HTA AND SAFETY

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

Tim Friede
Department of Medical Statistics
University Medical Center Göttingen
Göttingen, Germany
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
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. Unkel¹, M. Amiri², C. Ose², F. Langer³, G. Skipka⁴, N. Benda⁵, C. Schwenke⁶, D. Knoerzer⁷, T. Proctor⁸, C. Schmoor⁹, J. Beyersmann¹⁰, F. Voss¹¹, K. Unnebrink¹², F. Leverkus¹³, T. Friede¹

¹Department of Medical Statistics, University Medical Center Göttingen; ²Center for Clinical Trials, University Hospital Essen; ³Lilly Deutschland GmbH, Bad Homburg; ⁴Institute for Quality and Efficiency in Health Care, Cologne; ⁵Federal Institute for Drugs and Medical Devices, Bonn; ⁶Schwenke Consulting, Berlin; ⁷Roche Pharma AG, Grenzach; ⁸Institute of Medical Biometry and Informatics, Heidelberg University Medical Center; ⁹Clinical Trials Unit, University Medical Center Freiburg; ¹⁰Institute of Statistics, Ulm University; ¹¹Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim; ¹²AbbVie Deutschland GmbH & Co. KG, Ludwigshafen; ¹³Pfizer Deutschland GmbH, Berlin.
On estimands and the analysis of adverse events at varying follow-up times in the benefit assessment of therapies

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

\textsuperscript{1} Department of Medical Statistics, University Medical Center Goettingen, Germany

\textsuperscript{2} Center for Clinical Trials, University Hospital Essen, Germany

\textsuperscript{3} Lilly Deutschland GmbH, Bad Homburg, Germany

\textsuperscript{4} Institute for Quality and Efficiency in Health Care, Cologne, Germany

\textsuperscript{5} Biostatistics and Special Pharmacokinetics Unit
Federal Institute for Drugs and Medical Devices, Bonn, Germany

\textsuperscript{6} Schwenke Consulting: Strategies and Solutions in Statistics (SCO:SSIS)
Berlin, Germany

\textsuperscript{7} Roche Pharma AG, Grenzach, Germany
HIGHLIGHTS

- Estimand framework
- Estimators: event probabilities and group comparisons
- Meta-analysis
Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective
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 Study: Cardiac and Cerebrovascular Deaths

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

- safety problem ???

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Cardiac Deaths</th>
<th>Cerebrovascular Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>3207</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Control</td>
<td>3149</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>
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

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

METHODOLOGY

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

Rebecca M Turner,1* Jonathan Davey,1 Mike J Clarke,2 Simon G Thompson3 and Julian PT Higgins1

1MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK. 2All-Ireland Hub for Trials Methodology Research, Centre for Public Health, Queen’s University Belfast, Northern Ireland and 3Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.

*Corresponding author. MRC Biostatistics Unit, Institute of Public Health, Robinson Way, Cambridge CB2 0SR, UK. E-mail: rebecca.turner@mrc-bsu.cam.ac.uk
STANDARD METHOD FAILS

- 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)

**Crins et al. (2014) example: acute graft rejection**

<table>
<thead>
<tr>
<th>Method</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Heffron (2003)</td>
<td>0.10 [0.03, 0.32]</td>
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<tr>
<td>Spada (2006)</td>
<td>0.28 [0.08, 1.00]</td>
</tr>
<tr>
<td>normal</td>
<td>0.16 [0.06, 0.46]</td>
</tr>
<tr>
<td>HKSJ</td>
<td>0.16 [0.00, 129.26]</td>
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<tr>
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HSJK: Hartung-Knapp-Sidik-Jonkman; mHK: modified Knapp-Hartung; normal: DL
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)

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<tr>
<td>half–normal(1.0)</td>
<td>0.16 [0.04, 0.78]</td>
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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)
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

- 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

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.
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