ICH E9 estimands addendum: Old wine in new bottles or a genuine step forward?

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Methods, Collaboration, and Outreach Group, F. Hoffmann-La Roche, Basel
RSS Manchester local group Graham Dunn Seminar
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Acknowledgments

I borrowed from slides by **Hans-Jochen Weber** & **Renaud Capdeville**.

All our colleagues of the **industry working group on estimands in oncology**.

Regulatory colleagues around the world for regular discussion, their input, and feedback.

The intellectual illness of clinical drug evaluation that I have discussed here can be cured, and it will be cured when we restore intellectual primacy to the questions we ask, not the methods by which we answer them.

Lew Sheiner
American Clinical Pharmacologist

Sheiner (1991)

Agenda

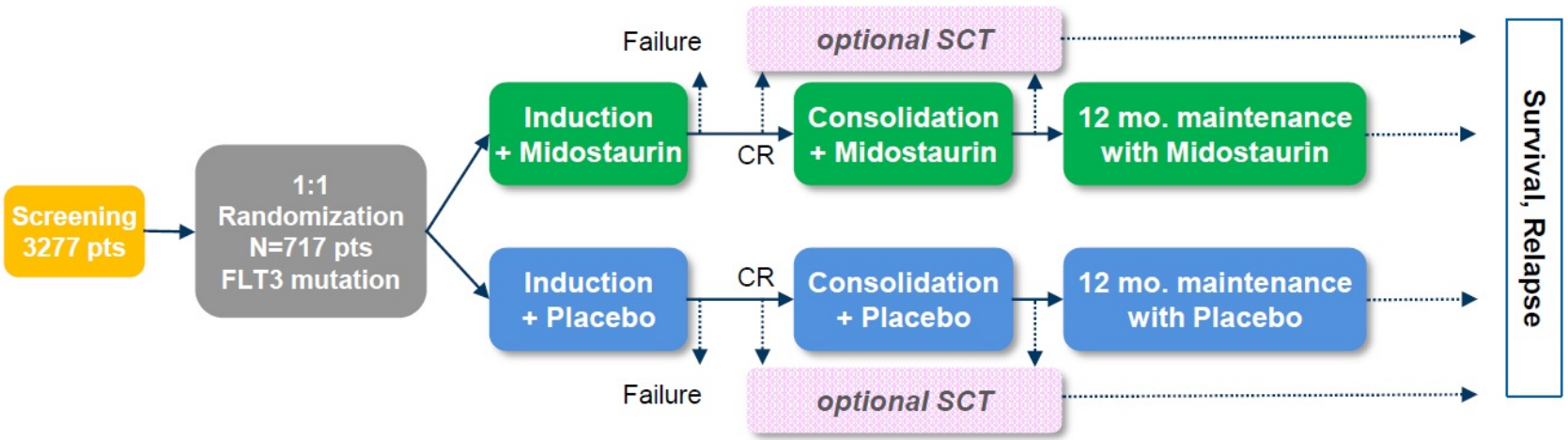
1. Case study: hematology
2. Impact and conclusions
3. Resources
4. Backup: ICH E9(R1) addendum: Why? And what's new?
5. Backup: Industry working group *Estimands in oncology*
6. Hypothetical strategy to address ICEs: application to Covid-19

Agenda

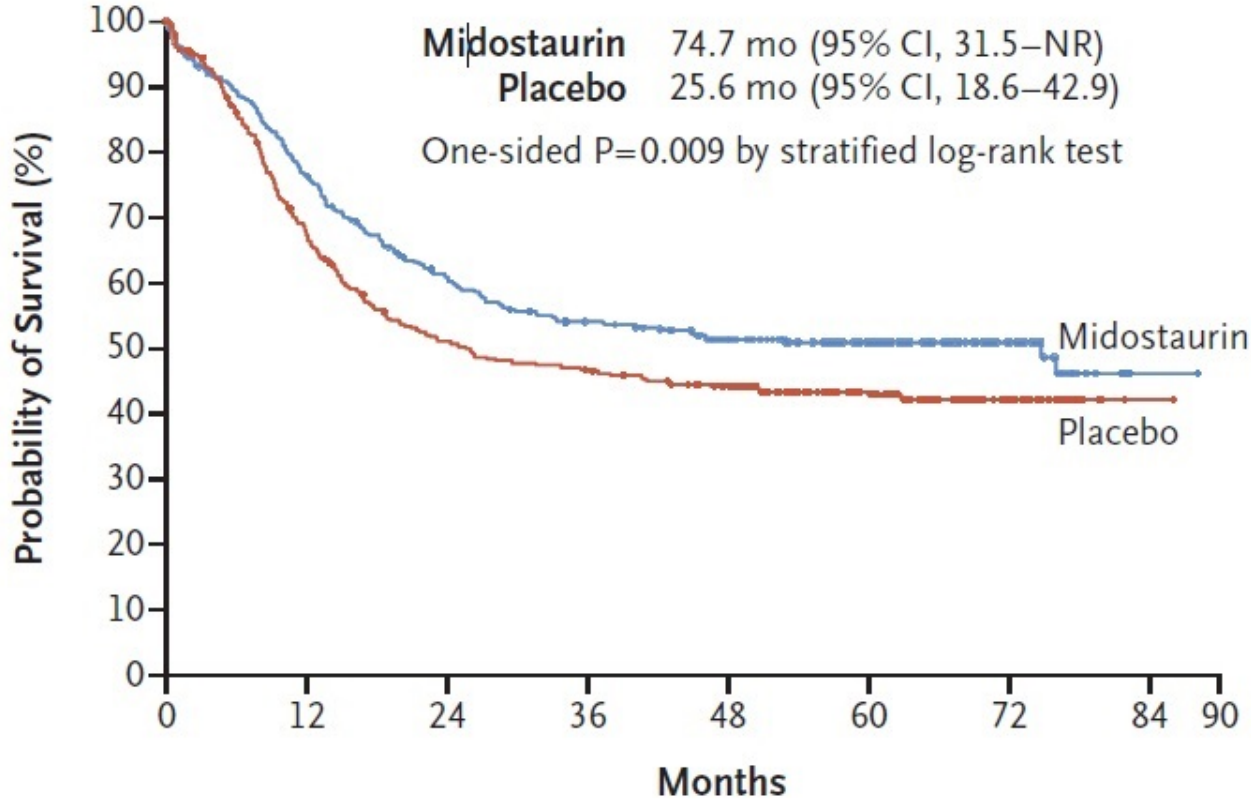
Case study: hematology

Complex treatment strategies in hematology

Ratify trial, Stone *et al.* (2017).



- **Randomized, phase III** double-blind clinical trial.
- **Population**: newly diagnosed AML with a FLT 3 mutation.
- **Comparison**: after completion of primary therapy: Midostaurin vs. placebo.
- **Primary endpoint**: OS.
- **Key secondary endpoint**: EFS.



No. at Risk

Midostaurin	360	269	208	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

OS was significantly longer in the midostaurin group than in the placebo group, as was EFS. [...] In both the primary analysis and an analysis in which **data for patients who underwent transplantation were censored**, *the benefit of midostaurin was consistent across all FLT3 subtypes.*

What question are we asking?

Protocol objective: To determine if the addition of midostaurin to induction, consolidation, and maintenance therapy improves OS in mutant AML patients.

- **Primary analysis**: survival regardless of receiving SCT or maintenance
  $\Rightarrow$ treatment effect = if SCT is part of treatment strategy.
- **Sensitivity analysis**: censoring at transplant $\Rightarrow$ treatment effect = **hypothetical** estimand strategy, if no SCT was given. Estimand is **implicit**!

Completely different clinical questions!

What question are we asking?

Protocol objective: To determine if the addition of midostaurin to induction, consolidation, and maintenance therapy improves OS in mutant AML patients.

What ended up in the label?

- **SmPC**: In combination with **induction** and **consolidation**, and for patients in complete response followed by single agent **maintenance** therapy.
- **USPI**: In combination with standard **induction** and **consolidation**.

AML: treatment strategy based on sequence of

- multiple decision points and
- treatment modalities.

RATIFY:

- Despite detailed description of objectives and treatment in protocol
  $\Rightarrow$ **insufficient alignment** on underlying question of interest.
- SCT:
  - Component of treatment strategy with potential major impact on B/R.
  - Impact not clearly outlined in trial objective.
- Maintenance: Despite explicit inclusion in trial objective $\Rightarrow$ **inconsistently included in approved labels EMA and FDA**.

How would we define the estimand today?

Clinical trial objective: To determine if the addition of midostaurin to induction, consolidation, and maintenance therapy with the option to receive SCT in CR improves OS in mutant AML patients.

Treatment strategy:

- Experimental: Daunorubicin-AraC induction + midostaurin, AraC + midostaurin consolidation in pts with a CR, midostaurin maintenance, option to receive SCT in CR.
- Control: Daunorubicin-AraC induction + placebo, AraC + placebo consolidation in pts with a CR, option to receive SCT in CR.

Population: newly diagnosed AML with a FLT 3 mutation eligible for intensive chemotherapy.

Variable: OS.

Intercurrent events: none left for OS - all integrated in treatment strategy attribute.

Summary measure: hazard ratio.

Complex (multiphase) strategies:

Non-proportional hazards?

Cure?

What do these findings have in common?

They can all be anticipated!

Clear formulation of
clinical trial objective is key.

DOI: 10.1002/pst.2108

MAIN PAPER

WIL

Estimands in hematologic oncology trials

Steven Sun[1] | Hans-Jochen Weber[2] | Emily Butler[3] | Kaspar Rufibach[4] | Satrajit Roychoudhury[5]

Sun *et al.* (2021):

- Three case studies.
- Categorization and discussion of sensitivity and supplementary analyses.
- Templates for protocol and SAP.

Agenda

Impact and conclusions

Impact on data collection and trial planning

- Definition of estimands(s) requires **multi-disciplinary** involvement from **earliest stages** of clinical trial development.
- Estimand **dictates data that need to be collected**.
- Each trial likely to have **multiple estimands** for **multiple stakeholders** $\Rightarrow$ different estimands might require different data!
- Impacts **design of eCRF** or other data collection tools, and monitoring strategy.
- Increased effort in recording reasons underlying **treatment or trial withdrawals, or missing data**.
- Might need to reflect estimand assumptions in **sample size computation**!

Novo Nordisk:

- Focussing on retention, keeping subjects in trial even after discontinuing trial drug.
- Increased completion rates from **90% to 98%** in type 1 diabetes and from **70% to over 90%** in obesity trials.
- Source: `https://www.dsbs.dk/moder/Estimands/HLynggaard.pdf`.

Broader impact

Aligning stakeholder's expectations for target treatment effect **upfront** has potential to give:

- Increased **transparency** and **clarity** with respect to assumptions, missing data, data analysis, and inference.
- Clarity about **added value** of drugs: **meaningful** descriptions of treatment effects for licensing and prescribing decisions.
- Clinical trials with designs that are **aligned to agreed objectives**.
- Clear language to describe and discuss different estimands required by different stakeholders.
- More **predictable** regulatory assessment procedures.
- **Reduction in total number of analyses** (primary + secondary + sensitivity).
- **Shift of resources** from analysis / filing to design.

Reference-based mean imputation for longitudinal data

Estimand framework surfaced for MMRM:

- How intransparent handling of intercurrent events is.
- How intransparent and strong assumptions are in presence of missing data.

Reference-based mean imputation:

- SAS macros existed, developed by LSHTM.
- Little documentation, not validated, etc.

R package rbmi on CRAN: Methodology and R package for reference-based mean imputation:

- **Separate models for imputation and analysis**. Increases transparency.
- Flexible handling of strategies for intercurrent events.
- Methodology published (on arxiv): Wolbers *et al.* (2021), Noci *et al.* (2021).
- Package well documented, formally validated, user-friendly.

Method implemented in Roche **Phase 3 Alzheimer trials** + more to come.

Agenda

Resources

Resources

- ICH E9 addendum, accompanying training material.
- Many publications in **statistical** and **clinical** journals.
- Industry association special interest groups: `www.oncoestimand.org`, Estimands in neuroscience, Estimands implementation working group.

A problem well put is half solved.

John Dewey
American Philosopher and Educator

Design trumps analysis.

Don Rubin, American Statistician

Rubin (2008)

Estimand framework is a genuine step forward!

Thank you for your attention.

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Backup

Agenda

Backup: ICH E9(R1) addendum: Why? And what's new?

ICH E9 draft addendum

ICH E9: "Statistical principles for Clinical Trials."

1998.

Why amend E9?

Lack of alignment between trial objectives and reported effect quantification.

Example: Dapagliflozin

ICH E9 working group toy example, Hemmings (2015).

Dapagliflozin:

- Anti-diabetic therapy to treat hyperglycemia.
- Discussed in 2011 in a public advisory committee at **FDA**.

Trial objective: Assess whether drug works compared to placebo.

Example: Dapagliflozin

	Sponsor	FDA
Proposed analysis	Remove data after rescue.	Use all data, irrespective of rescue.
Implied scientific question	Treatment effect of the initially randomized treatments **had no patient received rescue medication**.	Compare treatment **policies** "dapagliflozin + rescue" vs. "control + rescue".

What is going on?

- Implied objectives / scientific questions of interest **differ for sponsor and regulator**.
- Discussion only at time of **filing**, while this is actually a **design** question!
- Estimand hidden behind the method of estimation / handling of missing data $\Rightarrow$ statistics section defines trial objective!

"How should we handle missing data?" becomes
"What question are we really interested to answer?"

What is a “treatment effect”?

Treatment effect

Not defined in original E9!

How outcome compares to what would have happened to same subject under alternative treatment, e.g. had they

- **not** received treatment,
- received a **different** treatment.

Potential outcome $\Rightarrow$ causal inference!

Estimate average treatment effect from **randomized clinical trial**.

Understanding treatment effects

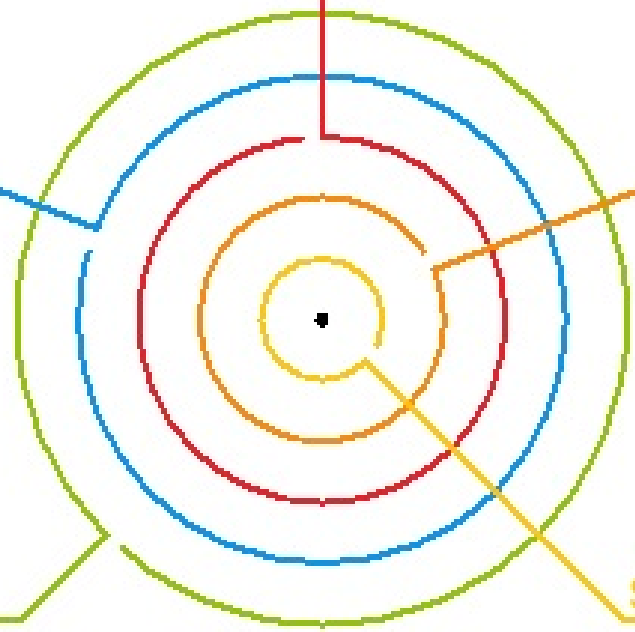
- Multiple definitions of **treatment effect**.
- Different definitions addressing **different scientific questions**.
- Not all equally acceptable for **regulatory decision making**.
- Not all alternatives can be reliably estimated! **Iterative** process of estimand - estimator definition.
- Stakeholders: regulators, HTA / payers, phyisicians, patients $\Rightarrow$ all need to **make decisions**.

How does the addendum fix this?

More precise definition of trial objective
$\Rightarrow$ estimand!

ESTIMAND

TARGET OF ESTIMATION



VARIABLE

The variable (or endpoint) to be obtained for each patient

POPULATION

The population of patients targeted by the clinical question

INTERCURRENT EVENTS

Other intercurrent events (not already addressed by treatment, population, and variable) and how they are addressed

TREATMENT

The treatment condition of interest

SUMMARY

A population-level summary for the variable which provides a basis for treatment comparison

Objective pre- and post-addendum

Pre:

Treatment difference between Gazyva and Rituximab on PFS.

Post:

The trial will compare 6 or 8 21-day cycles obinutuzumab D1 + C1D8, C1D15: 1000mg/m2 flat + site-specific choice of CT (CVP, Benda, CHOP) in induction followed in responding patients by 1000mg flat every 2 months until PD or up to 2y with 6 or 8 21-day cycles rituximab 375mg/m2 D1 + site-specific choice of CT (CVP, Benda, CHOP) in induction followed in responding patients by 375mg/m2 every 2 months until PD or up to 2y in first-line follicular lymphoma patients.

The primary comparison of interest is the hazard ratio of progression-free survival. The primary trial objective is to demonstrate superiority of the experimental over the control treatment.

The primary comparison of progression-free survival will be made regardless of whether patients withdraw from treatment or receive new-anti lymphoma therapy prior to disease progression.

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Estimand follows from precise trial objective (or vice-versa).

Agenda

Backup: Industry working group *Estimands in oncology*

Industry working group on estimands in oncology:

- Founded February 2018.
- Represents industry in Europe and US:
  - European special interest group "Estimands in oncology", sponsored by PSI and EFSPI.
  - ASA scientific working group of ASA biopharmaceutical section.
- **85** members (34 EU + 41 US + 10 Asia) representing **42** companies / institutions.
- Regularly interacts with **8 health authorities**.
- Presentations, webinars, papers.

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ICON
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phastar
Adelphi
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VANDA
Eisai
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BIRMINGHAM CANCER RESEARCH UK CLINICAL TRIALS UNIT
UNIVERSITY OF BIRMINGHAM

Papers

Published:

- Lawrance *et al.* (2020): What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials. link
- Degtyarev *et al.* (2020): Assessing the impact of COVID-19 on the objective and analysis of oncology clinical trials - application of the estimand framework. link
- Casey *et al.* (2021): Estimand framework: Are we asking the right question? A case study in the solid tumor setting. link
- Sun *et al.* (2021): Estimands in Hematology Trials. link
- Manitz *et al.* (2021): Estimands in clinical trials with treatment switching. link
- Bornkamp *et al.* (2021): Principal Stratum Strategy: Potential Role in Drug Development. link (incl. markdown file with code).
- Hampson *et al.* (2021): Comment on FDA paper on *Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes.* link

Link to publications

Task forces

- Estimands engagement.
- Principal stratification in clinical trials.
- Patient-reported outcomes.
- Duration of responses.
- Quantification of follow-up.
- Real-world data and estimands.
- Conditional vs. marginal effects.
- Time to event endpoints with prognostic or predictive biomarker subgroups.
- Early development estimand nexus (EDEN).
- Estimands for safety.

Agenda

Hypothetical strategy to address ICEs: application to Covid-19

Hypothetical estimands

- ICH E9(R1) addendum: acknowledges that some hypothetical scenarios likely of more clinical or regulatory interest than others.
  - CAR-T example: hypothetical estimand less relevant.
- Hypothetical estimands: often **implicitly** targeted by primary analysis in pivotal trials:
  - FDA guideline: Censor PFS at initiation of new anticancer therapy.
  - Routine use of MMRM when "missing data" is present.
- More explicitly: EMA guidelines for Alzheimer and Diabetes.

COVID-19 and estimands

Primary intention of ICH E9 addendum: **alignment** between clinical trial objectives and treatment effect estimation **prior** to start of trial.

ICH E9 addendum specific for **unforeseen** clinical events during trial conduct:

> *Addressing intercurrent events that were not foreseen at the design stage, and are identified during the conduct of the trial, should discuss not only the choices made for the analysis, but the effect on the estimand, that is, on the description of the treatment effect that is being estimated, and the interpretation of the trial results.*

Framework useful to discuss **impact of COVID-19 on ongoing and future trials.**

Assessing impact of COVID-19 on estimand

VARIABLE

The variable (or endpoint) to be obtained for each patient.
Q: Does the current endpoint reflect the treatment effect in the original scientific objective?

POPULATION

The population of patients targeted by the clinical question.
Q: Are the enrolled patients representative of the target population?

INTERCURRENT EVENTS (ICEs)

Other ICEs not already addressed by treatment, population and variable, and how they are handled.
Q: Can the original clinical trial objective be addressed without defining new strategies for ICEs related to COVID-19? (e.g. apply pre-specified rules for discontinuations to discontinuations due to COVID-19)

TREATMENT

The treatment condition of interest.
Q: Are the treatment conditions (e.g. non-compliance, drug discontinuation, subsequent therapy) representative of what would have been administered pre-COVID-19?

SUMMARY

A population-level summary for the variable which provides a basis for treatment comparison.
Q: Is the summary measure still interpretable?

COVID-19 and hypothetical estimand

Ongoing trials: implicitly designed assuming

- **no major disruption of healthcare systems** and
- **absence of highly infectious disease** with severe complications
- for which **no effective therapy** is available.

Trial objectives should relate to world without COVID-19 pandemic.

Intercurrent events primarily caused by disruption of healthcare system or patients' desire to minimize traveling independently of disease or treatment: **hypothetical strategy reasonable**.

Implication on estimation

Change in estimand does not always requires change in analysis.

Estimates from initially planned analysis: may still be sufficiently precise to assess effect in a world without COVID-19 pandemic.

Focus on questions of interest:

- Results in more clarity in interpretation.
- regardless of whether there is a change in analysis.

Degtyarev *et al.* (2020): Assessing the impact of COVID-19 on the objective and analysis of oncology clinical trials - application of the estimand framework. link

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.1.1 (2021-08-10)

Base packages: stats / graphics / grDevices / utils / datasets / methods / base

Other packages:

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