# **Checklist methods for GALENOS meta-analyses – lsr3**

Produce prediction intervals and show them in forest plot

SS: Prediction intervals were not presented given the small number of studies (as suggested before).

Report τ (estimate of heterogeneity)

SS: Tau-squared is reported along with I-squared in the forest plots and summary of the evidence tables.

Use Hartung-Knapp adjustment for confidence intervals (unless < 5 studies)

SS: Hartung-Knapp was used even if the number of studies <5 (as suggested before). Due to small CIs in some occasions, the adhoc.hakn.ci=”se’ was used throughout (“*use variance correction if HK standard error is smaller than standard error from classic random effects meta-analysis (Knapp and Hartung, 2003*”). Follow-up on 21.12.2023: I did not use HK correction.

For small sample sizes & rare outcomes: Mantel-Haenszel adjustment

SS: Fixed-effects and MH method was used for outcomes deemed as rare events, i.e., mortality and serious adverse events (many 0 event cells). It would be nice if you could check the other outcomes, in case you believe they could be considered rare outcomes.

Follow-up on 19.01.2024: Since there are less than 5 studies for all outcomes, fixed-effects estimates will also be presented in the forest plots for all outcomes.

Contour-enhanced funnel plots (if ≥ 10 studies)

SS: Funnel plots were not drawn as <5 studies available.

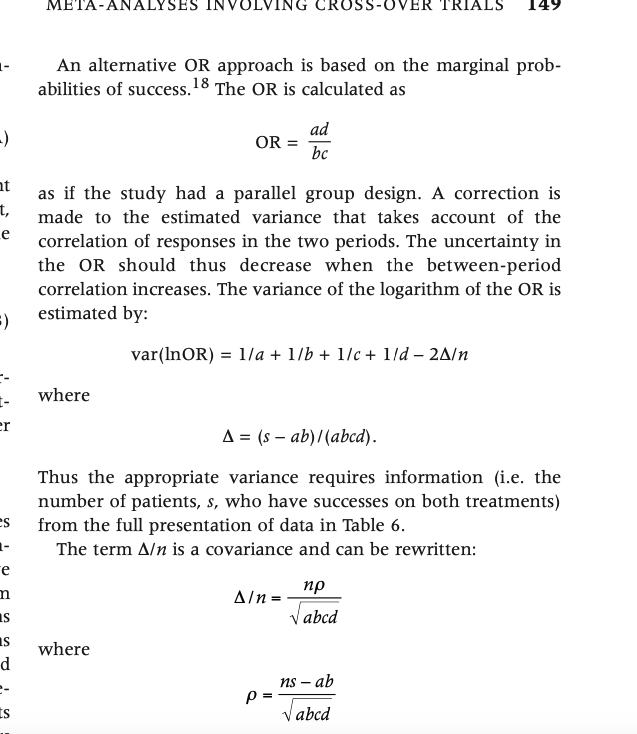
Sensitivity analysis restricting to only low risk of bias studies

SS: This sensitivity analysis was not conducted due to small number of studies AND no study with low risk of bias. (P.S. 4 studies essentially available for the primary outcome, no subgroup or sensitivity analysis was conducted). Follow up on 21.12.2023: No studies can be excluded in sensitivity analysis.

Additional comments

Crossover trials

* Dichotomous outcomes. Crossover studies did not report the first phase. I analysed them according to Elbourne et al. 2002 (<https://academic.oup.com/ije/article/31/1/140/655940?login=false>), and specifically (assuming 0 correlation as it may be appropriate probably for adverse events):



Follow-up on 19.01.2024: A correlation of 0.2 will be used using the above mentioned formula to correct the SE of logOR.

* One crossover study (Tsukada et al., 2023) reported data for a continuous outcome, i.e., QTc interval in msec taking into consideration the crossover periods, i.e., mixed-effect models and used the TE and seTE as reported from that study. However, the study reported multiple time points within a day (not equidistant). Therefore, I calculated the AUC and then divided it by 24 hours in order to have an estimate in msec, which allows the contextualization with the estimates in other studies that measure QTc intervals at single timepoints. For this reason, I used and computed the AUC for the point estimate, as well as the lower and upper boundaries of the 95% CI (subsequently I calculated the SE from them). See below (reported also in data/clean\_data.R)

#Function for calculating AUC

AUC <- function (conc, time)

{

auc <- 0

for (i in 2:(length(time))) {

auc <- auc + (time[i] - time[i - 1]) \* (conc[i] + conc[i - 1])/2

}

auc

}

Follow-up on 19.01.2024: The formula is based on the linear trapezoidal rule, which is classic in calculating AUC esp. in pharmacokinetics. The formula can be found in PMID: 731416.

#Calculate the mean AUC of QTc interval, and the divide by 24 hours in order to have an estimate in msec

qtc\_auc\_mean<-AUC(data\_qtc$TE, data\_qtc$timepoint)/24

#Calculate the lower boundary of the AUC of QTc interval, and the divide by 24 hours in order to have an estimate in msec

qtc\_aub\_lb<-AUC(data\_qtc$lb, data\_qtc$timepoint)/24

#Calculate the upper boundary of the AUC of QTc interval, and the divide by 24 hours in order to have an estimate in msec

qtc\_aub\_ub<-AUC(data\_qtc$ub, data\_qtc$timepoint)/24

qtc\_aub\_se<-(qtc\_aub\_ub-qtc\_aub\_lb)/3.92

* Another crossover study (Hopkins et al 2021) had three phases for 2 doses of ulotaront and one for placebo. I did not know how to analyse this, and thus, I excluded the lower dose of ulotaront. Do you know any other better way for this?

Follow-up on 19.01.2024: The three crossover studies with usable data (Hopkins et al, Tsukada et al, and Szabo et al). were discussed per email with Georgia and Virginia.

Specifically, the approach followed for each study:

1. Hopkins et al (2 two-period crossover cohorts, few data on side-effects) – consider it as a single crossover study since data on placebo are pooled among cohorts, use r=0.2 for dichotomous outcomes as stated above.
2. Szabo et al (3-period crossover, 2 doses of ulotaront and placebo) – try to pool the two doses, use r=0.2 for dichotomous outcomes as stated above.
3. Tsukada et al (3-period crossover, ulotaront, placebo and one ineligible drug) – use QTc intervals as above using the AUC, dichotomous outcomes using r=0.2, no need to correct for multiple controls given that

Action points:

* Consider corrections in SE for three multi-arm studies with 2 comparisons.
* Calculate absolute events to include in the tables.
* Change k and n 🡪 N and n
* Remove diamons when single studies