Disco III Cluster Robust SEs

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## Setup

library(tidyverse)  
library(lme4)  
library(broom)  
library(haven)  
library(sandwich)  
library(lmtest)  
library(tinytable)  
  
options(tinytable\_tt\_digits = 3, num\_suffix = TRUE)  
options(tinytable\_theme\_placement\_latex\_float = "H")

## Load Data

path <- "C:/Users/jomas/OneDrive/Dokumente/002\_Publications/2025-DISCO-III/data/disco\_data.dta"  
  
data\_raw <- read\_dta(path)  
  
#correctly format factors  
data <- data\_raw |>   
 mutate(  
 across(c(Placebo\_yes,   
 singlecenter,   
 Recruitpredict,   
 Industry,   
 ECapproval\_2016), factor))

## Custom Functions

rename\_variables <- function(data) {  
 data |>   
 mutate(term = case\_when(  
 term == "ASPIREprop\_10" ~ "Proportion of adequate SPIRIT reporting, median (IQR)",  
 term == "samplesize\_100" ~ "Planned target sample size, median (IQR)",  
 term == "Placebo\_yes1" ~ "Placebo controlled (vs not placebo controlled)",  
 term == "singlecenter1" ~ "Single-center (vs multicenter)",  
 term == "Recruitpredict1" ~ "Reported recruitment projection",  
 term == "Industry1" ~ "Industry sponsorship",  
 term == "ECapproval\_20161" ~ "Approval in 2016 (vs 2012)",  
 .default = term  
 ))  
}  
  
format\_model\_output <- function(data, accuracy = 0.01) {  
 data |>  
 rename\_variables() |>   
 mutate(p.value = scales::pvalue(p.value),  
 estimate = scales::number(estimate, accuracy = accuracy),  
 conf.high = scales::number(conf.high, accuracy = accuracy),  
 conf.low = scales::number(conf.low, accuracy = accuracy),  
 `95% CI` = paste(conf.low, " - ", conf.high)) |>   
 select(-c(std.error, statistic, conf.low, conf.high)) |>   
 rename(OR = estimate,  
 `P-value` = p.value) |>   
 relocate(term, OR, `95% CI`)  
}  
  
# Function to run univariable model with clustering adjustment  
run\_univariable\_model <- function(predictor) {  
 formula <- as.formula(paste("noresultsbefmid2020 ~", predictor))  
   
 # Fit the model  
 model <- glm(formula,  
 family = binomial(link = "logit"),  
 data = data[data$ECapproval\_2016 == 1, ])  
   
 # Get cluster-robust standard errors  
 robust\_results <- coeftest(model,  
 vcov = vcovCL(model,  
 cluster = ~ country\_ethics\_committee,  
 type = "HC3")) |>   
 tidy(conf.int = TRUE) |>   
 mutate(estimate = exp(estimate),  
 conf.low = exp(conf.low),  
 conf.high = exp(conf.high))  
   
 # Add predictor name  
 robust\_results$predictor <- predictor  
   
 return(robust\_results)  
}  
  
format\_mult\_model\_output <- function(data) {  
 data |>   
 data.frame() |>   
 rownames\_to\_column("term") |>  
 rename(  
 estimate = Estimate,  
 std.error = Std..Error,  
 statistic = z.value,  
 p.value = Pr...z..) |>   
 mutate(  
 conf.low = estimate - (1.96 \* std.error),  
 conf.high = estimate + (1.96 \* std.error),  
 estimate = exp(estimate),  
 conf.low = exp(conf.low),  
 conf.high = exp(conf.high)  
 )  
}

## Regression

Every code chunk aims to replicate the results from Beni’s Stata code with naive standard errors. I then calculate cluster robust standard errors. I used type HC3, which applies small sample bias adjustment, as we only have 4 clusters.

HC0 applies no small sample bias adjustment. HC1 applies a degrees of freedom-based correction, (n−1)/(n−k) where n is the number of observations and k is the number of explanatory or predictor variables in the model. HC1 is the most commonly used approach for linear models, and HC0 otherwise. Hence these are the defaults in vcovCL. However, HC0 and HC1 are less effective than HC2 and HC3 when the number of clusters is relatively small (Cameron et al. 2008). HC2 and HC3 types of bias adjustment are geared towards the linear model, but they are also applicable for GLMs (see Bell and McCaffrey 2002, and Kauermann and Carroll 2001, for details).

See [Sandwich Documentation](https://sandwich.r-forge.r-project.org/reference/vcovCL.html).

### Supplementary Table S7

# Non-availability of trial results -------------  
  
model.s7 <- glm(noresultsbefmid2020 ~ ASPIREprop\_10 + samplesize\_100 + Placebo\_yes +   
 singlecenter + Recruitpredict + Industry + ECapproval\_2016,  
 family = binomial(link = "logit"),  
 data = data)  
  
summary(model.s7)

Call:  
glm(formula = noresultsbefmid2020 ~ ASPIREprop\_10 + samplesize\_100 +   
 Placebo\_yes + singlecenter + Recruitpredict + Industry +   
 ECapproval\_2016, family = binomial(link = "logit"), data = data)  
  
Coefficients:  
 Estimate Std. Error z value Pr(>|z|)   
(Intercept) 0.726676 0.566622 1.282 0.199678   
ASPIREprop\_10 -0.300387 0.084054 -3.574 0.000352 \*\*\*  
samplesize\_100 -0.004784 0.008479 -0.564 0.572603   
Placebo\_yes1 0.366607 0.233622 1.569 0.116593   
singlecenter1 0.498380 0.251450 1.982 0.047476 \*   
Recruitpredict1 0.228678 0.238501 0.959 0.337654   
Industry1 -1.542341 0.273029 -5.649 1.61e-08 \*\*\*  
ECapproval\_20161 0.345717 0.229238 1.508 0.131525   
---  
Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
  
(Dispersion parameter for binomial family taken to be 1)  
  
 Null deviance: 660.59 on 672 degrees of freedom  
Residual deviance: 560.25 on 665 degrees of freedom  
AIC: 576.25  
  
Number of Fisher Scoring iterations: 5

# Naive SEs  
table\_s7\_a\_naive <- tidy(model.s7, conf.int = TRUE, exponentiate = TRUE) |>  
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()  
  
table\_s7\_a\_naive |>   
 save\_tt(output = "tables/table-s7a-non-robust-se.docx", overwrite = TRUE)  
  
table\_s7\_a\_naive

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 0.74 | 0.63 - 0.87 | <0.001 |
| Planned target sample size, median (IQR) | 1.00 | 0.98 - 1.01 | 0.573 |
| Placebo controlled (vs not placebo controlled) | 1.44 | 0.91 - 2.28 | 0.117 |
| Single-center (vs multicenter) | 1.65 | 1.00 - 2.69 | 0.047 |
| Reported recruitment projection | 1.26 | 0.78 - 2.00 | 0.338 |
| Industry sponsorship | 0.21 | 0.12 - 0.36 | <0.001 |
| Approval in 2016 (vs 2012) | 1.41 | 0.90 - 2.22 | 0.132 |

# Robust SEs  
table\_s7\_a\_robust <- coeftest(model.s7,  
 vcov = vcovCL(model.s7,  
 cluster = ~ country\_ethics\_committee,  
 type = "HC3")) |>   
 tidy(conf.int = TRUE) |>   
 mutate(estimate = exp(estimate),  
 conf.low = exp(conf.low),  
 conf.high = exp(conf.high)) |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()  
  
table\_s7\_a\_robust |>   
 save\_tt(output = "tables/table-s7a-robust-se.docx", overwrite = TRUE)  
  
table\_s7\_a\_robust

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 0.74 | 0.49 - 1.12 | 0.157 |
| Planned target sample size, median (IQR) | 1.00 | 0.94 - 1.06 | 0.877 |
| Placebo controlled (vs not placebo controlled) | 1.44 | 0.57 - 3.66 | 0.440 |
| Single-center (vs multicenter) | 1.65 | 0.92 - 2.94 | 0.091 |
| Reported recruitment projection | 1.26 | 0.56 - 2.82 | 0.580 |
| Industry sponsorship | 0.21 | 0.10 - 0.45 | <0.001 |
| Approval in 2016 (vs 2012) | 1.41 | 1.05 - 1.90 | 0.023 |

# Mixed model with random intercept  
  
model.s7.ri <- glmer(  
 noresultsbefmid2020 ~ ASPIREprop\_10 + samplesize\_100 + Placebo\_yes +   
 singlecenter + Recruitpredict + Industry + ECapproval\_2016 +   
 (1 | country\_ethics\_committee),  
 family = binomial(link = "logit"),  
 data = data)  
  
summary(model.s7.ri)

Generalized linear mixed model fit by maximum likelihood (Laplace  
 Approximation) [glmerMod]  
 Family: binomial ( logit )  
Formula: noresultsbefmid2020 ~ ASPIREprop\_10 + samplesize\_100 + Placebo\_yes +   
 singlecenter + Recruitpredict + Industry + ECapproval\_2016 +   
 (1 | country\_ethics\_committee)  
 Data: data  
  
 AIC BIC logLik deviance df.resid   
 578.2 618.8 -280.1 560.2 664   
  
Scaled residuals:   
 Min 1Q Median 3Q Max   
-1.3652 -0.5345 -0.2774 -0.2142 6.6781   
  
Random effects:  
 Groups Name Variance Std.Dev.  
 country\_ethics\_committee (Intercept) 0.002188 0.04678   
Number of obs: 673, groups: country\_ethics\_committee, 4  
  
Fixed effects:  
 Estimate Std. Error z value Pr(>|z|)   
(Intercept) 0.740641 0.600866 1.233 0.2177   
ASPIREprop\_10 -0.303399 0.094361 -3.215 0.0013 \*\*   
samplesize\_100 -0.004810 0.008502 -0.566 0.5716   
Placebo\_yes1 0.367334 0.233898 1.570 0.1163   
singlecenter1 0.495712 0.254429 1.948 0.0514 .   
Recruitpredict1 0.233526 0.248361 0.940 0.3471   
Industry1 -1.538800 0.277692 -5.541 3e-08 \*\*\*  
ECapproval\_20161 0.347245 0.230308 1.508 0.1316   
---  
Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
  
Correlation of Fixed Effects:  
 (Intr) ASPIRE sm\_100 Plcb\_1 snglc1 Rcrtp1 Indst1  
ASPIREpr\_10 -0.910   
samplsz\_100 -0.123 0.015   
Placebo\_ys1 -0.022 -0.103 0.012   
singlecntr1 -0.438 0.258 0.205 0.007   
Recrtprdct1 0.055 -0.255 -0.038 0.086 0.041   
Industry1 -0.010 -0.153 -0.010 -0.258 0.284 0.184   
ECppr\_20161 0.155 -0.355 0.057 0.001 -0.134 0.120 0.011

summary(model.s7.ri)$coefficients |>   
 format\_mult\_model\_output () |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 0.74 | 0.61 - 0.89 | 0.001 |
| Planned target sample size, median (IQR) | 1.00 | 0.98 - 1.01 | 0.572 |
| Placebo controlled (vs not placebo controlled) | 1.44 | 0.91 - 2.28 | 0.116 |
| Single-center (vs multicenter) | 1.64 | 1.00 - 2.70 | 0.051 |
| Reported recruitment projection | 1.26 | 0.78 - 2.06 | 0.347 |
| Industry sponsorship | 0.21 | 0.12 - 0.37 | <0.001 |
| Approval in 2016 (vs 2012) | 1.42 | 0.90 - 2.22 | 0.132 |

# Discontinued due to poor recruitment ----------------  
  
model.s7.b <- glm(disco\_poor\_recr ~ ASPIREprop\_10 + samplesize\_100 + Placebo\_yes +   
 singlecenter + Recruitpredict + Industry + ECapproval\_2016,  
 family = binomial(link = "logit"),  
 data = data[data$Discontinued != "NR", ])  
  
# Naive SEs  
summary(model.s7.b)

Call:  
glm(formula = disco\_poor\_recr ~ ASPIREprop\_10 + samplesize\_100 +   
 Placebo\_yes + singlecenter + Recruitpredict + Industry +   
 ECapproval\_2016, family = binomial(link = "logit"), data = data[data$Discontinued !=   
 "NR", ])  
  
Coefficients:  
 Estimate Std. Error z value Pr(>|z|)   
(Intercept) -1.73588 0.75973 -2.285 0.02232 \*   
ASPIREprop\_10 0.04616 0.10957 0.421 0.67357   
samplesize\_100 -0.04414 0.02398 -1.841 0.06567 .   
Placebo\_yes1 0.47473 0.25451 1.865 0.06214 .   
singlecenter1 -0.00318 0.31873 -0.010 0.99204   
Recruitpredict1 -0.24323 0.28686 -0.848 0.39648   
Industry1 -0.91773 0.29125 -3.151 0.00163 \*\*  
ECapproval\_20161 0.06633 0.25688 0.258 0.79624   
---  
Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
  
(Dispersion parameter for binomial family taken to be 1)  
  
 Null deviance: 499.94 on 634 degrees of freedom  
Residual deviance: 475.54 on 627 degrees of freedom  
AIC: 491.54  
  
Number of Fisher Scoring iterations: 7

table\_s7\_b\_naive <- tidy(model.s7.b, conf.int = TRUE, exponentiate = TRUE) |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

table\_s7\_b\_naive |>   
 save\_tt(output = "tables/table-s7b-non-robust-se.docx", overwrite = TRUE)  
  
table\_s7\_b\_naive

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 1.05 | 0.85 - 1.30 | 0.674 |
| Planned target sample size, median (IQR) | 0.96 | 0.90 - 0.99 | 0.066 |
| Placebo controlled (vs not placebo controlled) | 1.61 | 0.98 - 2.65 | 0.062 |
| Single-center (vs multicenter) | 1.00 | 0.53 - 1.85 | 0.992 |
| Reported recruitment projection | 0.78 | 0.44 - 1.35 | 0.396 |
| Industry sponsorship | 0.40 | 0.22 - 0.71 | 0.002 |
| Approval in 2016 (vs 2012) | 1.07 | 0.65 - 1.77 | 0.796 |

# Robust SEs  
table\_s7\_b\_robust <- coeftest(model.s7.b,  
 vcov = vcovCL(model.s7.b,  
 cluster = ~ country\_ethics\_committee,  
 type = "HC3")) |>   
 tidy(conf.int = TRUE) |>   
 mutate(estimate = exp(estimate),  
 conf.low = exp(conf.low),  
 conf.high = exp(conf.high)) |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()  
  
table\_s7\_b\_robust |>   
 save\_tt(output = "tables/table-s7b-robust-se.docx", overwrite = TRUE)  
  
table\_s7\_b\_robust

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 1.05 | 0.76 - 1.44 | 0.776 |
| Planned target sample size, median (IQR) | 0.96 | 0.67 - 1.36 | 0.805 |
| Placebo controlled (vs not placebo controlled) | 1.61 | 0.46 - 5.62 | 0.457 |
| Single-center (vs multicenter) | 1.00 | 0.31 - 3.17 | 0.996 |
| Reported recruitment projection | 0.78 | 0.51 - 1.21 | 0.274 |
| Industry sponsorship | 0.40 | 0.13 - 1.19 | 0.098 |
| Approval in 2016 (vs 2012) | 1.07 | 0.38 - 3.01 | 0.900 |

# With random intercept  
  
model.s7b.ri <- glmer(disco\_poor\_recr ~ ASPIREprop\_10 + samplesize\_100 +   
 Placebo\_yes + singlecenter + Recruitpredict +   
 Industry + ECapproval\_2016 + (1 | country\_ethics\_committee),  
 family = binomial(link = "logit"),  
 data = data[data$Discontinued != "NR", ])

boundary (singular) fit: see help('isSingular')

summary(model.s7b.ri) # Fails to estimate variance of random intercept

Generalized linear mixed model fit by maximum likelihood (Laplace  
 Approximation) [glmerMod]  
 Family: binomial ( logit )  
Formula: disco\_poor\_recr ~ ASPIREprop\_10 + samplesize\_100 + Placebo\_yes +   
 singlecenter + Recruitpredict + Industry + ECapproval\_2016 +   
 (1 | country\_ethics\_committee)  
 Data: data[data$Discontinued != "NR", ]  
  
 AIC BIC logLik deviance df.resid   
 493.5 533.6 -237.8 475.5 626   
  
Scaled residuals:   
 Min 1Q Median 3Q Max   
-0.6585 -0.4309 -0.3551 -0.2688 4.1752   
  
Random effects:  
 Groups Name Variance Std.Dev.  
 country\_ethics\_committee (Intercept) 0 0   
Number of obs: 635, groups: country\_ethics\_committee, 4  
  
Fixed effects:  
 Estimate Std. Error z value Pr(>|z|)   
(Intercept) -1.73588 0.75973 -2.285 0.02232 \*   
ASPIREprop\_10 0.04616 0.10957 0.421 0.67358   
samplesize\_100 -0.04414 0.02398 -1.841 0.06567 .   
Placebo\_yes1 0.47473 0.25451 1.865 0.06214 .   
singlecenter1 -0.00318 0.31873 -0.010 0.99204   
Recruitpredict1 -0.24323 0.28686 -0.848 0.39648   
Industry1 -0.91773 0.29125 -3.151 0.00163 \*\*  
ECapproval\_20161 0.06633 0.25688 0.258 0.79624   
---  
Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
  
Correlation of Fixed Effects:  
 (Intr) ASPIRE sm\_100 Plcb\_1 snglc1 Rcrtp1 Indst1  
ASPIREpr\_10 -0.922   
samplsz\_100 -0.089 -0.048   
Placebo\_ys1 -0.027 -0.089 0.038   
singlecntr1 -0.367 0.183 0.210 -0.016   
Recrtprdct1 0.012 -0.157 -0.047 0.080 0.054   
Industry1 -0.050 -0.135 -0.019 -0.275 0.400 0.159   
ECppr\_20161 0.145 -0.344 0.054 -0.005 -0.107 0.099 0.071  
optimizer (Nelder\_Mead) convergence code: 0 (OK)  
boundary (singular) fit: see help('isSingular')

summary(model.s7b.ri)$coefficients |>   
 format\_mult\_model\_output () |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 1.05 | 0.84 - 1.30 | 0.674 |
| Planned target sample size, median (IQR) | 0.96 | 0.91 - 1.00 | 0.066 |
| Placebo controlled (vs not placebo controlled) | 1.61 | 0.98 - 2.65 | 0.062 |
| Single-center (vs multicenter) | 1.00 | 0.53 - 1.86 | 0.992 |
| Reported recruitment projection | 0.78 | 0.45 - 1.38 | 0.396 |
| Industry sponsorship | 0.40 | 0.23 - 0.71 | 0.002 |
| Approval in 2016 (vs 2012) | 1.07 | 0.65 - 1.77 | 0.796 |

### Manuscript Table 4

#### Univariable analysis

Didn’t calculate naive SEs.

# List of predictor variables  
predictors <- c("ASPIREprop\_10", "samplesize\_100", "Placebo\_yes",   
 "singlecenter", "Recruitpredict", "Industry")  
  
# Run models for all predictors  
univariable\_results <- lapply(predictors, run\_univariable\_model) |>  
 bind\_rows()  
  
table\_4\_univ\_robust <- univariable\_results |>  
 arrange(predictor) |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 select(-predictor) |>   
 tt()  
  
table\_4\_univ\_robust |>   
 save\_tt(output = "tables/table-4-univariate.docx", overwrite = TRUE)  
  
table\_4\_univ\_robust

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 0.65 | 0.33 - 1.28 | 0.216 |
| Industry sponsorship | 0.18 | 0.10 - 0.33 | <0.001 |
| Placebo controlled (vs not placebo controlled) | 0.80 | 0.25 - 2.56 | 0.704 |
| Reported recruitment projection | 1.26 | 0.78 - 2.05 | 0.350 |
| Planned target sample size, median (IQR) | 0.84 | 0.01 - 96.18 | 0.943 |
| Single-center (vs multicenter) | 4.74 | 2.07 - 10.82 | <0.001 |

# Non-availability of trial results ----------------  
model.4.a <- glm(noresultsbefmid2020 ~ ASPIREprop\_10 + samplesize\_100 + Placebo\_yes +   
 singlecenter + Recruitpredict + Industry,  
 family = binomial(link = "logit"),  
 data = data[data$ECapproval\_2016 == 1, ])  
  
summary(model.4.a)

Call:  
glm(formula = noresultsbefmid2020 ~ ASPIREprop\_10 + samplesize\_100 +   
 Placebo\_yes + singlecenter + Recruitpredict + Industry, family = binomial(link = "logit"),   
 data = data[data$ECapproval\_2016 == 1, ])  
  
Coefficients:  
 Estimate Std. Error z value Pr(>|z|)   
(Intercept) 1.64475 0.92057 1.787 0.07399 .   
ASPIREprop\_10 -0.34004 0.11648 -2.919 0.00351 \*\*   
samplesize\_100 -0.07845 0.04219 -1.859 0.06296 .   
Placebo\_yes1 0.43551 0.32256 1.350 0.17696   
singlecenter1 0.40236 0.35295 1.140 0.25429   
Recruitpredict1 0.09131 0.33887 0.269 0.78759   
Industry1 -1.57474 0.38249 -4.117 3.84e-05 \*\*\*  
---  
Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
  
(Dispersion parameter for binomial family taken to be 1)  
  
 Null deviance: 351.67 on 346 degrees of freedom  
Residual deviance: 291.63 on 340 degrees of freedom  
AIC: 305.63  
  
Number of Fisher Scoring iterations: 6

table\_4\_a\_naive <- tidy(model.4.a, conf.int = TRUE, exponentiate = TRUE) |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()  
  
table\_4\_a\_naive |>   
 save\_tt(output = "tables/table-4a-naive.docx", overwrite = TRUE)  
  
table\_4\_a\_naive

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 0.71 | 0.56 - 0.89 | 0.004 |
| Planned target sample size, median (IQR) | 0.92 | 0.83 - 0.99 | 0.063 |
| Placebo controlled (vs not placebo controlled) | 1.55 | 0.82 - 2.93 | 0.177 |
| Single-center (vs multicenter) | 1.50 | 0.75 - 2.99 | 0.254 |
| Reported recruitment projection | 1.10 | 0.56 - 2.11 | 0.788 |
| Industry sponsorship | 0.21 | 0.10 - 0.43 | <0.001 |

# Robust SEs  
  
table\_4\_a\_robust <- coeftest(model.4.a,  
 vcov = vcovCL(model.4.a,  
 cluster = ~ country\_ethics\_committee,  
 type = "HC3")) |>   
 tidy(conf.int = TRUE) |>   
 mutate(estimate = exp(estimate),  
 conf.low = exp(conf.low),  
 conf.high = exp(conf.high)) |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()   
  
table\_4\_a\_robust |>   
 save\_tt(output = "tables/table-4a-robust.docx", overwrite = TRUE)  
  
table\_4\_a\_robust

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 0.71 | 0.38 - 1.32 | 0.280 |
| Planned target sample size, median (IQR) | 0.92 | 0.51 - 1.69 | 0.799 |
| Placebo controlled (vs not placebo controlled) | 1.55 | 0.14 - 16.83 | 0.721 |
| Single-center (vs multicenter) | 1.50 | 0.80 - 2.79 | 0.207 |
| Reported recruitment projection | 1.10 | 0.43 - 2.82 | 0.850 |
| Industry sponsorship | 0.21 | 0.04 - 0.98 | 0.047 |

# Random intercecpt  
  
model.4.a.ri <- glmer(noresultsbefmid2020 ~ ASPIREprop\_10 + samplesize\_100 +  
 Placebo\_yes + singlecenter + Recruitpredict +   
 Industry + (1 | country\_ethics\_committee),  
 family = binomial(link = "logit"),  
 data = data[data$ECapproval\_2016 == 1, ])

boundary (singular) fit: see help('isSingular')

summary(model.4.a.ri) # Fails to estimate variance of random intercept

Generalized linear mixed model fit by maximum likelihood (Laplace  
 Approximation) [glmerMod]  
 Family: binomial ( logit )  
Formula: noresultsbefmid2020 ~ ASPIREprop\_10 + samplesize\_100 + Placebo\_yes +   
 singlecenter + Recruitpredict + Industry + (1 | country\_ethics\_committee)  
 Data: data[data$ECapproval\_2016 == 1, ]  
  
 AIC BIC logLik deviance df.resid   
 307.6 338.4 -145.8 291.6 339   
  
Scaled residuals:   
 Min 1Q Median 3Q Max   
-1.5129 -0.4973 -0.2978 -0.1787 4.1946   
  
Random effects:  
 Groups Name Variance Std.Dev.  
 country\_ethics\_committee (Intercept) 0 0   
Number of obs: 347, groups: country\_ethics\_committee, 4  
  
Fixed effects:  
 Estimate Std. Error z value Pr(>|z|)   
(Intercept) 1.64475 0.92057 1.787 0.07399 .   
ASPIREprop\_10 -0.34004 0.11648 -2.919 0.00351 \*\*   
samplesize\_100 -0.07845 0.04219 -1.859 0.06299 .   
Placebo\_yes1 0.43551 0.32256 1.350 0.17696   
singlecenter1 0.40236 0.35295 1.140 0.25429   
Recruitpredict1 0.09131 0.33888 0.269 0.78759   
Industry1 -1.57474 0.38249 -4.117 3.84e-05 \*\*\*  
---  
Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
  
Correlation of Fixed Effects:  
 (Intr) ASPIRE sm\_100 Plcb\_1 snglc1 Rcrtp1  
ASPIREpr\_10 -0.937   
samplsz\_100 -0.171 0.013   
Placebo\_ys1 -0.021 -0.100 0.039   
singlecntr1 -0.439 0.227 0.277 -0.009   
Recrtprdct1 -0.119 0.004 -0.050 0.056 0.043   
Industry1 -0.245 0.115 0.002 -0.329 0.393 0.097  
optimizer (Nelder\_Mead) convergence code: 0 (OK)  
boundary (singular) fit: see help('isSingular')

summary(model.4.a.ri)$coefficients |>   
 format\_mult\_model\_output () |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 0.71 | 0.57 - 0.89 | 0.004 |
| Planned target sample size, median (IQR) | 0.92 | 0.85 - 1.00 | 0.063 |
| Placebo controlled (vs not placebo controlled) | 1.55 | 0.82 - 2.91 | 0.177 |
| Single-center (vs multicenter) | 1.50 | 0.75 - 2.99 | 0.254 |
| Reported recruitment projection | 1.10 | 0.56 - 2.13 | 0.788 |
| Industry sponsorship | 0.21 | 0.10 - 0.44 | <0.001 |

# Discontinued due to poor recruitment --------------  
  
model.4.b <- glm(disco\_poor\_recr ~ ASPIREprop\_10 + samplesize\_100 + Placebo\_yes +   
 singlecenter + Recruitpredict + Industry,  
 family = binomial(link = "logit"),  
 data = data[data$ECapproval\_2016 == 1 & data$Discontinued != "NR", ])  
  
summary(model.4.b)

Call:  
glm(formula = disco\_poor\_recr ~ ASPIREprop\_10 + samplesize\_100 +   
 Placebo\_yes + singlecenter + Recruitpredict + Industry, family = binomial(link = "logit"),   
 data = data[data$ECapproval\_2016 == 1 & data$Discontinued !=   
 "NR", ])  
  
Coefficients:  
 Estimate Std. Error z value Pr(>|z|)   
(Intercept) -1.65759 1.16893 -1.418 0.15618   
ASPIREprop\_10 0.04587 0.14687 0.312 0.75480   
samplesize\_100 -0.03646 0.03263 -1.117 0.26386   
Placebo\_yes1 0.67076 0.34478 1.945 0.05172 .   
singlecenter1 0.01872 0.42020 0.045 0.96447   
Recruitpredict1 -0.49183 0.40611 -1.211 0.22587   
Industry1 -1.13127 0.40384 -2.801 0.00509 \*\*  
---  
Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
  
(Dispersion parameter for binomial family taken to be 1)  
  
 Null deviance: 278.52 on 333 degrees of freedom  
Residual deviance: 262.03 on 327 degrees of freedom  
AIC: 276.03  
  
Number of Fisher Scoring iterations: 5

# Naive SEs  
table\_4\_b\_naive <- tidy(model.4.b, conf.int = TRUE, exponentiate = TRUE) |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()   
  
table\_4\_b\_naive |>   
 save\_tt(output = "tables/table-4b-non-robust-se.docx", overwrite = TRUE)  
  
table\_4\_b\_naive

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 1.05 | 0.79 - 1.41 | 0.755 |
| Planned target sample size, median (IQR) | 0.96 | 0.89 - 1.01 | 0.264 |
| Placebo controlled (vs not placebo controlled) | 1.96 | 1.00 - 3.88 | 0.052 |
| Single-center (vs multicenter) | 1.02 | 0.44 - 2.32 | 0.964 |
| Reported recruitment projection | 0.61 | 0.26 - 1.30 | 0.226 |
| Industry sponsorship | 0.32 | 0.14 - 0.71 | 0.005 |

# Robust SEs  
table\_4\_b\_robust <- coeftest(model.4.b,  
 vcov = vcovCL(model.4.b,  
 cluster = ~ country\_ethics\_committee,  
 type = "HC3")) |>   
 tidy(conf.int = TRUE) |>   
 mutate(estimate = exp(estimate),  
 conf.low = exp(conf.low),  
 conf.high = exp(conf.high)) |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()  
   
table\_4\_b\_robust |>   
 save\_tt(output = "tables/table-4b-robust-se.docx", overwrite = TRUE)  
  
table\_4\_b\_robust

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 1.05 | 0.70 - 1.57 | 0.825 |
| Planned target sample size, median (IQR) | 0.96 | 0.92 - 1.01 | 0.129 |
| Placebo controlled (vs not placebo controlled) | 1.96 | 0.22 - 17.10 | 0.544 |
| Single-center (vs multicenter) | 1.02 | 0.61 - 1.70 | 0.943 |
| Reported recruitment projection | 0.61 | 0.34 - 1.09 | 0.097 |
| Industry sponsorship | 0.32 | 0.16 - 0.64 | 0.001 |

# Random intercept  
  
model.4.b.ri <- glmer(disco\_poor\_recr ~ ASPIREprop\_10 + samplesize\_100 +   
 Placebo\_yes + singlecenter + Recruitpredict + Industry +  
 (1 | country\_ethics\_committee),  
 family = binomial(link = "logit"),  
 data = data[data$ECapproval\_2016 == 1 & data$Discontinued != "NR", ])

boundary (singular) fit: see help('isSingular')

summary(model.4.b.ri) # Fails to estimate variance of random intercept

Generalized linear mixed model fit by maximum likelihood (Laplace  
 Approximation) [glmerMod]  
 Family: binomial ( logit )  
Formula: disco\_poor\_recr ~ ASPIREprop\_10 + samplesize\_100 + Placebo\_yes +   
 singlecenter + Recruitpredict + Industry + (1 | country\_ethics\_committee)  
 Data: data[data$ECapproval\_2016 == 1 & data$Discontinued != "NR", ]  
  
 AIC BIC logLik deviance df.resid   
 278.0 308.5 -131.0 262.0 326   
  
Scaled residuals:   
 Min 1Q Median 3Q Max   
-0.7385 -0.4352 -0.3736 -0.2571 4.0813   
  
Random effects:  
 Groups Name Variance Std.Dev.  
 country\_ethics\_committee (Intercept) 0 0   
Number of obs: 334, groups: country\_ethics\_committee, 4  
  
Fixed effects:  
 Estimate Std. Error z value Pr(>|z|)   
(Intercept) -1.65759 1.16895 -1.418 0.15618   
ASPIREprop\_10 0.04587 0.14687 0.312 0.75480   
samplesize\_100 -0.03646 0.03265 -1.117 0.26414   
Placebo\_yes1 0.67076 0.34478 1.945 0.05172 .   
singlecenter1 0.01872 0.42020 0.045 0.96447   
Recruitpredict1 -0.49183 0.40612 -1.211 0.22587   
Industry1 -1.13127 0.40384 -2.801 0.00509 \*\*  
---  
Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
  
Correlation of Fixed Effects:  
 (Intr) ASPIRE sm\_100 Plcb\_1 snglc1 Rcrtp1  
ASPIREpr\_10 -0.954   
samplsz\_100 -0.164 0.048   
Placebo\_ys1 -0.033 -0.079 0.082   
singlecntr1 -0.416 0.244 0.227 -0.032   
Recrtprdct1 -0.079 -0.015 -0.034 0.040 0.052   
Industry1 -0.183 0.047 -0.030 -0.339 0.456 0.127  
optimizer (Nelder\_Mead) convergence code: 0 (OK)  
boundary (singular) fit: see help('isSingular')

summary(model.4.b.ri)$coefficients |>   
 format\_mult\_model\_output () |>   
 filter(term != "(Intercept)") |>   
 format\_model\_output() |>   
 tt()

| term | OR | 95% CI | P-value |
| --- | --- | --- | --- |
| Proportion of adequate SPIRIT reporting, median (IQR) | 1.05 | 0.79 - 1.40 | 0.755 |
| Planned target sample size, median (IQR) | 0.96 | 0.90 - 1.03 | 0.264 |
| Placebo controlled (vs not placebo controlled) | 1.96 | 0.99 - 3.84 | 0.052 |
| Single-center (vs multicenter) | 1.02 | 0.45 - 2.32 | 0.964 |
| Reported recruitment projection | 0.61 | 0.28 - 1.36 | 0.226 |
| Industry sponsorship | 0.32 | 0.15 - 0.71 | 0.005 |