Estimands in NASH clinical trials

Peter Mesenbrink PhD

Executive Director Biostatistics, Novartis Pharmaceuticals, Therapeutic Area Head, Transplantation and Hepatology

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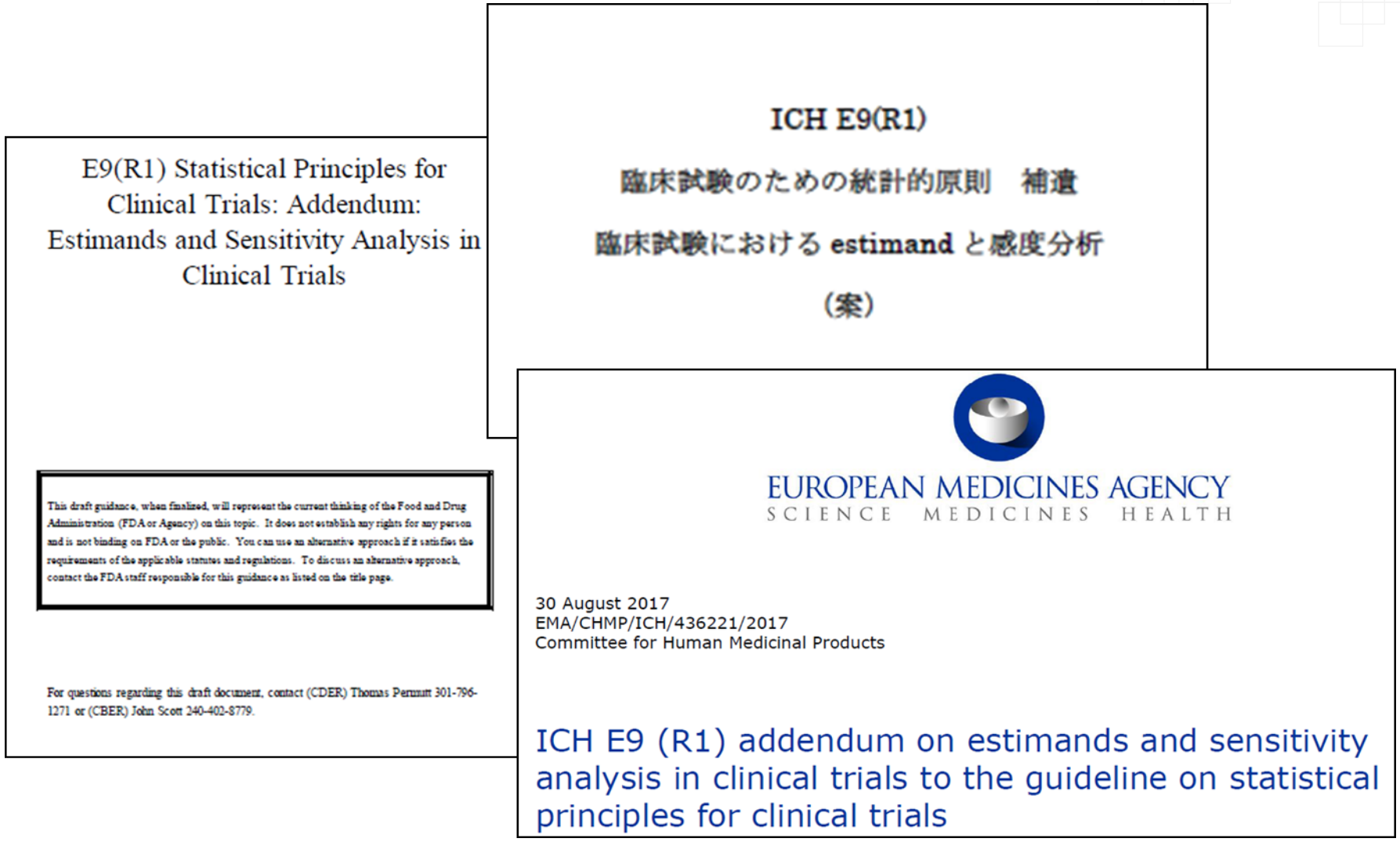
Why are estimands such a hot topic?



So what is an estimand?

- An ***estimand*** precisely defines the treatment effect of interest in a clinical trials
- This may lead to the question: Have we not always defined this in our clinical trials?
- The answer is: YES and NO
- YES: In the clinical trial setting, we define the **population**, **endpoint**, and **treatment comparison** of interest
- NO: We often do not adequately account for the diversity in patient journeys and how they may affect the assessment of clinical benefit of the investigational treatment

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Variability in patient journeys in NASH clinical trials

- Some patients may discontinue the assigned/randomized treatment due to an adverse reaction
- Some patients may start alternative treatment(s) before the endpoint of interest is measured or observed
- Some patients may experience a clinical event before the clinical endpoint of interest is measured or observed (e.g. liver transplant)
- Some patients may die to causes unrelated to the underlying disease before clinical endpoint of interest is measured or observed

These are all *events* that may themselves be related to the disease or the effects of the treatment

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What is the information inherent to such events?

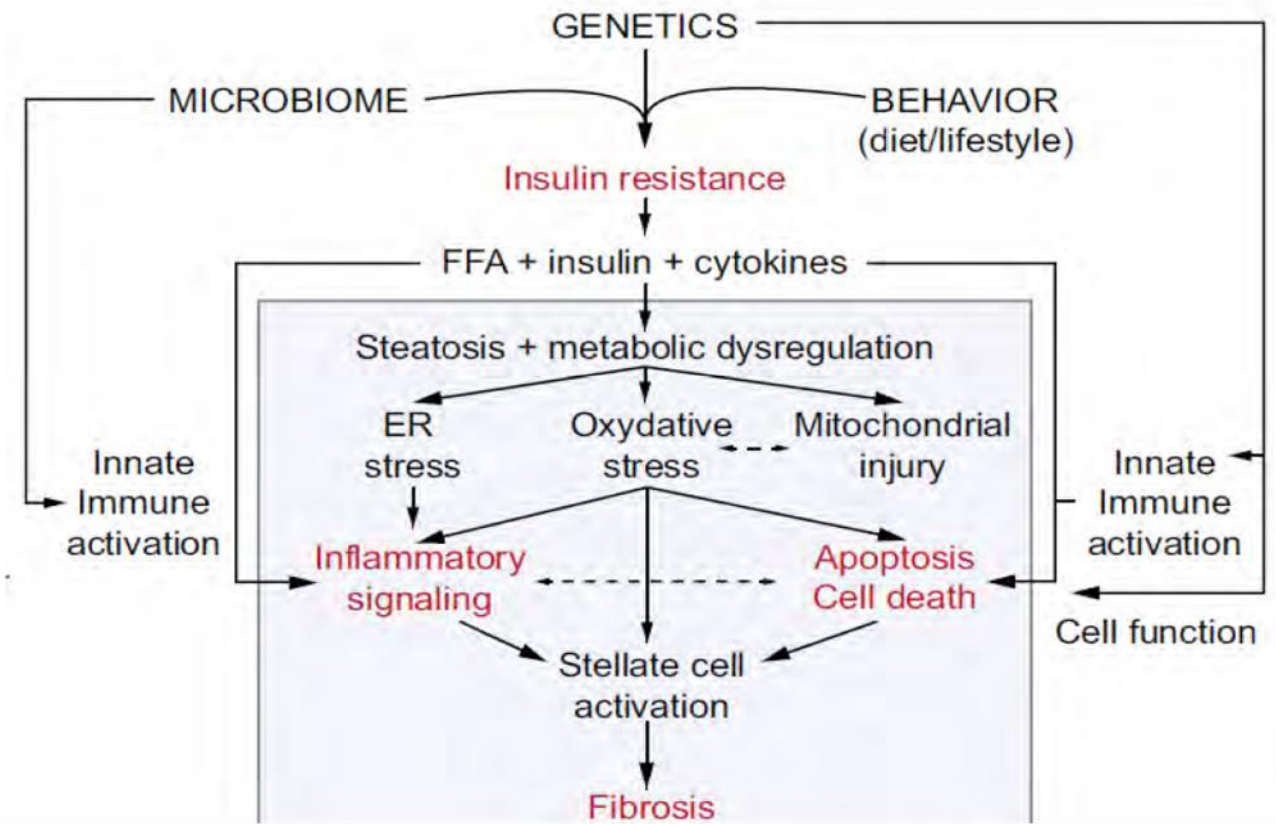
- Some events may have a positive or negative effect on treatment
  - This effect may not be directly captured through the endpoint or clinical outcome of interest
- Some events may impact the interpretation of the endpoint or clinical outcome of interest
  - E.g. measurements after change in T2D medication
- Some events may prevent the measurement of the endpoint or clinical outcome of interest
  - E.g. when patients undergo liver transplantation or they die

What does this mean for the future of clinical trials?

- In the clinical trial setting such events are referred to as intercurrent events
- The draft ICH E9/R1 guidance defines intercurrent events as:
  - "Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation"
- Intercurrent events raise an important question:

> How to define the treatment effect of interest ('estimand') in the study population, for the relevant primary endpoint in the presence of varied intercurrent events?

Why will defining estimands be challenging in NASH?



- NASH is a complex disease with many pharmacological targets and there will not be “one size fits all” solution.

Intercurrent events what do we need to control and what do we need to account for? (1/2)

- In a heterogeneous disease population, there are many factors that can confound determining how truly effective new investigational treatments in NASH can be
- Some of these factors can be potentially be controlled in the short- and mid-term through the design of the clinical trial
  - Diet
  - Exercise
- Other factor related to the co-morbidities of disease may be more difficult to control in the long-term
  - Maintaining stability of concomitant medications used to treat T2DM

Intercurrent events what do we need to control and what do we need to account for? (2/2)

- Should these intercurrent events be accounted for in estimating the treatment effect of NASH therapies on disease improvement?
- Are data collected after intercurrent events have been observed interpretable?
- Should the occurrence of intercurrent all be attributed to what is needed in the treatment of patients and assume that the impact will be the same for all treatment groups?
- There is likely not a “one size fits all” answer

Example: T2DM disease and medication changes

- Patient enters a Phase 3 NASH clinical trial for Drug X with controlled T2DM on a stable dose of liraglutide and continues on that dose for 6 months.
- A worsening of their T2DM requires an increase in the dose of liraglutide
- Points for consideration:
  - Is the intercurrent event the change in T2DM or the worsening of the T2DM?
  - Do we believe that the increase in the dose of liraglutide could have an effect on liver histology efficacy endpoints?
  - If the answer to the first two questions is yes, and the assessment of the effect of Drug X is confounded what should be the estimand of interest

Example: T2DM disease and medication changes How should we handle this situation?

- **Treatment policy:**
  - Treatment effect estimated regardless of the change in T2DM and/or worsening of disease
  - For histology endpoints, the treatment comparison focuses on effects of Drug X+ potential change in T2DM meds over 12/18 months vs. control trt + potential change in T2DM over 12/18 months
- **Hypothetical:**
  - Treatment effect estimated in the hypothetical scenario where no patient changes their T2DM medication over 12/18 months (values of medication changes are assumed missing and a value is imputed based on observed data)
  - If T2DM medication will change in clinical practice would handling the intercurrent event in this way have real world applicability

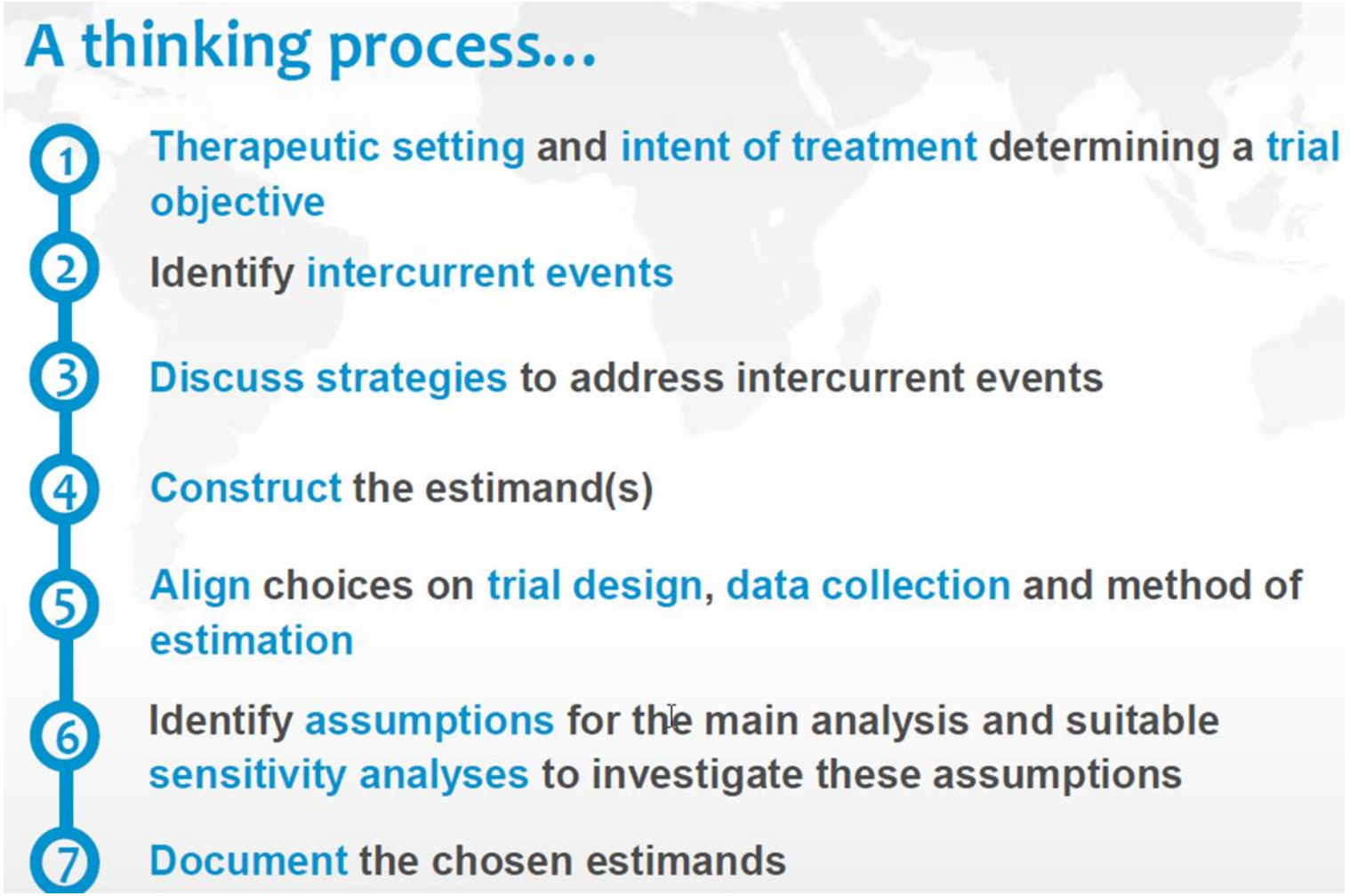
Example: T2DM disease and medication changes How should we handle this situation?

- **Composite:**
  - Treatment effect estimated based on a composite endpoint where patients who change their T2DM medication are considered as non-responders to treatment
  - Change the histology endpoint at 12/18 months which is already considering multiple scenarios to a more complex composite endpoint

Which strategy would you choose?

Likely the strategy may be different depending on the treatment or combination of treatments that are being studied

Thinking process for developing estimands has been recommended as part of ICH E9 (draft) addendum



This is a topic which requires strong collaboration between clinicians, statisticians and regulators

- In current practice, the choice of study design and/or statistical methods often drives (implicitly and unknowingly) which estimand is assessed
- Intercurrent events are often considered as a nuisance which are ‘mislabeled’ as missing data through some statistical approach (the ‘HOW’)
  - E.g. Mulitiple estimation, last-observation carried forward, missing implies failure, etc.
- Revision of the ICH E9 was triggered by concerns that we often focus on the HOW rather than on the WHAT (the ‘estimand’)
- Within the Liver Forum, how do we plan to address?

Liver Forum Working Groups already tackling NASH estimands

- Standard of Care Co-Morbidity Management Working Group (manuscript being developed)
- Standard of care Lifestyle Management Working Group (manuscript near final)
- Estimands in NASH Working Group (First meeting held 13-May, and group is meeting monthly

Members of Estimands in NASH Working Group

Katherine Barradas, Forum for Collaborative Research
Lars Damgaard, Novo Nordisk A/S
Judith Ertle, Boehringer Ingelheim
Douglas Lee, Pfizer, Inc.
Ann-Kristin Leuchs, BfArM
Eduardo Bruno Martins, Allergan
Peter Mesenbrink, Novartis Pharmaceuticals
Veronica Miller, Forum for Collaborative Research
Joachim Musaus, European Medicines Agency
Arun Sanyal, Virginia Commonwealth University
Johannes Taminiau, European Medicines Agency PDCO
Lixia Wang, Intercept Pharmaceuticals

Objectives of Estimands in NASH Working Group

- Identify what are the different types of estimands to be considered in NASH clinical trials (different estimands will be needed for short-term mid-term and long-term endpoints)
- What are the points to consider in determining the best way to handle missing data caused by intercurrent events for the different types of estimands
- What are the intercurrent events that should be collected in NASH clinical trials so that their impact on efficacy can be accounted for?
- Develop a commentary manuscript for a peer-reviewed journal on NASH estimands and what should be considered when developing a new NASH therapy
- Update Liver Forum on progress and importance of this on the future in the design of NASH clinical trials
- Synergize with SoC Liver Forum working groups

Potential intercurrent events for histological endpoints

- Changes in diet
- Changes in exercise
- Changes to dose in T2DM medication
- Changes to dose in lipid lower medications
- Changes to dose of Vitamin E if taken concomitantly
- Stopping of treatment prematurely due to adverse event/reaction
- Decreasing of dose of study treatment due to adverse event/reaction
- Death
- Liver Transplant
- Others?

Potential intercurrent events for long-term clinical outcomes

- Changes in baseline disease co-morbidities (new and/or worsening)
- Changes to doses for concomitant medications to treat disease co-morbidities
- Changes to dose in T2DM medication
- Stopping of treatment prematurely due to adverse event/reaction
- Decreasing of dose of study treatment permanently due to adverse event/reaction
- Liver Transplant
- Changes to standard of care for NASH and adding of a new approved NASH treatment to manage the condition
- Others?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dank je
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Backup slides

Intercurrent events and handling of missing data according to EMA Position Paper (1/2)

The scientific question(s) of interest, i.e., what the trial seeks to address and ultimately, the target of estimation (estimand) should be specified. The trial planning, design, conduct, analysis and interpretation must be aligned with the estimand. It is referred to ICH E9(R1) Draft Addendum on estimands and Sensitivity Analysis in Clinical Trials (EMA/CHMP/ICH/436221/2017).

In order to determine the appropriate strategy for a trial in NASH, a full review of potential intercurrent events is necessary. Relevant intercurrent events expected are those associated with almost all clinical trials, such as treatment discontinuation and use of additional medication. Contrary to other fields of development, the use of rescue medication may – for the time being – not be relevant because no specific treatments are available, but could become more relevant in the future. However, a change in background medication (including excessive life-style changes with weight loss, or uptake of relevant alcohol intake) may relevantly affect the outcome, and may need to be considered.

For the intermediate endpoints, the outcome regardless of the occurrence of intercurrent events is of primary interest (i.e. a treatment policy strategy discussed in the addendum).Therefore, data with regard to the outcomes of interest should be collected independently from the occurrence of an intercurrent event. Data that is nevertheless not collected, for example in case the endpoint is based on liver biopsy and the biopsy is missing or not evaluable, results in a missing data problem with regard to subsequent statistical inference.

Choices made regarding statistical analysis, including the handling of missing data, must be aligned with the target of estimation. Considering a patient with missing data as a non-responder usually results in a conservative estimate of the treatment effect with regard to the question of primary interest, but alternative handling of missing data may also be acceptable (possibly taking occurrence of intercurrent events and the reason for missing data into account). For example, for patients on treatment who refuse biopsy, replacing missing data using multiple imputation based on response

Intercurrent events and handling of missing data according to EMA Position Paper (2/2)

probability of patients still on treatment (possibly taking additional covariates into account) could be considered.

The outcome regardless of occurrence of intercurrent events is also of primary interest for the hard endpoints. Aiming at a complete follow-up for the outcome events is of particular importance as patients that are not completely followed are likely to have a different prognosis than patients who complete the study, implying that censoring such patients is probably informative and leads to bias. As a biopsy during the follow-up is only scheduled if there is a high likelihood of a cirrhosis (e.g. based on surveillance with non-invasive methods such as fibroscan), non-performance of a scheduled biopsy should be considered as an event.