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Supplementary Material for Meta-Analysis of Clinical Trials with Rare Events

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Meta-analysis of rare event studies has recently become a subject of controversy and debate. We will argue and demonstrate in this paper that the occurrence of zero events in clinical trials or cohort studies, even if zeros occur in both arms (the case of a double-zero trial), is less problematic, at least from a statistical perspective, if the available statistical tools are applied in the appropriate way. In particular, it is neither necessary nor advisable to exclude studies with zero events from the meta–analysis. In terms of statistical tools we will focus here on Mantel-Haenszel techniques, mixed Poisson regression and related regression models.

Key words: Meta-analysis; Rare event analysis; Zero and double-zero studies; Mantel-Haenszel estimation; Poisson regression with random effects;

STATA files

STATA do-file to produce Table 3:

```
*
* Mantel-Haenszel estimation of relative risk evaluating
*treatment and controlling for study (study_seq)
ir mi treatment PersonTime, by(study_seq)
*
```

STATA do-file to produce Table 4:

```
* Poisson regression for treatment effect
* with log-Person-Time as offset
poisson mi treatment, exposure(PersonTime) irr
*
* Poisson regression for treatment effect
* with log-Person-Time as offset and random-study effect (intercept)
mepoisson mi treatment , exposure(PersonTime) || study_seq:, irr
*
* Poisson regression for treatment effect
* with log-Person-Time as offset and random-study effect (intercept)
* and random-study treatment effect
```

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```
mepoisson mi treatment , exposure(PersonTime) || study_seq: treatment, irr
*
```

STATA do-file to produce Table 6:

```
* Zero-inflated Poisson regression with treatment in both parts of the
* model and with log-Person-Time as offset in the Poisson part
zip mi treatment, inflate(treatment) exposure(PersonTime) irr
*
* Zero-inflated Poisson regression with treatment only in the Poisson part
* of the model, constant zero-inflation and with log-Person-Time as offset
* in the Poisson part
zip mi treatment, inflate(_cons) exposure(PersonTime) irr
```

SAS files

SAS `proc nlmixed` to fit ZIP-model with constant inflation and random intercept effect:

```
proc nlmixed data=rs_trial;
parms b0=-10 b1=.2 c0=0 s2u2=0.6;
  x=c0; p0=exp(x)/(1+exp(x)); * p0=0 for Poisson only with random effect;
  eta= b0+b1*treatment+logPT +U2 ;
  lambda=exp(eta);
if mi=0 then
  loglike = log(p0 +(1-p0)*exp(-lambda));
else loglike =
  log(1-p0)+mi*log(lambda)-lambda-lgamma(mi+1);
model mi~general(loglike);
Random U2~N(0,s2u2) subject=study ;
*N([0,0],[s2u1,s1s2,s2u2]);
run;
```

SAS `proc nlmixed` to fit ZIP-model separate random intercept effects for the Poisson and for the zero-inflation part:

```
proc nlmixed data=rs_trial;
parms b0=-10 b1=.2 c0=0 c1=5 s2u2=0.6 s2u1=1;
  x=c0+c1+ U1; p0=exp(x)/(1+exp(x));
  eta= b0+b1*treatment+logPT +U2 ;
  lambda=exp(eta);
if mi=0 then
  loglike = log(p0 +(1-p0)*exp(-lambda));
else loglike =
  log(1-p0)+mi*log(lambda)-lambda-lgamma(mi+1);
model mi~general(loglike);
* here it is possible to include correlated random effects
* by replacing 0 between s2u1 and s2u2 with some parameter
* however this is not possible for this data set due to
* identifiability issues;
Random U1 U2 ~ N([0,0],[s2u1,0,s2u2]) subject=study;
run;
```

