Supporting Information for Individual participant data meta-analysis of intervention studies with time-to-event outcomes: A review of the methodology and an applied example

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1 Search filters

1.1 Search filter for Pubmed

("individual patient" OR "individual participant" OR "IPD" OR "patient level data" OR "patient-level data")
AND
("meta-analysis" OR "meta-analyses" OR "systematic review" OR hierarchical OR cluster OR "multi-level" OR "mixed model" OR "mixed effect" OR "mixed effects" OR "random coefficient" OR "random-effects model" OR "random-parameter model")
AND
("survival" OR Cox OR "Royston-Parmar" OR Weibull OR Failure OR Hazard OR hazards OR AFT OR Frailty OR "time-to-event" OR "Kaplan-Meier" OR Gompertz)

1.2 Search Filter for advanced search of Web of Science

(TS=(("individual patient" OR "individual participant" OR "IPD" OR "patient level data" OR patient-level data)
AND
("meta-analysis" OR "meta-analyses" OR "systematic review" OR hierarchical OR cluster OR "multi-level" OR mixed model OR mixed effect OR mixed effects OR random coefficient OR random-effects model OR random-parameter model)
AND
(survival OR Cox OR Royston-Parmar OR Weibull OR Failure OR Hazard OR hazards OR AFT OR Frailty OR time-to-event OR Kaplan-Meier OR Gompertz)))

2 Code used in applied example

This code is also available from `https://github.com/VMTdeJong/Epilepsy`

2.1 The data

```
library(survminer)


# Kaplan meier
km <- survfit(Surv(SEZTIME, SCENS) ~  Drug + Epilepsy, data = epi)
ggsurvplot(km)

# Some new functions
# Center a variable
Center <- function(x, trial.id) {
  for (trial in sort(unique(trial.id)))
  {
    selection.id <- trial.id == trial
    selection <- x[selection.id]
    x[selection.id] <- selection - mean(selection, na.rm = T)
  }
  x
}

# Trial mean of a variable
TrialMean  <- function(x, trial.id) {
  for (trial in sort(unique(trial.id)))
  {
    selection.id <- trial.id == trial
    x[selection.id] <- mean(x[selection.id], na.rm = T)
  }
  x
}

# Computing the centered and trial mean variables
epi$EPTYPE.trialmean  <- TrialMean(epi$EPTYPE,  epi$TRIAL)
epi$EPTYPE.center     <- Center(epi$EPTYPE,  epi$TRIAL)
```

2.2 Model fitting

```
# Some new functions
# Extract the standard error from a model fit.
se <- function(object)
  sqrt(diag(vcov(object)))

# Extract the confidence interval from a coxme fit.
confint.coxme <- function(object, level = .95, digits = 2) {
  z <- qnorm(1 - (1 - level)/2)
  b <- coef(object)
  s <- se(object)

  ci.lb <- b - z * s
  ci.ub <- b + z * s

  out <- data.frame(b, ci.lb, ci.ub, s, exp(b), exp(ci.lb), exp(ci.ub))
```

```
  out <- round(out, digits = digits)
  colnames(out) <- c("coef", "ci.lb(coef)", "ci.ub(coef)", "se(coef)",
                     "exp(coef)", "ci.lb(exp(coef))", "ci.ub(exp(coef))")
  out$`Wald p` <- round(pnorm(b/s, lower.tail = F) * 2, digits + 1)

  out$CI <- paste(out$`ci.lb(exp(coef))`, " to ", out$`ci.ub(exp(coef))`,
                  sep = "", collapse = NULL)
  out
}

# Running the Cox models
library(coxme)
cox.drug.ri.re <- coxme(Surv(SEZTIME, SCENS) ~ DRUG + (1 + DRUG |TRIAL),
                        data = epi)
cox.drug.ri.re.cov <- coxme(Surv(SEZTIME, SCENS)
                            ~ DRUG
                            + (1 + DRUG |TRIAL)
                            + EPTYPE.center
                            + EPTYPE.trialmean
                            + EPTYPE.center : DRUG
                            , data = epi)

# Applying our functions to obtain confidence intervals for the models
confint(cox.drug.ri.re)
confint(cox.drug.ri.re.cov)
```

2.3 Heterogeneity

The function MHRnormal is adapted from Austin PC, Wagner P, Merlo J. The median hazard ratio: a useful measure of variance and general contextual effects in multilevel survival analysis. Stat Med. November 2016. doi:10.1002/sim.7188

```
# Let var.re denote the estimate variance of the random effects,
# following a normal distribution.
MHRnormal <- function(var.re) exp(sqrt(var.re) * qnorm(0.75) * sqrt(2))

# Computing the MHR
MHRnormal(cox.drug.ri.re$vcoef[["TRIAL"]]["DRUG","DRUG"])
```

3 Overview of included articles

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