0,0,

0,0,0.0001,0,

0,0,0,0.0001),nrow=4) # covariance of prior

 **# 3.3 Model input and output ####**

data\_obs<-list("POINTS","PEOPLE","mmse","vt","id","alpha","tau.BF","mu.BF")

# Combines all data needed to fit the model into a single list

params\_obs<-list("theta")

# parameters to save outputs from the model for, can add others to this list

inits\_obs<-list(list(BF=c(22,-1,2,-0.9),

delta=0.45,sigma=3,sigma.b0=5,sigma.b2=2.1,rho=0.5,

B=matrix(rnorm(2\*PEOPLE,0,2),nrow=PEOPLE,ncol=2)),

 list(BF=c(18,-3,0,-2.9),

delta=0.15,sigma=1,sigma.b0=3,sigma.b2=0.1,rho=-0.5,

B=matrix(rnorm(2\*PEOPLE,0,2),nrow=PEOPLE,ncol=2)))

# initial values for model – some plausible values are needed as a starting point to fit the model

 **# 3.4 Fitting model and examining output ####**

model\_obs<-BRugsFit("obs\_model.txt",data=data\_obs,inits=inits\_obs,

numChains=2,parametersToSave=params\_obs,

nBurnin=burn\_in,nIter=iterations,nThin=thin)

# Bayesian model fitting – this command calls to BUGS (and therefore requires this is installed on your machine. The model this refers to is provided later in this supplementary material

ARE\_obs<-model\_obs[[1]][1,1] # cohort only ARE estimator

SE\_obs<-model\_obs[[1]][1,2] # SE of cohort only ARE estimator

**# 4. Fitting model to both data sources ####**

 **# 4.1 Informative prior and trial eligibility indicator ####**

mu\_theta<-ARE\_trial # informative prior mean – based on trials only data

tau\_theta<-1/(SE\_trial^2) # informative prior precision – based on trials only data

mu\_bf<-c(0,0,mu\_theta,0,0,0,0,0,0) # mean of informative prior dstn

tau\_bf<-matrix(c( 0.0001,0,0,0,0,0,0,0,0,

0,0.0001,0,0,0,0,0,0,0,

0,0,tau\_theta,0,0,0,0,0,0,

0,0,0,0.0001,0,0,0,0,0,

0,0,0,0,0.0001,0,0,0,0,

0,0,0,0,0,0.0001,0,0,0,

0,0,0,0,0,0,0.0001,0,0,

0,0,0,0,0,0,0,0.0001,0,

0,0,0,0,0,0,0,0,0.0001), nrow=9) # covariance of informative prior distribution

S <- obs\_data[,4] # where this is a variable that indicates for each row of the cohort data whether or not the patient this row refers to met trial eligibility criteria

**# 4.2 Model input and output ####**

data\_comb<-list("POINTS", "PEOPLE", "mmse", "vt", "id", "alpha", "mu\_bf", "tau\_bf", "S")

# combines all the data needed to fit the model into a single list

params\_comb<-list("ARE","ARE1","ARE2")

# parameters to save from model, can add others to this list

inits\_comb<-list(list(BF=c(18,-3,-0.5,-2.9,22,-1,2.5,-2,-1),

delta=0.15,pi=0.55,sigma=1,sigma.b0=3,sigma.b2=0.1,rho=-0.5,

B=matrix(rnorm(2\*PEOPLE,0,2),nrow=PEOPLE,ncol=2)),

 list(BF=c(22,-1,1.5,-0.9,18,-3,0.5,-2.9,1),

delta=0.45,pi=0.95,sigma=3,sigma.b0=5,sigma.b2=2.1,rho=0.5,

B=matrix(rnorm(2\*PEOPLE,0,2),nrow=PEOPLE,ncol=2)))

# initial values for model – some plausible values are needed as a starting point to fit the model

 **# 4.3 Model fitting and outputs ####**

model\_comb<-BRugsFit("comb\_model.txt",data=data\_comb,inits=inits\_comb,

numChains=2,parametersToSave=params\_comb,

nBurnin=burn\_in,nIter=iterations,nThin=thin)

# Bayesian model fitting – this command calls to BUGS (and therefore requires this is installed on your machine. The model this refers to is provided later in this supplementary material

ARE\_comb<-model\_comb[[1]][1,1] # combined estimator of ARE

SE\_comb<-model\_comb[[1]][1,2] # SE of combined ARE estimator

ARE1\_comb<-model\_comb[[1]][2,1] # estimator of ARE in P1

SE1\_comb<-model\_comb[[1]][2,2] # SE of ARE in P1 estimator

ARE2\_comb<-model\_comb[[1]][3,1] # estimator of ARE in P2

SE2\_comb<-model\_comb[[1]][3,2] # SE of ARE in P2 estimator

*BUGS models*

Cohort only model, used as obs\_model.txt in the R code provided above:

model{

for(i in 1:POINTS){

mmse[i] ~ dnorm(mu[i], tau)

mu[i] <- beta0 + b0[id[i]] + beta1\*(t1[i] + c1\*t2[i]) +

(theta + b2[id[i]])\*c2\*t2[i] + beta3\*(t3[i] + c3\*t2[i])

t1[i] <- vt[i]\*step(0-vt[i])

t2[i] <- vt[i]\*step(vt[i]-0)\*step(delta-vt[i]) +

delta\*step(vt[i]-delta)

t3[i] <- (vt[i]-delta)\*step(vt[i]-delta)

}

c1 <- 1\*step(delta-alpha) + (alpha/delta)\*step(alpha-delta)

c2 <- (1/alpha)\*step(delta-alpha) + (1/delta)\*step(alpha-delta)

c3 <- (1 -(alpha/delta))\*step(alpha-delta)

beta0 <- BF[1]

beta1 <- BF[2]

theta <- BF[3]

beta3 <- BF[4]

BF[1:4] ~ dmnorm(mu.BF[1:4], tau.BF[,])

tau <- 1/pow(sigma,2)

sigma ~ dunif(0,100)

delta ~ dunif(0,3)

for(j in 1:PEOPLE){

b0[j] <- B[j,1]

b2[j] <- B[j,2]

B[j,1:2] ~ dmnorm(B.hat[j,], Tau.B[,])

B.hat[j,1] <- 0

B.hat[j,2] <- 0

}

Tau.B[1:2,1:2] <- inverse(Sigma.B[,])

Sigma.B[1,1] <- pow(sigma.b0,2)

sigma.b0 ~ dunif(0, 100)

Sigma.B[2,2] <- pow(sigma.b2,2)

sigma.b2 ~ dunif(0, 100)

Sigma.B[1,2] <- rho\*sigma.b0\*sigma.b2

Sigma.B[2,1] <- rho\*sigma.b0\*sigma.b2

rho ~ dunif(-1,1)

}

Combined model, referred to as comb\_model.txt in the above:

model{

for(i in 1:POINTS){

mmse[i] ~ dnorm(mu[i], tau)

mu[i] <- (beta01\*step(S[id[i]]-0.5)+beta02\*step(0.5-S[id[i]]))+

b0[id[i]] + (beta11\*step(S[id[i]]-0.5)+

beta12\*step(0.5-S[id[i]]))\*(t1[i] + c1\*t2[i]) +

(theta1\*step(S[id[i]]-0.5) +

theta2\*step(0.5-S[id[i]])+b2[id[i]])\*c2\*t2[i] +

(beta31\*step(S[id[i]]-0.5) +

beta32\*step(0.5-S[id[i]]))\*(t3[i]+c3\*t2[i])

t1[i] <- vt[i]\*step(0-vt[i])

t2[i] <- vt[i]\*step(vt[i]-0)\*step(delta-vt[i]) +

delta\*step(vt[i]-delta)

t3[i] <- (vt[i]-delta)\*step(vt[i]-delta)

}

c1 <- 1\*step(delta-alpha) + (alpha/delta)\*step(alpha-delta)

c2 <- (1/alpha)\*step(delta-alpha) + (1/delta)\*step(alpha-delta)

c3 <- (1 -(alpha/delta))\*step(alpha-delta)

beta01 <- BF[1]

beta11 <- BF[2]

theta1 <- ARE1 + f

ARE1 <- BF[3]

beta31 <- BF[4]

beta02 <- BF[5]

beta12 <- BF[6]

theta2 <- ARE2 + f

ARE2 <- BF[7]

beta32 <- BF[8]

f <- BF[9]

BF[1:9] ~ dmnorm(mu\_bf[1:9],tau\_bf[,])

delta ~ dunif(0,3)

tau <- 1/pow(sigma,2)

sigma ~ dunif(0,100)

for(j in 1:PEOPLE){

b0[j] <- B[j,1]

b2[j] <- B[j,2]

B[j,1:2] ~ dmnorm(B.hat[j,], Tau.B[,])

B.hat[j,1] <- 0

B.hat[j,2] <- 0

S[j] ~ dbin(pi,1)

}

Tau.B[1:2,1:2] <- inverse(Sigma.B[,])

Sigma.B[1,1] <- pow(sigma.b0,2)

sigma.b0 ~ dunif(0, 100)

Sigma.B[2,2] <- pow(sigma.b2,2)

sigma.b2 ~ dunif(0, 100)

Sigma.B[1,2] <- rho\*sigma.b0\*sigma.b2

Sigma.B[2,1] <- rho\*sigma.b0\*sigma.b2

rho ~ dunif(-1,1)

pi ~ dunif(0,1)

ARE<- pi\*ARE1 + (1-pi)\*ARE2

gen <- ARE1-ARE

}

1. **Simulations study results**

Results from all input combination explored in the simulation study are provided. Simulations investigated the ability of the model to estimate treatment effects at 3, 6, and 12 months after treatment offer. Cohort sample and trial sample sizes were both explored at 6 months. Due to computing time cohort sample size was fixed at 3 months (n2=3000) and trial sample size was fixed at 12 months (n1=1000).

**Table 1**: Simulation study results estimating treatment effects at 3 months after treatment offer (n2=3000)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ζ** | **φ** | **π** | **n1** | **Absolute bias** | **MSE** | **SE** | **Projection interval** | **Generalisabilty interval** |
| **Trials** | **Cohort** | **Combined** | **Trials** | **Cohort** | **Combined** | **Trials** | **Cohort** | **Combined** |
| -0.5 | -0.5 | 50 | 3000 | 0.508 | 0.536 | 0.019 | 0.289 | 0.298 | 0.040 | 0.177 | 0.103 | 0.200 | 0.950 | 0.960 |
| -0.5 | -0.5 | 70 | 10000 | 0.506 | 0.522 | 0.004 | 0.266 | 0.282 | 0.017 | 0.099 | 0.099 | 0.129 | 0.954 | 0.970 |
| -0.5 | -0.5 | 90 | 1000 | 0.512 | 0.504 | 0.003 | 0.347 | 0.265 | 0.087 | 0.293 | 0.103 | 0.295 | 0.920 | 0.954 |
| -0.5 | 0 | 50 | 1000 | 0.512 | 0.010 | 0.016 | 0.347 | 0.013 | 0.095 | 0.293 | 0.115 | 0.308 | 0.928 | 0.938 |
| -0.5 | 0 | 70 | 3000 | 0.508 | 0.024 | 0.001 | 0.289 | 0.013 | 0.039 | 0.177 | 0.113 | 0.197 | 0.938 | 0.958 |
| -0.5 | 0 | 90 | 10000 | 0.506 | 0.001 | 0.002 | 0.266 | 0.013 | 0.012 | 0.099 | 0.112 | 0.109 | 0.962 | 0.950 |
| -0.5 | 0.5 | 50 | 10000 | 0.506 | 0.496 | 0.009 | 0.266 | 0.261 | 0.017 | 0.099 | 0.123 | 0.131 | 0.962 | 0.936 |
| -0.5 | 0.5 | 70 | 1000 | 0.512 | 0.487 | 0.004 | 0.347 | 0.251 | 0.091 | 0.293 | 0.120 | 0.302 | 0.924 | 0.944 |
| -0.5 | 0.5 | 90 | 3000 | 0.508 | 0.502 | 0.000 | 0.289 | 0.267 | 0.033 | 0.177 | 0.120 | 0.183 | 0.934 | 0.958 |
| 0 | -0.5 | 50 | 10000 | 0.006 | 0.523 | 0.011 | 0.010 | 0.285 | 0.016 | 0.099 | 0.107 | 0.126 | 0.970 | 0.954 |
| 0 | -0.5 | 70 | 1000 | 0.012 | 0.523 | 0.007 | 0.086 | 0.285 | 0.090 | 0.293 | 0.108 | 0.300 | 0.924 | 0.942 |
| 0 | -0.5 | 90 | 3000 | 0.008 | 0.525 | 0.007 | 0.031 | 0.287 | 0.033 | 0.177 | 0.108 | 0.181 | 0.948 | 0.950 |
| 0 | 0 | 50 | 3000 | 0.008 | 0.001 | 0.013 | 0.031 | 0.013 | 0.038 | 0.177 | 0.115 | 0.195 | 0.960 | 0.956 |
| 0 | 0 | 70 | 10000 | 0.006 | 0.002 | 0.001 | 0.010 | 0.013 | 0.015 | 0.099 | 0.114 | 0.121 | 0.956 | 0.936 |
| 0 | 0 | 90 | 1000 | 0.012 | 0.002 | 0.011 | 0.086 | 0.014 | 0.086 | 0.293 | 0.117 | 0.293 | 0.932 | 0.944 |
| 0 | 0.5 | 50 | 1000 | 0.012 | 0.504 | 0.017 | 0.086 | 0.270 | 0.094 | 0.293 | 0.124 | 0.306 | 0.934 | 0.950 |
| 0 | 0.5 | 70 | 3000 | 0.008 | 0.508 | 0.002 | 0.031 | 0.273 | 0.038 | 0.177 | 0.120 | 0.194 | 0.954 | 0.938 |
| 0 | 0.5 | 90 | 10000 | 0.006 | 0.505 | 0.005 | 0.010 | 0.270 | 0.011 | 0.099 | 0.125 | 0.104 | 0.944 | 0.950 |
| 0.5 | -0.5 | 50 | 1000 | 0.488 | 0.535 | 0.014 | 0.324 | 0.297 | 0.094 | 0.293 | 0.105 | 0.307 | 0.938 | 0.974 |
| 0.5 | -0.5 | 70 | 3000 | 0.492 | 0.524 | 0.001 | 0.274 | 0.285 | 0.039 | 0.177 | 0.099 | 0.197 | 0.952 | 0.968 |
| 0.5 | -0.5 | 90 | 10000 | 0.494 | 0.504 | 0.012 | 0.254 | 0.264 | 0.013 | 0.099 | 0.101 | 0.113 | 0.942 | 0.962 |
| 0.5 | 0 | 50 | 10000 | 0.494 | 0.010 | 0.015 | 0.254 | 0.014 | 0.018 | 0.099 | 0.119 | 0.133 | 0.974 | 0.960 |
| 0.5 | 0 | 70 | 1000 | 0.488 | 0.023 | 0.006 | 0.324 | 0.014 | 0.091 | 0.293 | 0.115 | 0.301 | 0.924 | 0.954 |
| 0.5 | 0 | 90 | 3000 | 0.492 | 0.000 | 0.013 | 0.274 | 0.012 | 0.034 | 0.177 | 0.110 | 0.185 | 0.938 | 0.952 |
| 0.5 | 0.5 | 50 | 3000 | 0.492 | 0.498 | 0.016 | 0.274 | 0.264 | 0.039 | 0.177 | 0.124 | 0.198 | 0.960 | 0.952 |
| 0.5 | 0.5 | 70 | 10000 | 0.494 | 0.485 | 0.003 | 0.254 | 0.250 | 0.016 | 0.099 | 0.123 | 0.125 | 0.960 | 0.948 |
| 0.5 | 0.5 | 90 | 1000 | 0.488 | 0.502 | 0.017 | 0.324 | 0.266 | 0.088 | 0.293 | 0.119 | 0.296 | 0.928 | 0.952 |

**Table 2:** Simulation study results estimating treatment effects at 6 months after treatment offer

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ζ** | **φ** | **π** | **n2** | **n1** | **Absolute bias** | **MSE** | **SE** | **Projection interval** | **Gen. interval** |
| **Trials** | **Cohort** | **Combined** | **Trials** | **Cohort** | **Combined** | **Trials** | **Cohort** | **Combined** |
| -0.5 | -0.5 | 50 | 1000 | 1500 | 0.507 | 0.528 | 0.014 | 0.361 | 0.326 | 0.139 | 0.323 | 0.219 | 0.373 | 0.920 | 0.930 |
| -0.5 | -0.5 | 50 | 3000 | 3000 | 0.508 | 0.521 | 0.016 | 0.289 | 0.291 | 0.048 | 0.177 | 0.139 | 0.218 | 0.954 | 0.940 |
| -0.5 | -0.5 | 50 | 10000 | 6000 | 0.497 | 0.505 | 0.001 | 0.257 | 0.265 | 0.017 | 0.097 | 0.099 | 0.131 | 0.964 | 0.960 |
| -0.5 | -0.5 | 70 | 1000 | 6000 | 0.492 | 0.511 | 0.006 | 0.333 | 0.271 | 0.098 | 0.302 | 0.102 | 0.312 | 0.890 | 0.948 |
| -0.5 | -0.5 | 70 | 3000 | 1500 | 0.511 | 0.509 | 0.012 | 0.293 | 0.304 | 0.052 | 0.179 | 0.214 | 0.228 | 0.938 | 0.934 |
| -0.5 | -0.5 | 70 | 10000 | 3000 | 0.506 | 0.518 | 0.002 | 0.266 | 0.287 | 0.020 | 0.099 | 0.138 | 0.141 | 0.958 | 0.922 |
| -0.5 | -0.5 | 90 | 1000 | 3000 | 0.512 | 0.507 | 0.007 | 0.347 | 0.276 | 0.088 | 0.293 | 0.138 | 0.296 | 0.928 | 0.960 |
| -0.5 | -0.5 | 90 | 3000 | 6000 | 0.507 | 0.495 | 0.003 | 0.291 | 0.255 | 0.036 | 0.184 | 0.099 | 0.189 | 0.918 | 0.934 |
| -0.5 | -0.5 | 90 | 10000 | 1500 | 0.513 | 0.483 | 0.008 | 0.273 | 0.279 | 0.015 | 0.097 | 0.212 | 0.124 | 0.956 | 0.950 |
| -0.5 | 0 | 50 | 1000 | 6000 | 0.492 | 0.002 | 0.007 | 0.333 | 0.009 | 0.098 | 0.302 | 0.095 | 0.312 | 0.920 | 0.962 |
| -0.5 | 0 | 50 | 3000 | 1500 | 0.511 | 0.010 | 0.010 | 0.293 | 0.038 | 0.069 | 0.179 | 0.195 | 0.262 | 0.952 | 0.930 |
| -0.5 | 0 | 50 | 10000 | 3000 | 0.506 | 0.006 | 0.014 | 0.266 | 0.016 | 0.025 | 0.099 | 0.126 | 0.158 | 0.960 | 0.944 |
| -0.5 | 0 | 70 | 1000 | 3000 | 0.512 | 0.001 | 0.003 | 0.347 | 0.017 | 0.093 | 0.293 | 0.130 | 0.305 | 0.922 | 0.928 |
| -0.5 | 0 | 70 | 3000 | 6000 | 0.507 | 0.002 | 0.008 | 0.291 | 0.009 | 0.040 | 0.184 | 0.094 | 0.199 | 0.910 | 0.946 |
| -0.5 | 0 | 70 | 10000 | 1500 | 0.513 | 0.019 | 0.013 | 0.273 | 0.041 | 0.027 | 0.097 | 0.201 | 0.162 | 0.936 | 0.928 |
| -0.5 | 0 | 90 | 1000 | 1500 | 0.507 | 0.017 | 0.003 | 0.361 | 0.045 | 0.110 | 0.323 | 0.212 | 0.331 | 0.908 | 0.956 |
| -0.5 | 0 | 90 | 3000 | 3000 | 0.508 | 0.007 | 0.003 | 0.289 | 0.019 | 0.034 | 0.177 | 0.138 | 0.184 | 0.946 | 0.958 |
| -0.5 | 0 | 90 | 10000 | 6000 | 0.497 | 0.005 | 0.006 | 0.257 | 0.010 | 0.011 | 0.097 | 0.099 | 0.105 | 0.950 | 0.928 |
| -0.5 | 0.5 | 50 | 1000 | 3000 | 0.512 | 0.493 | 0.019 | 0.347 | 0.259 | 0.103 | 0.293 | 0.126 | 0.320 | 0.938 | 0.942 |
| -0.5 | 0.5 | 50 | 3000 | 6000 | 0.507 | 0.498 | 0.009 | 0.291 | 0.257 | 0.040 | 0.184 | 0.096 | 0.20 | 0.936 | 0.962 |
| -0.5 | 0.5 | 50 | 10000 | 1500 | 0.513 | 0.513 | 0.011 | 0.273 | 0.301 | 0.053 | 0.097 | 0.194 | 0.229 | 0.938 | 0.932 |
| -0.5 | 0.5 | 70 | 1000 | 1500 | 0.507 | 0.521 | 0.006 | 0.361 | 0.311 | 0.123 | 0.323 | 0.200 | 0.351 | 0.908 | 0.936 |
| -0.5 | 0.5 | 70 | 3000 | 3000 | 0.508 | 0.501 | 0.001 | 0.289 | 0.267 | 0.042 | 0.177 | 0.130 | 0.206 | 0.952 | 0.928 |
| -0.5 | 0.5 | 70 | 10000 | 6000 | 0.497 | 0.502 | 0.001 | 0.257 | 0.261 | 0.014 | 0.097 | 0.094 | 0.118 | 0.962 | 0.944 |
| -0.5 | 0.5 | 90 | 1000 | 6000 | 0.492 | 0.505 | 0.011 | 0.333 | 0.265 | 0.093 | 0.302 | 0.100 | 0.305 | 0.900 | 0.924 |
| -0.5 | 0.5 | 90 | 3000 | 1500 | 0.511 | 0.518 | 0.006 | 0.293 | 0.313 | 0.040 | 0.179 | 0.211 | 0.199 | 0.950 | 0.952 |
| -0.5 | 0.5 | 90 | 10000 | 3000 | 0.506 | 0.494 | 0.002 | 0.266 | 0.263 | 0.012 | 0.099 | 0.137 | 0.111 | 0.964 | 0.958 |
| 0 | -0.5 | 50 | 1000 | 6000 | 0.008 | 0.503 | 0.007 | 0.091 | 0.262 | 0.097 | 0.302 | 0.096 | 0.312 | 0.926 | 0.956 |
| 0 | -0.5 | 50 | 3000 | 1500 | 0.011 | 0.527 | 0.011 | 0.032 | 0.324 | 0.064 | 0.179 | 0.217 | 0.254 | 0.940 | 0.940 |
| 0 | -0.5 | 50 | 10000 | 3000 | 0.006 | 0.515 | 0.013 | 0.010 | 0.283 | 0.025 | 0.099 | 0.133 | 0.157 | 0.954 | 0.936 |
| 0 | -0.5 | 70 | 1000 | 3000 | 0.012 | 0.510 | 0.005 | 0.086 | 0.279 | 0.093 | 0.293 | 0.136 | 0.305 | 0.926 | 0.932 |
| 0 | -0.5 | 70 | 3000 | 6000 | 0.007 | 0.5 | 0.008 | 0.034 | 0.259 | 0.040 | 0.184 | 0.092 | 0.199 | 0.916 | 0.948 |
| 0 | -0.5 | 70 | 10000 | 1500 | 0.013 | 0.516 | 0.014 | 0.010 | 0.315 | 0.025 | 0.097 | 0.221 | 0.156 | 0.930 | 0.936 |
| 0 | -0.5 | 90 | 1000 | 1500 | 0.007 | 0.520 | 0.005 | 0.104 | 0.317 | 0.108 | 0.323 | 0.218 | 0.329 | 0.920 | 0.958 |
| 0 | -0.5 | 90 | 3000 | 3000 | 0.008 | 0.516 | 0.006 | 0.031 | 0.284 | 0.034 | 0.177 | 0.133 | 0.183 | 0.940 | 0.948 |
| 0 | -0.5 | 90 | 10000 | 6000 | 0.003 | 0.500 | 0.005 | 0.009 | 0.259 | 0.011 | 0.097 | 0.092 | 0.102 | 0.952 | 0.946 |
| 0 | 0 | 50 | 1000 | 3000 | 0.012 | 0.005 | 0.019 | 0.086 | 0.016 | 0.102 | 0.293 | 0.125 | 0.320 | 0.940 | 0.944 |
| 0 | 0 | 50 | 3000 | 6000 | 0.007 | 0.001 | 0.008 | 0.034 | 0.009 | 0.040 | 0.184 | 0.095 | 0.201 | 0.936 | 0.958 |
| 0 | 0 | 50 | 10000 | 1500 | 0.013 | 0.011 | 0.012 | 0.010 | 0.037 | 0.052 | 0.097 | 0.192 | 0.227 | 0.940 | 0.936 |
| 0 | 0 | 70 | 1000 | 1500 | 0.007 | 0.020 | 0.007 | 0.104 | 0.040 | 0.123 | 0.323 | 0.198 | 0.351 | 0.910 | 0.928 |
| 0 | 0 | 70 | 3000 | 3000 | 0.008 | 0.001 | 0.000 | 0.031 | 0.016 | 0.042 | 0.177 | 0.127 | 0.205 | 0.948 | 0.930 |
| 0 | 0 | 70 | 10000 | 6000 | 0.003 | 0.001 | 0.001 | 0.009 | 0.008 | 0.014 | 0.097 | 0.090 | 0.118 | 0.962 | 0.942 |
| 0 | 0 | 90 | 1000 | 6000 | 0.008 | 0.001 | 0.010 | 0.091 | 0.008 | 0.093 | 0.302 | 0.091 | 0.304 | 0.898 | 0.940 |
| 0 | 0 | 90 | 3000 | 1500 | 0.011 | 0.017 | 0.008 | 0.032 | 0.038 | 0.038 | 0.179 | 0.194 | 0.194 | 0.948 | 0.956 |
| 0 | 0 | 90 | 10000 | 3000 | 0.006 | 0.005 | 0.004 | 0.010 | 0.016 | 0.012 | 0.099 | 0.125 | 0.109 | 0.958 | 0.946 |
| 0 | 0.5 | 50 | 1000 | 1500 | 0.007 | 0.513 | 0.005 | 0.104 | 0.300 | 0.135 | 0.323 | 0.191 | 0.367 | 0.930 | 0.932 |
| 0 | 0.5 | 50 | 3000 | 3000 | 0.008 | 0.495 | 0.015 | 0.031 | 0.260 | 0.048 | 0.177 | 0.125 | 0.218 | 0.960 | 0.938 |
| 0 | 0.5 | 50 | 10000 | 6000 | 0.003 | 0.498 | 0.001 | 0.009 | 0.257 | 0.017 | 0.097 | 0.095 | 0.130 | 0.966 | 0.956 |
| 0 | 0.5 | 70 | 1000 | 6000 | 0.008 | 0.501 | 0.006 | 0.091 | 0.259 | 0.097 | 0.302 | 0.090 | 0.312 | 0.904 | 0.940 |
| 0 | 0.5 | 70 | 3000 | 1500 | 0.011 | 0.522 | 0.011 | 0.032 | 0.311 | 0.051 | 0.179 | 0.197 | 0.225 | 0.938 | 0.924 |
| 0 | 0.5 | 70 | 10000 | 3000 | 0.006 | 0.502 | 0.001 | 0.010 | 0.267 | 0.020 | 0.099 | 0.126 | 0.140 | 0.956 | 0.924 |
| 0 | 0.5 | 90 | 1000 | 3000 | 0.012 | 0.495 | 0.010 | 0.086 | 0.261 | 0.087 | 0.293 | 0.125 | 0.295 | 0.932 | 0.944 |
| 0 | 0.5 | 90 | 3000 | 6000 | 0.007 | 0.501 | 0.005 | 0.034 | 0.259 | 0.036 | 0.184 | 0.091 | 0.189 | 0.922 | 0.944 |
| 0 | 0.5 | 90 | 10000 | 1500 | 0.013 | 0.519 | 0.011 | 0.010 | 0.306 | 0.014 | 0.097 | 0.192 | 0.116 | 0.948 | 0.956 |
| 0.5 | -0.5 | 50 | 1000 | 3000 | 0.488 | 0.519 | 0.019 | 0.324 | 0.289 | 0.102 | 0.293 | 0.140 | 0.320 | 0.940 | 0.938 |
| 0.5 | -0.5 | 50 | 3000 | 6000 | 0.493 | 0.504 | 0.009 | 0.277 | 0.264 | 0.040 | 0.184 | 0.100 | 0.200 | 0.932 | 0.954 |
| 0.5 | -0.5 | 50 | 10000 | 1500 | 0.487 | 0.527 | 0.002 | 0.246 | 0.324 | 0.054 | 0.097 | 0.216 | 0.232 | 0.936 | 0.934 |
| 0.5 | -0.5 | 70 | 1000 | 1500 | 0.493 | 0.504 | 0.006 | 0.347 | 0.301 | 0.123 | 0.323 | 0.217 | 0.351 | 0.912 | 0.936 |
| 0.5 | -0.5 | 70 | 3000 | 3000 | 0.492 | 0.519 | 0.001 | 0.274 | 0.289 | 0.042 | 0.177 | 0.139 | 0.205 | 0.950 | 0.928 |
| 0.5 | -0.5 | 70 | 10000 | 6000 | 0.503 | 0.512 | 0.002 | 0.262 | 0.272 | 0.014 | 0.097 | 0.101 | 0.118 | 0.964 | 0.944 |
| 0.5 | -0.5 | 90 | 1000 | 6000 | 0.508 | 0.503 | 0.009 | 0.349 | 0.263 | 0.093 | 0.302 | 0.101 | 0.304 | 0.896 | 0.956 |
| 0.5 | -0.5 | 90 | 3000 | 1500 | 0.489 | 0.481 | 0.011 | 0.272 | 0.275 | 0.039 | 0.179 | 0.209 | 0.197 | 0.944 | 0.952 |
| 0.5 | -0.5 | 90 | 10000 | 3000 | 0.494 | 0.507 | 0.007 | 0.254 | 0.275 | 0.013 | 0.099 | 0.134 | 0.114 | 0.956 | 0.944 |
| 0.5 | 0 | 50 | 1000 | 1500 | 0.493 | 0.011 | 0.004 | 0.347 | 0.038 | 0.135 | 0.323 | 0.193 | 0.367 | 0.928 | 0.938 |
| 0.5 | 0 | 50 | 3000 | 3000 | 0.492 | 0.004 | 0.015 | 0.274 | 0.016 | 0.048 | 0.177 | 0.127 | 0.218 | 0.954 | 0.938 |
| 0.5 | 0 | 50 | 10000 | 6000 | 0.503 | 0.001 | 0.001 | 0.262 | 0.009 | 0.017 | 0.097 | 0.097 | 0.131 | 0.964 | 0.956 |
| 0.5 | 0 | 70 | 1000 | 6000 | 0.508 | 0.000 | 0.007 | 0.349 | 0.009 | 0.098 | 0.302 | 0.092 | 0.313 | 0.896 | 0.940 |
| 0.5 | 0 | 70 | 3000 | 1500 | 0.489 | 0.021 | 0.012 | 0.272 | 0.041 | 0.051 | 0.179 | 0.203 | 0.225 | 0.942 | 0.938 |
| 0.5 | 0 | 70 | 10000 | 3000 | 0.494 | 0.001 | 0.000 | 0.254 | 0.017 | 0.020 | 0.099 | 0.130 | 0.140 | 0.954 | 0.926 |
| 0.5 | 0 | 90 | 1000 | 3000 | 0.488 | 0.006 | 0.012 | 0.324 | 0.018 | 0.088 | 0.293 | 0.134 | 0.297 | 0.926 | 0.944 |
| 0.5 | 0 | 90 | 3000 | 6000 | 0.493 | 0.003 | 0.006 | 0.277 | 0.010 | 0.036 | 0.184 | 0.101 | 0.190 | 0.918 | 0.956 |
| 0.5 | 0 | 90 | 10000 | 1500 | 0.487 | 0.021 | 0.013 | 0.246 | 0.044 | 0.015 | 0.097 | 0.208 | 0.123 | 0.960 | 0.950 |
| 0.5 | 0.5 | 50 | 1000 | 6000 | 0.508 | 0.499 | 0.006 | 0.349 | 0.258 | 0.097 | 0.302 | 0.097 | 0.312 | 0.920 | 0.956 |
| 0.5 | 0.5 | 50 | 3000 | 1500 | 0.489 | 0.513 | 0.008 | 0.272 | 0.300 | 0.068 | 0.179 | 0.192 | 0.261 | 0.948 | 0.940 |
| 0.5 | 0.5 | 50 | 10000 | 3000 | 0.494 | 0.496 | 0.014 | 0.254 | 0.262 | 0.025 | 0.099 | 0.127 | 0.158 | 0.962 | 0.946 |
| 0.5 | 0.5 | 70 | 1000 | 3000 | 0.488 | 0.499 | 0.005 | 0.324 | 0.266 | 0.094 | 0.293 | 0.130 | 0.307 | 0.918 | 0.930 |
| 0.5 | 0.5 | 70 | 3000 | 6000 | 0.493 | 0.500 | 0.008 | 0.277 | 0.259 | 0.040 | 0.184 | 0.093 | 0.199 | 0.914 | 0.936 |
| 0.5 | 0.5 | 70 | 10000 | 1500 | 0.487 | 0.523 | 0.014 | 0.246 | 0.314 | 0.027 | 0.097 | 0.202 | 0.164 | 0.942 | 0.934 |
| 0.5 | 0.5 | 90 | 1000 | 1500 | 0.493 | 0.521 | 0.007 | 0.347 | 0.315 | 0.109 | 0.323 | 0.208 | 0.330 | 0.918 | 0.944 |
| 0.5 | 0.5 | 90 | 3000 | 3000 | 0.492 | 0.494 | 0.008 | 0.274 | 0.262 | 0.035 | 0.177 | 0.134 | 0.186 | 0.954 | 0.944 |
| 0.5 | 0.5 | 90 | 10000 | 6000 | 0.503 | 0.497 | 0.003 | 0.262 | 0.258 | 0.011 | 0.097 | 0.101 | 0.104 | 0.950 | 0.954 |

**Table 3:** Simulation study results estimating treatment effects at 12 months after treatment offer (n1=1000)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ζ** | **φ** | **π** | **n2** | **Absolute bias** | **MSE** | **SE** | **Projection interval** | **Generalisability interval** |
| **Trials** | **Cohort** | **Combined** | **Trials** | **Cohort** | **Combined** | **Trials** | **Cohort** | **Combined** |
| -0.5 | -0.5 | 50 | 1500 | 0.507 | 0.545 | 0.037 | 0.361 | 0.408 | 0.207 | 0.323 | 0.332 | 0.454 | 0.944 | 0.930 |
| -0.5 | -0.5 | 70 | 6000 | 0.492 | 0.502 | 0.004 | 0.333 | 0.273 | 0.105 | 0.302 | 0.146 | 0.325 | 0.92 | 0.942 |
| -0.5 | -0.5 | 90 | 3000 | 0.512 | 0.506 | 0.005 | 0.347 | 0.300 | 0.090 | 0.293 | 0.210 | 0.299 | 0.932 | 0.950 |
| -0.5 | 0.5 | 50 | 3000 | 0.512 | 0.494 | 0.022 | 0.347 | 0.283 | 0.128 | 0.293 | 0.199 | 0.356 | 0.944 | 0.942 |
| -0.5 | 0.5 | 70 | 1500 | 0.507 | 0.528 | 0.005 | 0.361 | 0.375 | 0.148 | 0.323 | 0.310 | 0.384 | 0.918 | 0.934 |
| -0.5 | 0.5 | 90 | 6000 | 0.492 | 0.503 | 0.012 | 0.333 | 0.276 | 0.095 | 0.302 | 0.152 | 0.308 | 0.908 | 0.936 |
| -0.5 | 0 | 50 | 6000 | 0.492 | 0.007 | 0.005 | 0.333 | 0.022 | 0.108 | 0.302 | 0.148 | 0.328 | 0.928 | 0.952 |
| -0.5 | 0 | 70 | 3000 | 0.512 | 0.005 | 0.000 | 0.347 | 0.041 | 0.104 | 0.293 | 0.201 | 0.322 | 0.940 | 0.934 |
| -0.5 | 0 | 90 | 1500 | 0.507 | 0.027 | 0.002 | 0.361 | 0.102 | 0.115 | 0.323 | 0.318 | 0.340 | 0.930 | 0.956 |
| 0.5 | -0.5 | 50 | 3000 | 0.488 | 0.515 | 0.022 | 0.324 | 0.309 | 0.128 | 0.293 | 0.209 | 0.357 | 0.948 | 0.944 |
| 0.5 | -0.5 | 70 | 1500 | 0.493 | 0.493 | 0.002 | 0.347 | 0.348 | 0.146 | 0.323 | 0.324 | 0.382 | 0.924 | 0.930 |
| 0.5 | -0.5 | 90 | 6000 | 0.508 | 0.506 | 0.009 | 0.349 | 0.279 | 0.094 | 0.302 | 0.153 | 0.307 | 0.908 | 0.958 |
| 0.5 | 0.5 | 50 | 6000 | 0.508 | 0.494 | 0.006 | 0.349 | 0.266 | 0.106 | 0.302 | 0.150 | 0.326 | 0.924 | 0.952 |
| 0.5 | 0.5 | 70 | 3000 | 0.488 | 0.503 | 0.001 | 0.324 | 0.294 | 0.104 | 0.293 | 0.200 | 0.322 | 0.938 | 0.936 |
| 0.5 | 0.5 | 90 | 1500 | 0.493 | 0.530 | 0.006 | 0.347 | 0.378 | 0.115 | 0.323 | 0.313 | 0.339 | 0.926 | 0.942 |
| 0.5 | 0 | 50 | 1500 | 0.493 | 0.012 | 0.003 | 0.347 | 0.089 | 0.187 | 0.323 | 0.298 | 0.432 | 0.938 | 0.934 |
| 0.5 | 0 | 70 | 6000 | 0.508 | 0.005 | 0.006 | 0.349 | 0.021 | 0.106 | 0.302 | 0.144 | 0.325 | 0.914 | 0.952 |
| 0.5 | 0 | 90 | 3000 | 0.488 | 0.004 | 0.01 | 0.324 | 0.043 | 0.091 | 0.293 | 0.207 | 0.302 | 0.93 | 0.950 |
| 0 | -0.5 | 50 | 6000 | 0.008 | 0.508 | 0.005 | 0.091 | 0.280 | 0.106 | 0.302 | 0.148 | 0.326 | 0.926 | 0.948 |
| 0 | -0.5 | 70 | 3000 | 0.012 | 0.507 | 0.000 | 0.086 | 0.300 | 0.103 | 0.293 | 0.207 | 0.321 | 0.944 | 0.938 |
| 0 | -0.5 | 90 | 1500 | 0.007 | 0.539 | 0.004 | 0.104 | 0.403 | 0.114 | 0.323 | 0.335 | 0.337 | 0.938 | 0.950 |
| 0 | 0.5 | 50 | 1500 | 0.007 | 0.514 | 0.006 | 0.104 | 0.352 | 0.185 | 0.323 | 0.295 | 0.431 | 0.938 | 0.932 |
| 0 | 0.5 | 70 | 6000 | 0.008 | 0.497 | 0.005 | 0.091 | 0.266 | 0.106 | 0.302 | 0.141 | 0.325 | 0.920 | 0.946 |
| 0 | 0.5 | 90 | 3000 | 0.012 | 0.497 | 0.007 | 0.086 | 0.286 | 0.090 | 0.293 | 0.196 | 0.300 | 0.926 | 0.946 |
| 0 | 0 | 50 | 3000 | 0.012 | 0.005 | 0.022 | 0.086 | 0.039 | 0.128 | 0.293 | 0.198 | 0.357 | 0.944 | 0.938 |
| 0 | 0 | 70 | 1500 | 0.007 | 0.026 | 0.006 | 0.104 | 0.094 | 0.147 | 0.323 | 0.306 | 0.384 | 0.922 | 0.926 |
| 0 | 0 | 90 | 6000 | 0.008 | 0.004 | 0.010 | 0.091 | 0.020 | 0.095 | 0.302 | 0.141 | 0.308 | 0.900 | 0.942 |