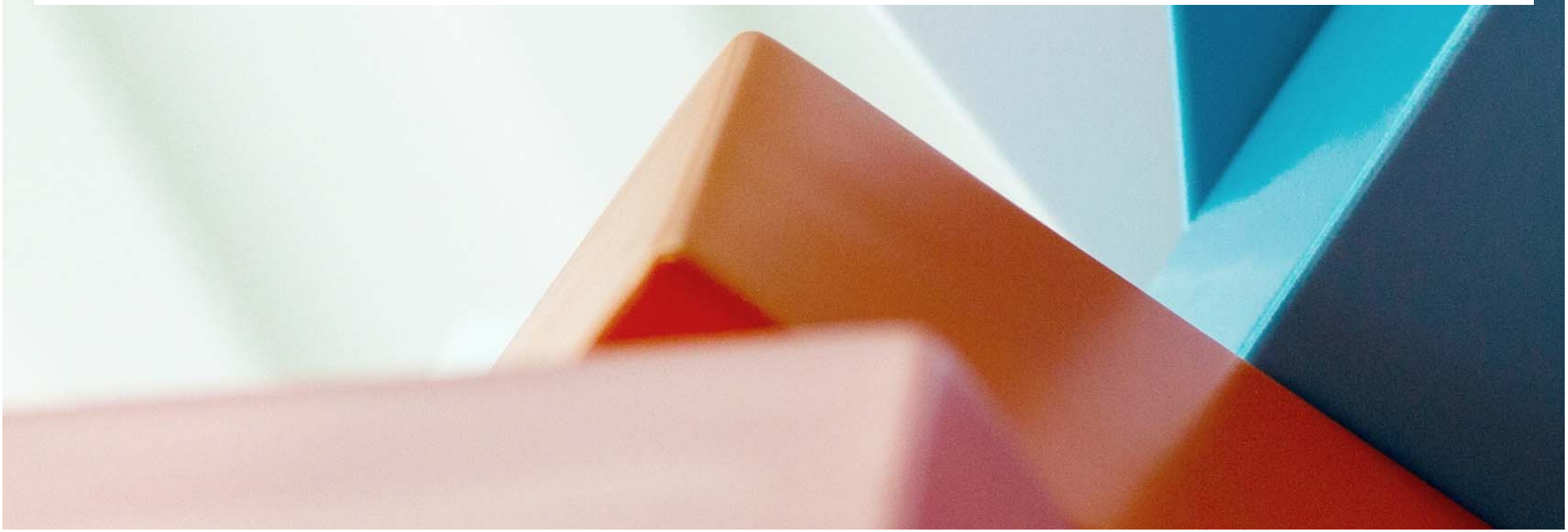
Federal Institute
for Drugs
and Medical Devices

Regulator's experience with estimands

Andreas Brandt



Disclaimer

The views expressed in this presentation are the presenter‘s personal views and not necessarily the views of BfArM or EMA

Introduction

- Draft ICH E9(R1) published September 2017
- ICH E9 (R1) was adopted by CHMP in January 2020 and came into effect on 30 July 2020
- Three areas of regulatory experience with estimands
    - Assessment of marketing authorization applications (MAAs)
    - Scientific advice
    - Guidelines and policies

General observations

- The estimand framework has arrived in the system
- Almost no new (confirmatory) studies planned without mentioning estimands
- Variation in experience and understanding
    - Between companies
    - Between regulators
    - Between therapeutic areas

New borders, or back to the roots?

- Industry perception: new possibilities
  - Addendum allows deviation from ITT analysis!
  - Interest in hypothetical strategies, principal stratum strategy
- Regulator‘s perception: back to the roots
  - Going back to treatment policy where hypothetical was implicitly accepted
- Estimand framework offers new possibilities, but any change from current standards needs to be well justified

During MAA assessment

- Transition phase: many clinical studies supporting marketing authorisation applications were planned before the addendum
- What estimand was actually implicitly targeted?
- Companies define estimand retrospectively
- Regulators raise issues related to targeted estimand and alternatives
- Limitations due to design not aligned to estimand of interest
    - Not all potential issues can be addressed retrospectively in an optimal way

Issues raised

- Is the implicitly targeted estimand the one of primary regulatory interest?
- What intercurrent events occured, what was their frequency?
- Were strategies for handling IEs appropriate?
- Additional sensitivity and supplementary analyses requested
- What is the appropriate estimand to be included in section 5.1 of the Summary of Product Characteristics?

Scientific advice

- Frequent topic
    - If company does not raise it, regulators do
- Estimand framework serves its purpose: provides common language, transparency
- Deficiencies in application of the framework
- Disagreements regarding estimand to be targeted
- Alignment of estimand, design and estimator?

Deficiencies

- Specifiying estimand at late stage of study planning
- Considering estimand as a purely statistical issue
    - Referring to the SAP for estimand
- Mixing definition of estimand and analysis issues
    - Missing data handling!
- Incomplete list of intercurrent events, lack of granularity
- One strategy fits all solutions without justification
- Sample size calculation not aligned to estimand

Disagreements

- What is the estimand of interest (for phase 3)?
- Companies tend to propose hypothetical (or principal stratum) strategy for “wrong“ reasons
  - “Pharmacological effect“ or “effect if the patient follows the instructions on the label“ are usually not the effects of primary regulatory interest in phase 3 (superiority) studies
- Treatment policy strategy for non-inferiority studies
  - Ongoing discussion

Alignment of design and analysis with estimand

- Changes in study design
  - Better follow-up!
- Changes seen for statistical analysis to align estimand and estimator
  - Reference-based (multiple) imputation developing towards new standard missing data approach
  - Changed censoring rules

Disalignment of design and analysis with estimand

- Disalignment of estimand and estimator
  - Missing at Random not appropriate for treatment policy estimand
- Estimand-Estimator gap: No well-established methods for estimation of estimand of interest in some areas
  - Time to event!

Implementation in Guidelines

- Therapeutic area specific guidelines
  - Finalized: Alzheimer‘s disease, Crohn‘s disease, Ulcerative colitis
  - Public consultation: Diabetes mellitus, Chronic non-infectious liver diseases
- To be continued….
  - EMA BCP due to relocation, pandemic changed priorities
- Statistical guidelines: need for alignment with ICH E9(R1)
- New areas: RWE, registries

Learnings from therapeutic area specific GLs

- Separate estimand section and statistical analysis section!
- Estimand section: Joint work of clinicians and statisticians
  - Identify relevant treatments to be compared, intercurrent events in therapeutic area
  - Explain implications of different strategies
  - Clinicians primarily decide on question(s) of interest
- Clinicians usually have clear ideas what they prefer
  - Treatment policy for treatment discontinuation
  - Hypothetical for rescue medication: ‚if patient had not taken rescue, but would have discontinued', or composite strategies

Challenges

- Reluctance to adapt the concept in some therapeutic areas
- Different traditions to handle intercurrent events and missingness in different therapeutic areas
    - Continuous endpoints: Nuisance
    - Time to event, response: strategies already in place!
- Reluctance to change well-established approaches
- Clinicians need to be convinced from added value
    - Specific examples!

Conclusions

- Addendum fulfills its purpose
- Framework provides common language to phrase question of interest in a transparent way
- Better alignment of study objectives with design and analysis
- More experience needed
- Specific problems: estimand/estimator gap requires new thinking and methods
- More collaboration with clinicians needed
- Promising beginning but still a long journey

Acknowledgements

BSWP
Finbarr Leacy
Norbert Benda
Christian Gartner
Maria Grünewald
Armin Koch
Thomas Lang
Christian B. (Kit) Roes (Chair)
Anja Schiel
Steven Teerenstra
Jörg Zinserling (Vice-Chair)
+ additional assessors

BfArM
Ann-Kristin Leuchs
Astrid Schäfer

BSWP secreteriat
Ina-Christine Rondak + colleagues

Thank you very much for your attention!

Contact

Federal Institute for Drugs and Medical Devices
Division Research, Unit Biostatistics and Special Pharmacokinetics
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn

Contact person
Dr. Andreas Brandt
andreas.brandt@bfarm.de
www.bfarm.de
Tel. +49 (0)228 99 307-3797

Federal Institute for Drugs and Medical Devices

Example: Crohn‘s disease

- Estimand section separated from statistical methods!
- Treatment discontinuation
    - Induction of remission: Treatment policy
    - Maintenance of remission: Composite strategy
- Changes in other medications (rescue, change in background, failure to taper steroids)
    - Composite strategy
    - Minor deviation of tapering not considered as intercurrent event
- Secondary objectives with evaluation on continuous scale
    - Treatment effect disregarding steroid intake is usually not of interest when steroid intake has a positive influence on the outcome