IQWiG im Dialog 2019

Liefern Kausalmodelle Belege für kausale Zusammenhänge?

– Einführung –

Ralf Bender

Ressort *"Medizinische Biometrie"*

Köln, den 21.06.2019

„Estimands – Nützlich für die Nutzenbewertung?“

10.00 - 10.15	**Begrüßung und Einführung** Ralf Bender, IQWiG
10.15 - 10.45	**Die Bedeutung von Estimands in der Arzneimittelzulassung** Norbert Benda, BfArM, Bonn
10.45 - 11.15	**Kausales Denken und Strategien zur Definition des Behandlungseffekts** Heinz Schmidli, Novartis, Basel
11.15 - 12.00	**Diskussion**
12.00 - 13.00	**Mittagspause**
13.00 - 13.30	**Estimands aus HTA-Sicht – Alter „ITT vs. PP“-Wein in neuen „Strategie“-Schläuchen?** Guido Skipka, IQWiG, Köln
13.30 - 14.00	**Haben wir schon längst aus den Augen verloren, was wir in der Überlebenszeitanalyse schätzen sollten?** Jan Beyersmann, Universität Ulm
14.00 - 14.30	**Welche wissenschaftlichen Fragen können mit Estimands adressiert werden?** Werner Brannath, KKSB, Universität Bremen

Estimands

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 August 2017
EMA/CHMP/ICH/436221/2017
Committee for Human Medicinal Products

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

Step 2b

- 4 Attribute zur Definition von Estimands
- 5 Strategien zur Auswahl eines Estimands

Estimands

Im Rahmen der Nutzenbewertung als primäre Analyse geeignet:

- 1. Treatment-Policy-Strategie
- 2. Composite-Strategie

Nur geeignet für Sensitivitätsanalysen oder ergänzende Analysen:

- 3. Hypothetische Strategie
- 4. Principal-Stratum-Strategie
- 5. While-on-Treatment-Strategie

Estimands

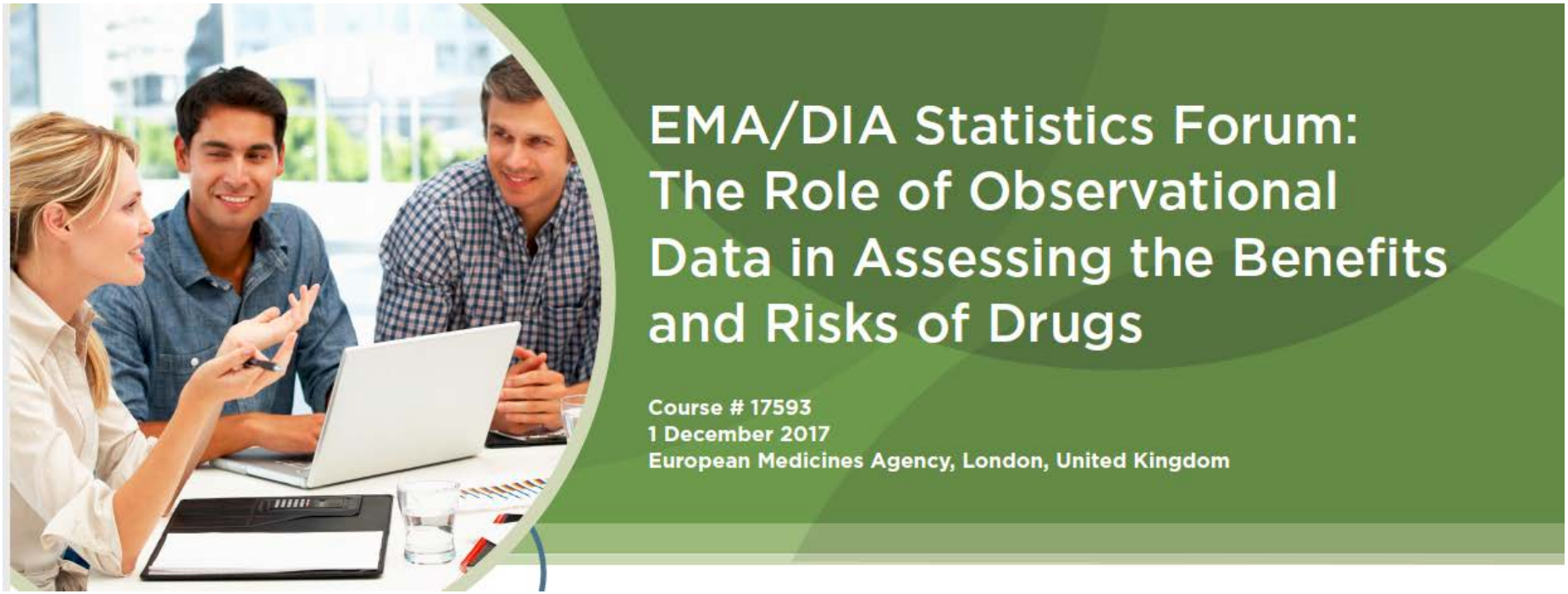
Zitate aus dem ICH E9 (R1) Addendum:

- *"Randomised trials are expected to be **free from baseline confounding** ..."*
- Principal-Stratum-Strategie:

  *"In contrast, estimation of a treatment effect from any analysis where membership is based on intercurrent events on the assigned treatments is **liable to confounding** ..."*
- While-on-Treatment-Strategie:

  *"… so that the treatment effect would be confounded with patient characteristics that affect the subjects' propensity to switch to rescue medication. An appropriate analysis needs to **account for this confounding** …"*

"Real World" Data



U.a.:

Designs und Methoden der kausalen Inferenz für Beobachtungsstudien

Kausalmodelle

- Strukturgleichungsmodelle
- Jöreskog (1978): LISREL

Multivariate Behavioral Research, 1983, 18, 115-126

Notes and Commentary

SOME CAUTIONS CONCERNING THE APPLICATION OF CAUSAL MODELING METHODS

NORMAN CLIFF
University of Southern California

ABSTRACT

Literal acceptance of the results of fitting "causal" models to correlational data can lead to conclusions that are of questionable value. The long-established principles of scientific inference must still be applied. In particular, the possible influence of variables that are not observed must be considered; the well-known difference between correlation and causation is still relevant, even when variables are separated in time; the distinction between measured variables and their theoretical counterparts still exists; and ex post facto analyses are not tests of models. There seems to be some danger of overlooking these principles when complex computer programs are used to analyze correlational data, even though these new methods provide great increases in the rigor with which correlational data can be analyzed.

Kausale Zusammenhänge?

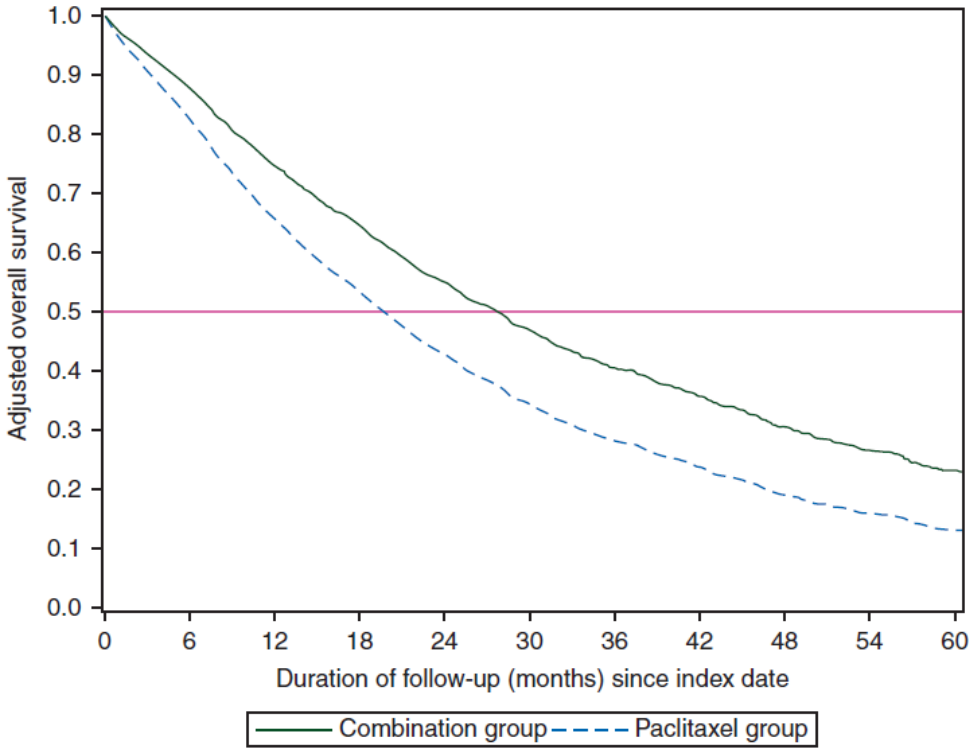
- Liefert die Anwendung von Kausalmodellen Belege für kausale Zusammenhänge?
  - Bei RCTs für Estimands jenseits von ITT?
  - Bei Beobachtungsstudien?
  - Nur unter bestimmten Bedingungen?

Beispiel: Bevacizumab

- "Real-World“-Evidence-Studie
- Epidemiological Strategy & Medical Economics (ESME)-Programm
  - Französisches Netzwerk von Krebszentren
  - 1/3 aller Krebsfälle in Frankreich
- Analyse der HER2-negativen metastatischen Brustkrebspatientinnen bei Paclitaxel-Erstlininientherapie mit (Kombinationsgruppe) oder ohne Bevacizumab (Paclitaxel-Gruppe)
- Vergleich Kombination vs. Paclitaxel
- Endpunkte: Overall Survival, PFS

Delaloge et al. (2016):
Annals of Oncology 27, 1725-1732

Beispiel: Bevacizumab



Adjusted median survival times: 27.7 months (combination); 19.8 months (paclitaxel)

Adjustment for: group, time between metastatic diagnosis and index date, period of care, SBR grade III, age, triple-negative breast cancer status, type of metastases (visceral versus non visceral) and number of sites, time between initial diagnosis and metastatic diagnosis, initial management (adjuvant chemotherapy and/or adjuvant endocrine therapy)

Figure 2. Adjusted overall survival analyses.

In the multivariate analysis, **OS** adjusted on major prognostic factors **was longer for the combination group than for the paclitaxel group**, with the median survival times of 27.7 months (95% CI 25.7–29.0) and 19.8 months (18.3–21.0), respectively (**HR 0.672**; 95% CI **0.601–0.752**)

Conclusion:

- Whether the observed difference is linked to the treatment itself, to prescription bias, or to a mixed effect of both cannot be ascertained
- Based on the present study, **data cannot support** extension of current **use of bevacizumab** in MBC

Beispiel: Bevacizumab

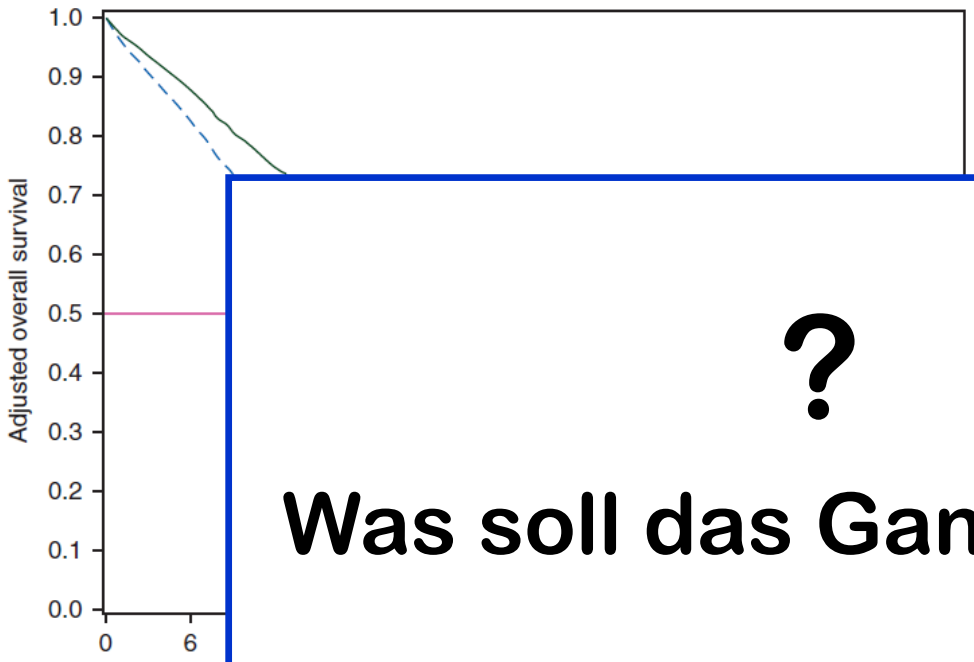


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Figure 2. Adjusted overall survival analyses.

?

Was soll das Ganze dann?

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Moderation: Ralf Bender

10.00 - 10.10	**Begrüßung und Einführung** Ralf Bender, IQWiG
10.10 - 10.50	**Prinzipien und Methoden der kausalen Inferenz** Vanessa Didelez, BIPS, Bremen
10.50 - 11.20	**Randomisierte vs. nicht randomisierte Studien: Evidenz aus der Meta-Epidemiologie** Oliver Kuß, DDZ, Düsseldorf
11.20 - 12.00	**Diskussion**
12.00 - 13.00	**Mittagspause**
13.00 - 13.30	**Kausale Inferenz und Estimands in der Arzneimittelzulassung** Ann-Kristin Leuchs, BfArM, Bonn
13.30 - 13.50	**Real Biased Data? Ein Vergleich von „Real World“ Daten und RCTs in der Telekardiologie** Lisa Schell, IQWiG, Köln
13.50 - 14.30	**Randomisation und kausale Inferenz in klinischen Studien** Martin Schumacher, IMBI, Freiburg
14.30- 15.15	**Diskussion** Diskutant: Armin Koch, Institut für Biometrie, Hannover
15.15 - 16.00	**Ausklang mit Kaffee und Gebäck**