

APPENDIX

A practical guide to the meta-analysis of rare events

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1 Software codes

1.1 Fitting models in R

In this section we provide the software codes needed to perform all frequentist analyses presented in the main paper. All comments are shown in blue font.

Start by installing needed libraries – this step is only needed once

```
install.packages("meta")  
install.packages("mmeta") # this library is needed for fitting the beta-binomial model
```

Call the libraries

```
library("meta")  
library("mmeta")
```

Load the dataset

#(the following dataset corresponds to LAI-AP vs placebo, see main paper)

```
y1=c(1, 0, 0, 0, 2, 0, 0, 0, 0, 2, 0, 0, 0, 1, 1, 0, 0, 0) #events, LAI-AP  
n1=c(269, 168, 415, 41, 27, 35, 23, 306, 160, 164, 221, 206, 163, 391, 488, 160,  
302, 235) #number of patients, LAI-AP  
y2=c(0, 0, 1, 0, 0, 1, 1, 0, 0, 0, 0, 0, 0, 1, 0, 1, 1, 0) #events, placebo  
n2=c(134, 172, 207, 40, 27, 35, 22, 98, 145, 170, 135, 204, 84, 127, 164, 164, 98,  
119) #number of patients, placebo
```

#(the following dataset corresponds to LAI-AP vs OAP, see main paper)

```
y1=c(0, 1, 0, 0, 2, 0, 0, 0, 0, 0, 0, 1, 1, 0, 2, 0, 3, 0, 2, 1, 0, 0, 2, 0, 0) #events,  
LAI-AP  
n1=c(265, 228, 27, 20, 55, 127, 23, 141, 264, 599, 230, 352, 25, 153, 319, 329, 153,  
247, 179, 44, 20, 190, 43, 26) #number of patients, LAI-AP  
y2= c(1, 1, 0, 0, 0, 1, 1, 1, 2, 0, 0, 1, 0, 4, 1, 2, 0, 6, 1, 0, 0, 2, 0, 0) #events,  
OAP
```

```
n2= c(266, 227, 61, 24, 50, 132, 28, 142, 260, 322, 220, 363, 25, 152, 321, 382, 52, 300, 176, 41, 21, 192, 43, 20) #number of patients, OAP
```

Perform the analyses

```
# inverse-variance odds-ratio with 0.5 continuity correction
```

```
OR.IV <- metabin(y1, n1, y2, n2, sm="OR", method = "Inverse", incr=0.5)  
print(summary(OR.IV), digits=2)
```

```
# inverse-variance odds-ratio with "treatment-arm" continuity correction
```

```
OR.IV2 <- metabin(y1, n1, y2, n2, sm="OR", method = "Inverse", incr="TACC")  
print(summary(OR.IV2), digits=2)
```

```
# Peto odds-ratio
```

```
MH.Peto <- metabin(y1, n1, y2, n2, sm="OR", method = "Peto")  
print(summary(MH.Peto), digits=2)
```

```
# Mantel-Haenszel odds-ratio with no continuity correction
```

```
MH.OR <- metabin(y1, n1, y2, n2, sm="OR", MH.exact=TRUE)  
print(summary(MH.OR), digits=2)
```

```
# Mantel-Haenszel odds-ratio with "treatment-arm" continuity correction
```

```
MH.OR1 <- metabin(y1, n1, y2, n2, sm="OR", MH.exact=F, incr="TACC")  
print(summary(MH.OR1), digits=2)
```

```
# Mantel-Haenszel odds-ratio with 0.5 continuity correction
```

```
MH.OR2 <- metabin(y1, n1, y2, n2, sm="OR", MH.exact=F, incr=0.5)  
print(summary(MH.OR2), digits=2)
```

```
# Mantel-Haenszel risk-difference with no continuity correction
```

```
MH.RD<- metabin(y1, n1, y2, n2, sm="RD", MH.exact=TRUE)  
print(summary(MH.RD), digits=5)
```

```
# Beta-binomial with correlated responses
```

```
study=c(1:length(y1))  
B=data.frame(y1=y2,y2=y1,n1=n2,n2=n1)  
B$studynames=study  
Beta.Bin<- multiplatables(data=B, measure="OR",model="Sarmanov",method="sampling",  
nsam=1000)  
summary(Beta.Bin)
```

```
# Arcsine difference
```

```
ASD <- metabin(y1, n1, y2, n2, sm="ASD")  
print(summary(ASD), digits=3)
```

Create the forest plot

```
forest(OR2, label.right = "favors LAI-AP", label.left = "favors OAP",  
overall=T,squaresize = 0)
```

1.2 Fitting models in OpenBUGS

All results of the Bayesian analyses presented in the paper pertain to 1,000,000 iterations, after an initial 200,000 burn-in period and a thinning of 50. For the case of random effects meta-analyses, the median posterior estimates for the variance of the random effects (i.e. the heterogeneity variance, τ^2) were 0.02 (95% Credible Interval [0.002; 0.32]) for the meta-analysis of LAI-AP vs placebo, and 0.01[0.001; 0.19] for the meta-analysis of LAI-AP vs OAP.

Here we provide the codes we used.

1.2.1 Fixed-effects meta-analysis

```
model{
for (i in 1:NS){    ### i cycles through the number of studies
events.control[i]~dbin(p.control[i],total.control[i])
events.treat[i]~dbin(p.treat[i],total.treat[i])
logit(p.control[i]) <- u[i]
logit(p.treat[i]) <- u[i]+lor
u[i] ~dnorm(0,0.001) ### prior distribution for the log odds at the control
}
lor~dnorm(0,0.001) ### prior distribution for the log odds ratio
or<-exp(lor)
}
```

Data for the LAI-AP vs OAP example

```
list(
NS=24,
events.treat=c(0, 1, 0, 0, 2, 0, 0, 0, 0, 0, 1, 1, 0, 2, 0, 3, 0, 2, 1, 0,
0, 2, 0, 0),
total.treat=c(265, 228, 27, 20, 55, 127, 23, 141, 264, 599, 230, 352, 25,
153, 319, 329, 153, 247, 179, 44, 20, 190, 43, 26),
events.control=c(1, 1, 0, 0, 0, 1, 1, 1, 2, 0, 0, 1, 0, 4, 1, 2, 0, 6, 1, 0,
0, 2, 0, 0),
total.control=c(266, 227, 61, 24, 50, 132, 28, 142, 260, 322, 220, 363, 25,
152, 321, 382, 52, 300, 176, 41, 21, 192, 43, 20))
```

A set of initial values for the parameters may be needed, e.g.:

```
list(lor = 1.361,u = c(2.624,-5.582,-11.65,-14.04,-3.656,
-8.944,-4.384,0.001,-7.143,-17.38,-5.772,1.97,-13.03,-3.628,-6.356,-4.189,-11.91,-3.
615,-6.477, 3.79,
-7.397,-3.77, 2.88,1.675))
```

1.2.2 Random-effects meta-analysis

```
model{
for (i in 1:NS){    ### i cycles through the number of studies
events.control[i]~dbin(p.control[i],total.control[i])
events.treat[i]~dbin(p.treat[i],total.treat[i])
logit(p.control[i]) <- u[i]
logit(p.treat[i]) <- u[i]+lor[i]
u[i] ~dnorm(0,0.001)
lor[i]~dnorm(mu,prec.tau)
}
prec.tau<-1/tauOR.s
tauOR.s~dlnorm(-4.18,inv.sd2) ###prior based on empirical priors
inv.sd2<-1/(1.41*1.41) ###prior based on empirical priors
mu~dnorm(0,0.001)
or<-exp(mu)
}
```

Data are exactly as in the fixed effects meta-analysis.

A set of initial values for the parameters may be needed, e.g.:

```
list(lor =  
c(-0.2565,-0.6751,-0.6719,-0.2435,-0.2081,-0.07849,-0.3697,-0.6819,-0.655,-0.1374,-0  
.1624,-0.5858,-0.6593,-0.3722,-0.5081,-0.2838,-0.599,-0.4624,-0.5108,-0.3789,-0.241,  
-0.7983,-0.5308,-0.4028),mu = -0.5211,tauOR.s = 0.04736,u =  
c(-6.572,-4.79,-11.98,-4.946,-3.566,-5.413,-2.917,-4.257,-4.206,-8.771,-6.916,-6.12,  
-4.202,-4.361,-6.744,-4.817,-5.887,-3.585,-6.414,-3.455,  
-4.652,-4.216,-5.906,-4.053))
```