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HTA AND SAFETY

Some results of the ATF / APF Project Group, an ongoing empirical investigation and some personal views

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ATF / APF PROJECT GROUP

- Joint project group "Analysis of adverse events at varying follow-up times in the context of benefit assessments“
  - Working Group Therapeutic Research (ATF) of the German Society for Medical Informatics, Biometrics and Epidemiology (GMDS)
  - Working Group Pharmaceutical Research (APF) of the German Region of the International Biometric Society (IBS-DR)
- Members include statisticians from academia, pharmaceutical industry, BfArM and IQWiG

ATF / APF PROJECT GROUP

- Worked commenced in Autumn 2016
- Series of TC and F2F meetings
- **Output** so far includes
  - **Presentations**
    - GMDS 2017 in Oldenburg
    - Biometric Colloquium 2018 in Frankfurt
  - **Manuscript** (almost final) draft
    - To be submitted to Pharmaceutical Statistics

PRESENTATION BIOMETRIC COLLOQUIUM 2018

On estimands and the analysis of adverse events at varying follow-up times in the benefit assessment of therapies: recommendations by the ATF/APF project group

S. Unkel[1], M. Amiri[2], C. Ose[2], F. Langer[3], G. Skipka[4], N. Benda[5], C. Schwenke[6], D. Knoerzer[7], T. Proctor[8], C. Schmoor[9], J. Beyersmann[10], F. Voss[11], K. Unnebrink[12], F. Leverkus[13], T. Friede[1]

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On estimands and the analysis of adverse events at varying follow-up times in the benefit assessment of therapies

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HIGHLIGHTS

- Estimand framework
- Estimators: event probabilities and group comparisons
- Meta-analysis

ESTIMAND FRAMEWORK

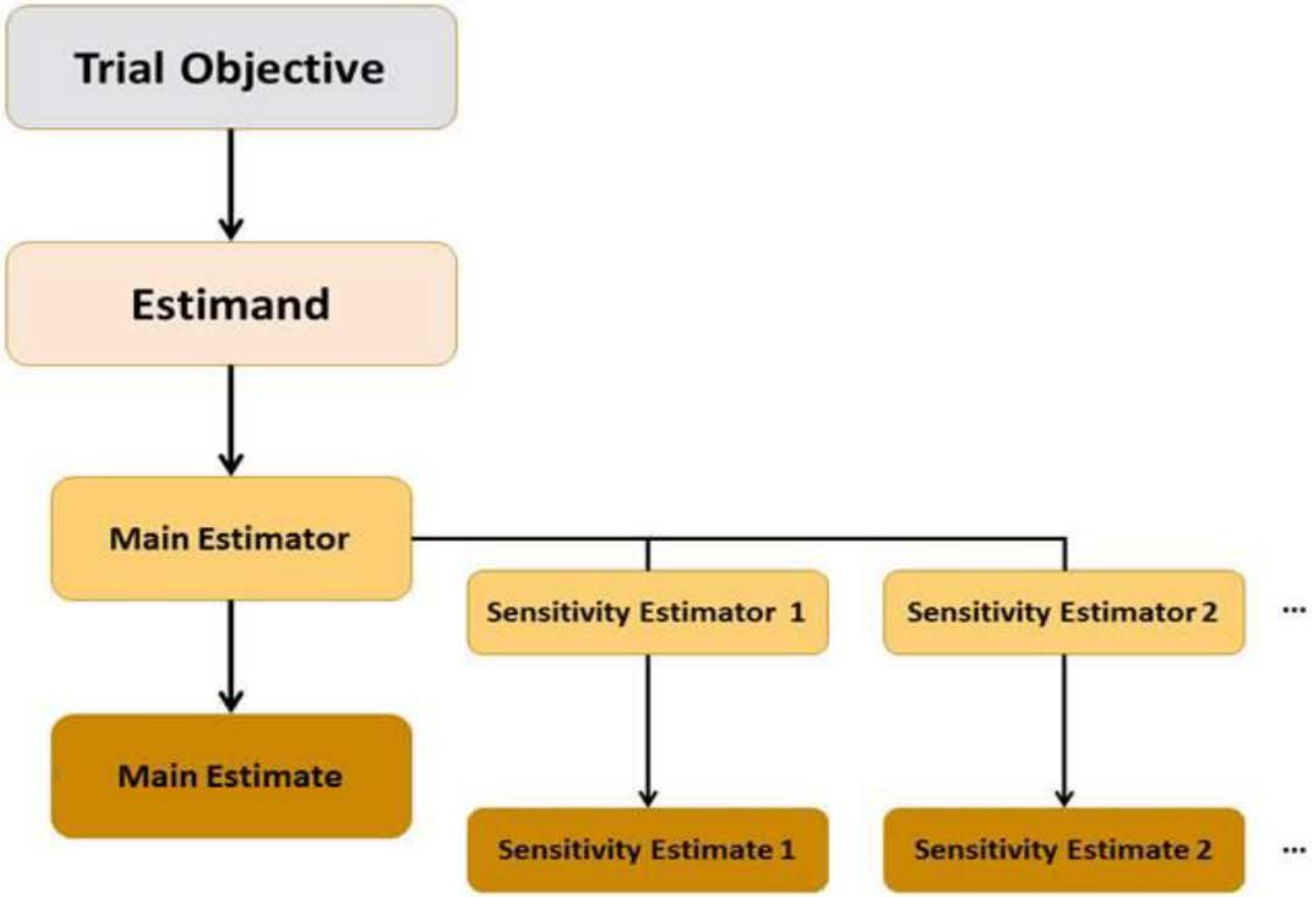

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

DRAFT ICH E9 (R1) addendum

CLASSES OF ESTIMANDS

- **Classes of estimands proposed in the draft ICH E9 (R1) addendum**
  - Treatment policy
  - Composite
  - Hypothetical
  - Principal stratum
  - While on treatment
- **Some criticism from HTA bodies …**

ESTIMATING ADVERSE EVENT PROBABILITIES

- **Incidence proportion** (# patients with AE within time t / n)
  - Underestimates AE probability in the presence of censoring
- **1 - Kaplan-Meier** (censoring competing events)
  - Overestimates AE probability
- **Aalen-Johansen estimator** of the cumulative incidence function
  - generalizes the KM estimator to multiple event types
- **Nelson-Aalen estimator** of the cumulative hazard
  - cumulative nonparametric counterpart of commonly used incidence rate

COMPARING TWO GROUPS

- Risk difference, relative risk or odds ratio of incidence proportion potentially misleading (comparing two quantities that both underestimate the probability of interest)
- Alternatives include
  - Cox proportional hazards regression
  - Fine & Gray proportional subdistribution hazards model
- Model not only the AE but also the censoring competing event

EXAMPLE

Example Study: Cardiac and Cerebrovascular Deaths

- more than twice the number of cardiac and cerebrovascluar deaths in the experimental group compared to control

- safety problem ???

Treatment	n	Cardiac Deaths	Cerebrovascular Deaths
Experimental	3207	24	8
Control	3149	10	2

EXAMPLE

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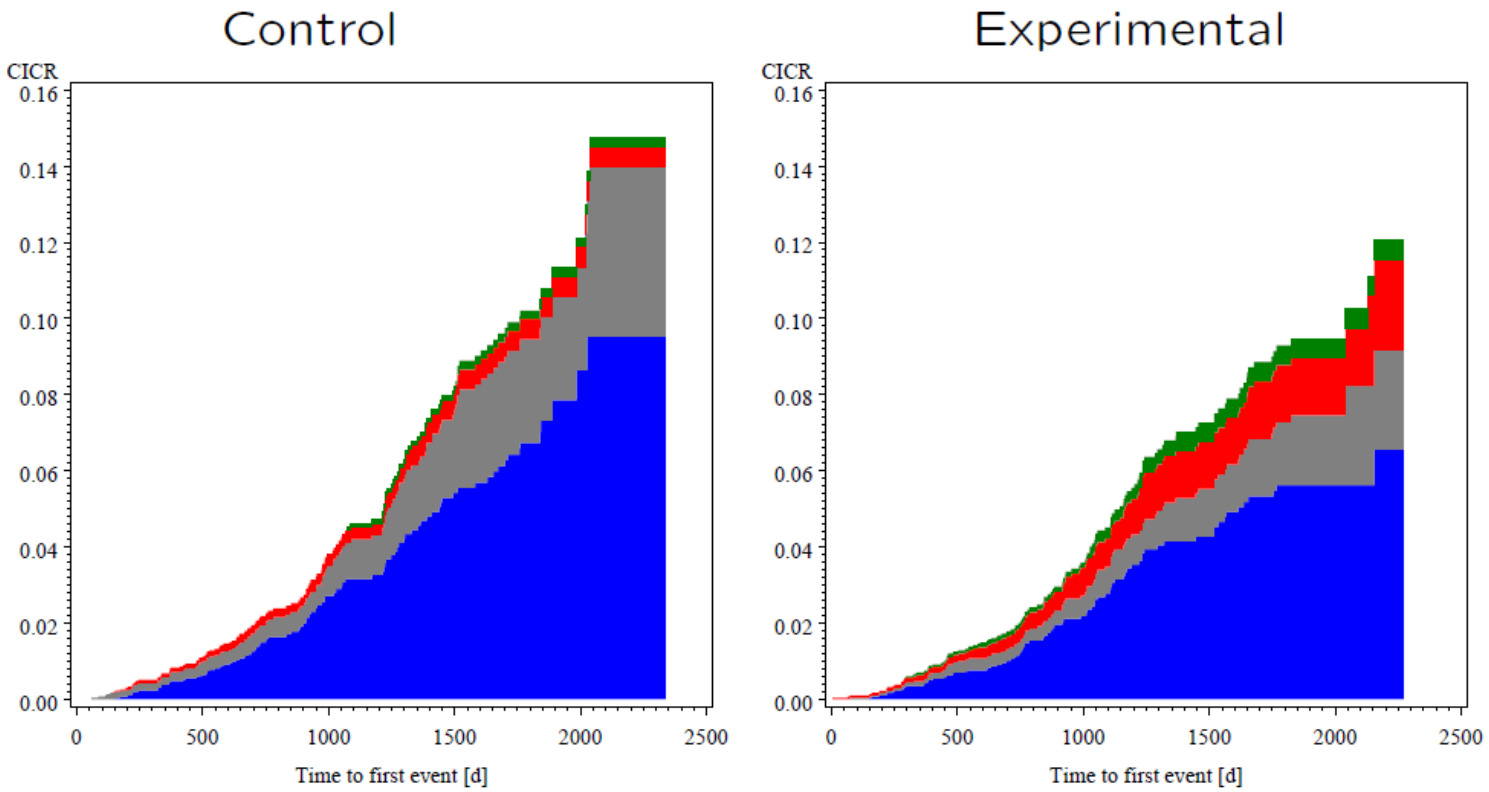
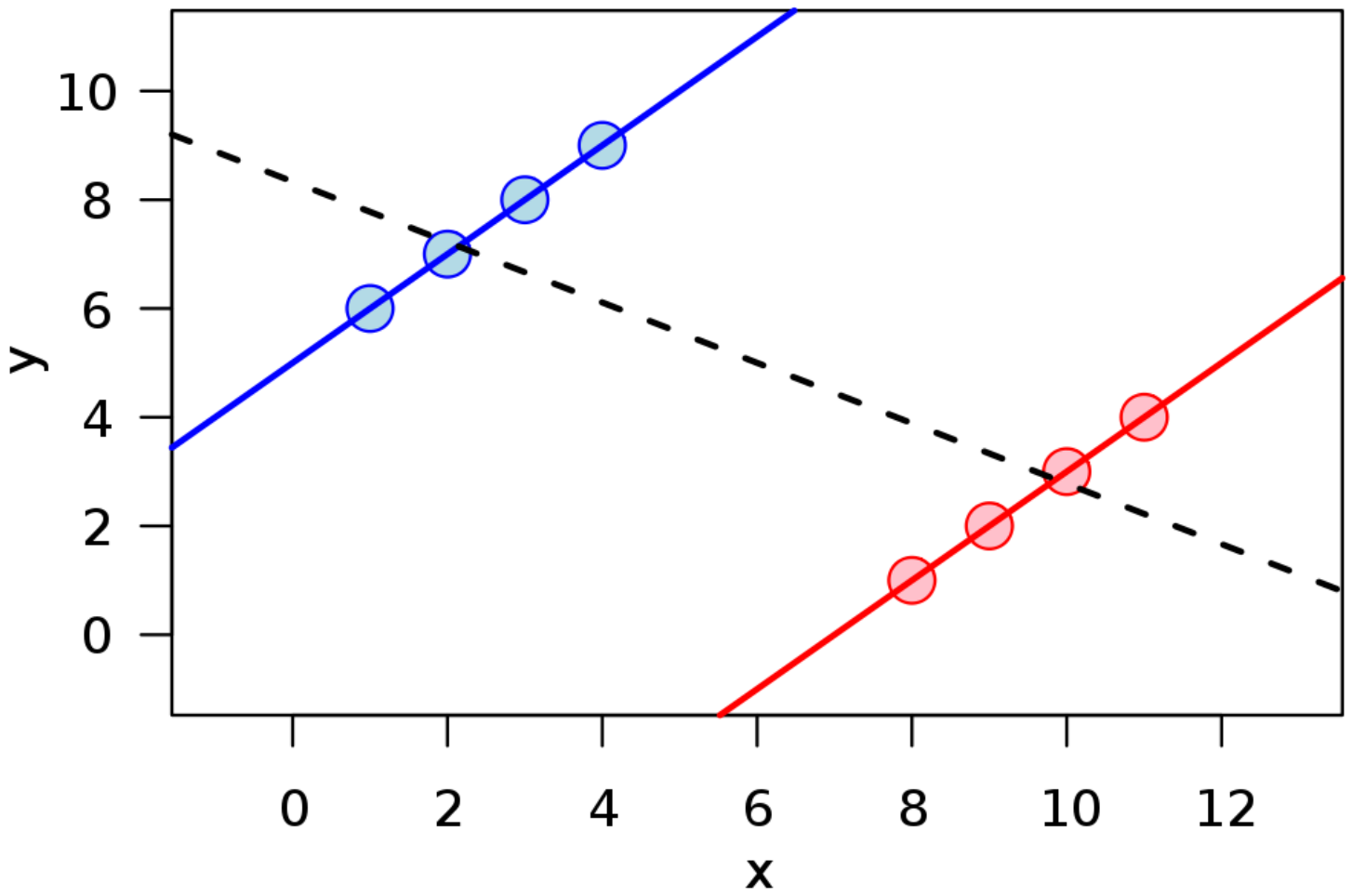
Cumulative Incidence Functions: Causes of Death



cerebrovascular (green), cardiac (red), cancer (blue), other (grey)

SIMPSON‘S PARADOX



http://en.wikipedia.org/wiki/Simpson%27s_paradox

META-ANALYSES OF FEW STUDIES IN THE PRESENCE OF HETEROGENEITY

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- In the context of HTA: Meta-analyses of (very) **few studies** common
- **Extent of between-trial heterogeneity**

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METHODOLOGY

Predicting the extent of heterogeneity in meta-analysis, using empirical data from the *Cochrane Database of Systematic Reviews*

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STANDARD METHOD FAILS

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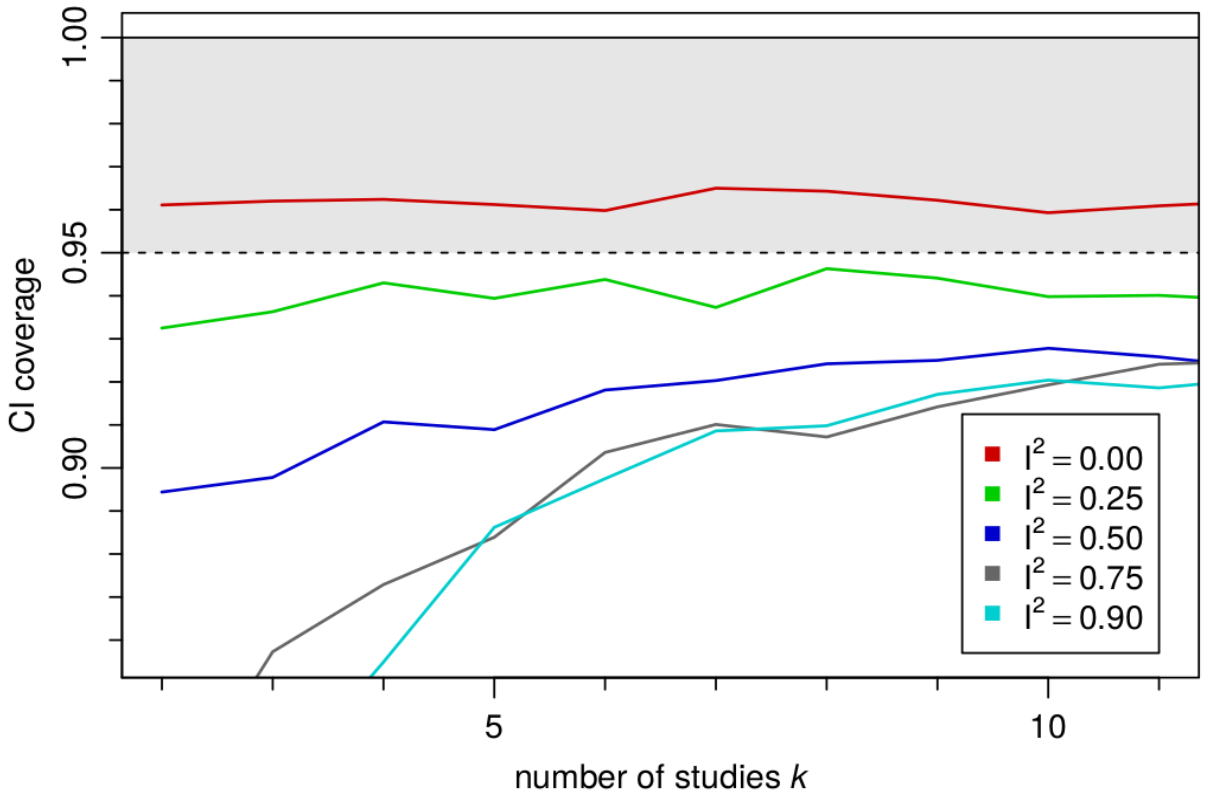
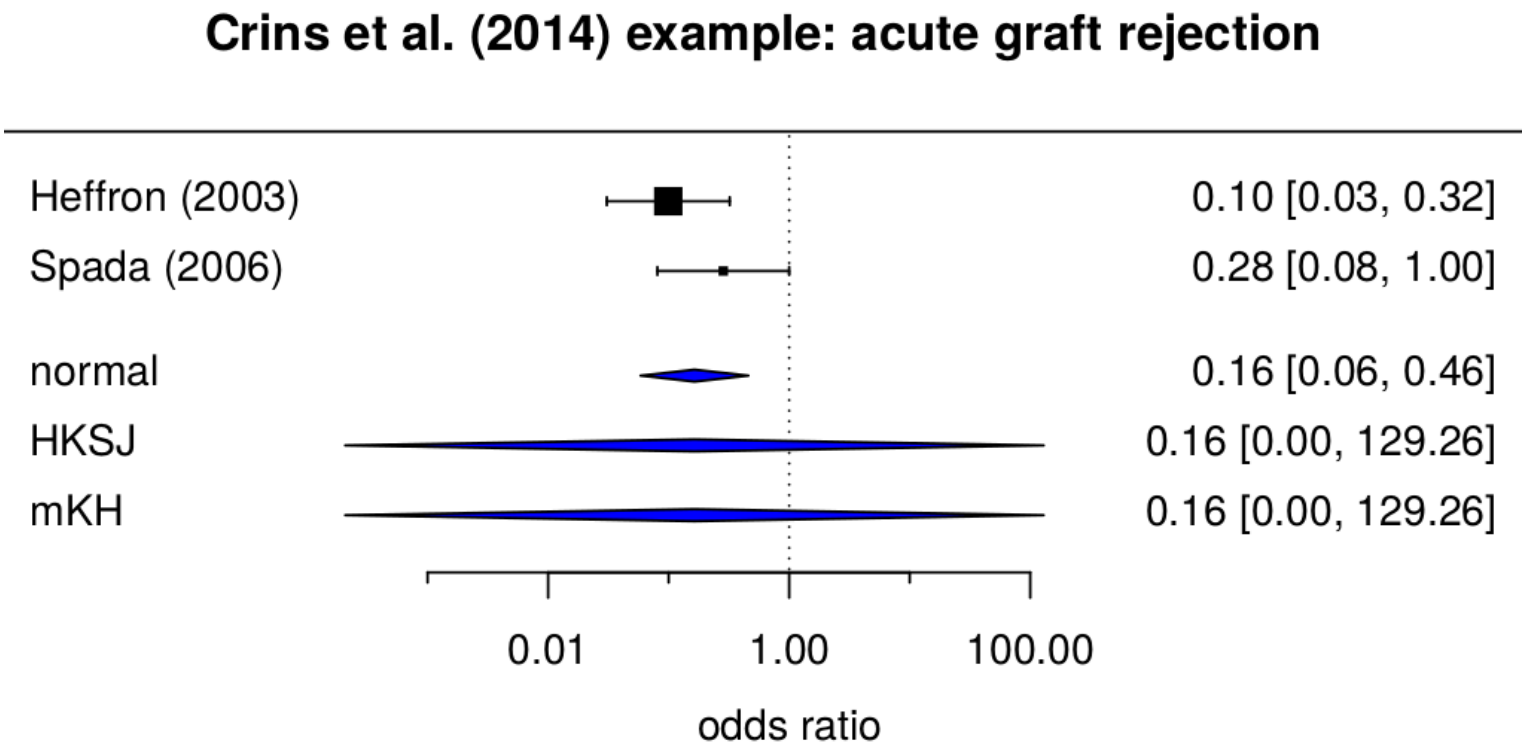
- Standard method (DerSimonian-Laird, DL)
  - Underestimates between-study heterogeneity
  - Fails to account for uncertainty in estimation of heterogeneity



IntHout et al, 2014; Röver et al, 2015

WITH VERY FEW STUDIES: KNAPP-HARTUNG METHOD DOES NOT SOLVE THE PROBLEM

- 97.5% quantile of t-distribution with 1 df = 12.7 !!!
- Example from Friede et al (2017b)



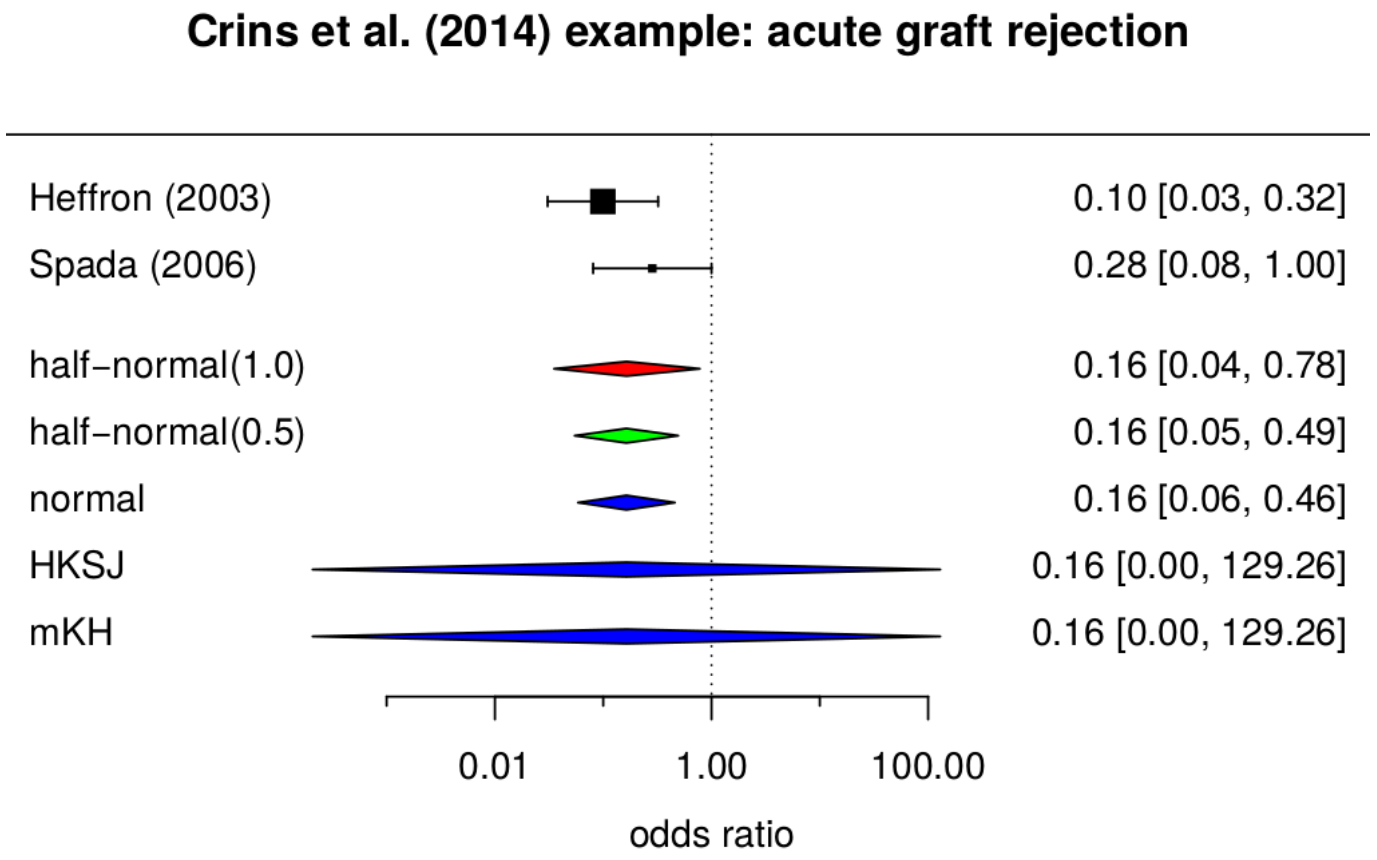
HSJK: Hartung-Knapp-Sidik-Jonkman; mHK: modified Knapp-Hartung; normal: DL

BAYESIAN META-ANALYSIS

- **Idea**: Weakly informative prior on between-trial heterogeneity for meta-analysis with few studies (Spiegelhalter et al, 2004), with uninformative prior on treatment effect
  - Avoids zero estimates of between-trial heterogeneity
  - Accounts for uncertainty in the estimation
- **Easy to compute**
  - Application of DIRECT algorithm (Röver & Friede, 2017a) (which is faster than MCMC sampling and does not require inspection of convergence diagnostics)
  - R package **`bayesmeta`** (available from CRAN)

EXAMPLE REVISITED

- **Bayesian intervals** appear to be a reasonable compromise (supported by simulation studies in e.g. Friede et al, 2017a,b)



META-ANALYSES OF RARE EVENTS

- **Normal approximations** of the distributions of effects, e.g. log HR or log OR, **break down** with low event rates
- Particular problem: studies with no events (**0 – 0 studies**)
- **Proposed solutions**
  - continuity corrections (Bradburn et al. 2007)
  - models of the counts such as binomial distributions fitted using likelihood or Bayesian methods (Spiegelhalter et al. 2004; Böhning et al. 2008; Kuß, 2015)
- **Few studies with rare events**: Bayesian random-effects MA with weakly informative priors for between-study heterogeneity and treatment effects (Günhan et al, in preparation)

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ANALYSIS OF ADVERSE EVENTS WITH VARYING FOLLOW-UP TIMES

Proposal of an empirical investigation

THE COLLABORATORS

- Jan Beyersmann (Ulm)
- Claudia Schmoor (Freiburg)
- Tim Friede (Göttingen)

OBJECTIVES

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- **Compare common** (but biased or incomplete) **analyses of AEs with methods accounting for competing risks in time-to-event studies** and in terms of safety comparison between treatment groups.
- For the present investigation, consider **time-to-first AE** (of a certain kind), observation of which may be precluded by death, some other time-to-event outcome under consideration or limited recording (censoring) of AEs over a restricted period of time.
- The target quantity (estimand) in this investigation is the **probability to acquire such an AE** over the course of time in order to **compare these probabilities between treatment groups**.
- The aim is to **investigate** in a large number of RCTs **whether the different analyses of AEs lead to different decisions** when comparing safety between groups.

PLANNED STATISTICAL ANALYSES

Trial level analyses using the following estimation methods:

- Incidence proportions
- Incidence densities
- Kaplan-Meier
- Incidence densities accounting for competing risks: The incidence density of AE divided by the sum of the incidence density of AE plus the incidence density of competing risks is an estimator of the probability of an AE event.
- Aalen-Johansen estimator of the cumulative event-probability of an AE event

PLANNED STATISTICAL ANALYSES

Trial level analyses

- All safety **comparisons between treatment groups shall be based on confidence intervals using the difference and/or ratio** of the respective estimators.
- Additionally, the logrank test for the comparison of the event-specific hazards and the Gray test for the comparison of the cumulative AE probabilities will be investigated.

PLANNED STATISTICAL ANALYSES

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Meta-analytic approach

- **Assessment of bias** in scatterplots of (AE probability) risks, risk differences and (log) rate ratios obtained by the different methods against Aalen-Johansen approach as gold standard.
- **Comparison of conclusions derived from the various approaches** including statistical significance, clinical relevance and benefit assessment criteria from the various approaches against the Aalen-Johansen approach as gold standard in frequency tables.
- **Assessment of precision**: standard errors / width of confidence intervals against Aalen-Johansen approach as gold standard for those methods with at most small to moderate bias
- More formal assessments in (random effects) **meta-analyses / meta-regressions** will be considered. Assessment and exploration of heterogeneity in (random effects) meta-analyses / meta-regressions (e.g. by indication), if indicated.

REQUESTED (AGGREGATED) DATA

- The **trial level analyses** will be **run within the sponsor company / organization using R or SAS code provided** by the project collaborators.
- Therefore it is not required to release any individual patient data to the project collaborators.
- Only aggregated data summarizing the results of the analyses described above will be shared with the project collaborators.
- Furthermore, some information on the studies including maximum time of AE follow-up, maximum follow-up time for primary efficacy endpoint and therapeutic area is requested.

EXPECTED OUTPUT

- We expect to publish the results of this collaborative project in a peer-reviewed journal.
- The results will also be presented at a conference.

NEXT STEPS

- Commitment by companies / organizations
- Identification of suitable clinical trials
  - Pseudonymization of study codes (confidentiality agreements)
- Development of statistical analysis plan and data structure in collaboration with committed companies / organizations
- Development of R and SAS codes
- Validation and test runs

SOME REFERENCES

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