Implementation of the ICH E9 addendum: RATIFY - A case study in hematology

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On behalf of the Hematology Subteam of the Oncology Estimand Working Group.
Estimands in Oncology WG

- initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- main purpose: ensure common understanding and consistent definitions for key estimands in Oncology across industry
- 31 members (14 from Europe and 17 from US) representing 19 companies
- established as EFSPi SIG for Estimands in Oncology in Nov 2018
- close collaboration with regulators from EMA, FDA, China, Taiwan and Canada
Estimands in Oncology WG
Communication plan for 2019

- whitepaper(s) and presentations at statistical and clinical conferences
- plans to further engage with Clinical community beyond ASCO

- **DAGStat (Munich)**: Session with 4 WG talks
- **LiDS (Pittsburgh)**: Session with 3 WG talks + EMA discussant
- **PSI (London)**: 2 WG talks
- **ISCB (Leuven)**: 2 abstracts submitted
- **ASA Biopharm Section Regulatory-Industry Statistics Workshop (Washington)**: Session with 2 WG talks + FDA talk
- **ASCO (Chicago)**: 3 abstracts submitted in collaboration with KOLs and industry clinicians
- **JSM (Denver)**: Session with 4 WG talks + FDA discussant

ASCO: American Society of Clinical Oncology
LiDS: Lifetime Data Science (ASA Section)
Why a dedicated estimand subteam for hematology?

• In hematologic malignancies, treatments are often given in a sequence based on a certain algorithm (e.g. AML: induction, consolidation, maintenance)

• **Stem cell transplantation** (SCT) as option for cure

• Response to treatment is usually assessed using **composite endpoints**
  – Consisting of blood counts, bone marrow aspirate and other components

• Multiple **new classes of drugs** available recently providing new options after treatment failure/ relapse

⇒ **Specific topics requiring dedicated considerations in the estimand framework**
Treatment strategy in newly diagnosed AML patients

1 in patients tolerating chemotherapy (e.g. NCCN guidelines 2.2019)
AML – acute myeloid leukemia
SCT – stem cell transplantation
Motivating example: RATIFY study in AML (Acute Myeloid Leukemia) Stone et al (2017)

- Population: newly diagnosed AML patients
- Primary Objective: to determine if the addition of new drug to induction, consolidation, and maintenance therapy improves Overall Survival (OS)
- Key-secondary endpoint: Event-free survival (EFS)
- Design: Phase 3, randomized, double-blinded, placebo-controlled

RATIFY study: Scientific question

- Does the new drug improve overall survival in the study population when added to induction, consolidation and maintenance?
  - Primary objective describes a treatment sequence consisting of induction, consolidation and maintenance
  - There are different treatment paths like receiving stem cell transplant (SCT)
    - In case of SCT patients did not resume study treatment but have been followed for survival and disease assessments
  - Investigate the treatment strategy including the treatment sequence and optional treatment paths
  ⇒ Should we describe the treatment strategy in another attribute of an estimand?
RATIFY study: Scientific question and Health Authority discussion

- **Treatment strategy**: Implications
  - Maintenance treatment is not part of a standard AML treatment strategy
  - Health authorities wanted to know the contribution of the maintenance treatment to the overall treatment effect
  - Understanding the contribution of maintenance treatment to the overall effect was not part of the underlying scientific question
  - Study was not designed to address the isolated maintenance effect
  - What would agencies expect in order to approve a drug in a modified treatment sequence?
**RATIFY study: Intercurrent events**

- **Example: Stem cell transplantation**
  - SCT is part of standard AML treatment strategy
  - Confounding?
  - RATIFY: Not detailed in objectives how to deal with SCT
    - Patients had to be followed for OS and EFS beyond SCT
  - Overall survival and EFS are assessed regardless of SCT (implicit)
    - SCT ignored as intercurrent event (treatment policy)

⇒ «ignoring SCT» is in line with approach to assess a treatment strategy having SCT as treatment option
RATIFY study: Intercurrent events

• Example: New antineoplastic therapies
  – **Start of a new therapy** means failure of the treatment strategy or study treatment is not tolerated
    – Meaning of new therapies is different situation than SCT
  – Primary estimand overall survival was assessed *regardless of use of new therapies*
    – «Traditional» OS approach as per FDA guideline endpoints in oncology
    – Underlying question: Effect regardless of subsequent therapies
      – Treatment policy approach
      – What does this mean if new efficacious therapies are available or treatment switching?
RATIFY study: **OS analyses** as per study protocol

- **OS primary analysis**
  - Event: death due to any reason; ignore SCT and start of new therapies

- **OS «sensitivity analysis»**
  - **«Per-protocol analysis»**: excluding patients with a broad range of compliance issues (e.g., in-/exclusion criteria, treatment compliance, randomization issues)
    - Includes pre-randomization information but also intercurrent events (e.g., treatment compliance)
    - How to interpret?

- **Secondary objective**
  - **OS censored for SCT**: different estimand
RATIFY study: **OS testing & estimation**

- **RATIFY**
  - Testing: stratified log-rank test
  - Estimation: HR per stratified Cox PH

- **Assumption of proportional hazards**
  - Early deaths due to chemotherapy
  - Plateau at late phase (cure)

- **Consistency of testing and estimation?**
  Rufibach (2019)
# RATIFY: Key OS estimands

<table>
<thead>
<tr>
<th>Scientific question:</th>
<th>Will adding new drug to newly diagnosed AML treatment strategy prolong the time to ...... death regardless of new therapies and SCT</th>
<th>... death regardless of new therapies if no SCT is given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>All randomized patients</td>
<td>All randomized patients</td>
</tr>
<tr>
<td>Variable</td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td>Intercur. event: SCT</td>
<td>Treatment policy</td>
<td>Hypothetical</td>
</tr>
<tr>
<td>Intercur. event: Maintenance, new therapy</td>
<td>Treatment policy</td>
<td>Treatment policy</td>
</tr>
<tr>
<td>Summary measure</td>
<td>HR</td>
<td>HR</td>
</tr>
<tr>
<td>Analysis</td>
<td>Estimate HR using stratified Cox model and reported survival times, stratified log-rank test</td>
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<td>Treatment strategy</td>
<td>Adding new drug to induction, consolidation and maintenance; patients in remission after induction may receive SCT</td>
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</tr>
</tbody>
</table>
Conclusions

• Investigating a **treatment strategy** requires to make this explicit for the estimand definition
  – Consider treatment strategy as another estimand attribute?

• Specify also **intercurrent events that are ignored** for the treatment policy strategy like SCT and start of new therapies

• Be specific about what is assessed in **sensitivity analyses**
  – Move away from what is done always to what makes sense in your setting

• **Testing and estimating** the effect for time to event endpoints
  – Understand potential indication-specific deviations from PH assumption and whether the hazard ratio is the estimator of choice

• Great **opportunity** for **statisticians to guide estimand discussion**!
References

• FDA guidance: *Clinical trial endpoints for the approval of cancer drugs and biologics* (2007, 2018)

• ICH E9 working group (2017). E9 (R1) *Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analysis in Clinical Trials*


Thank you