Estimand Framework: A New Lens for Single-Arm Early Clinical Trials in Oncology

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Acknowledgement

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Disclaimer

Stefan Englert is an employee of J&J / Janssen-Cilag GmbH.

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Early development estimand nexus (EDEN)

Established with the goal to implement the ICH-E9 addendum and to reflect on the challenges it presents in early clinical development studies

Such challenges may include:

- absence of control group
- varying dose, but also dosing schedule across treatment arms (a.k.a. cohorts)
- presence of anti-drug antibody (ADA)
- compassionate within-patient dose escalation.

Motivation of the Talk

"Foster the understanding that the Estimand Framework is a core Design Tool that statisticians bring to project discussion to align on the *actual* clinical question of interest"

Background: Estimands in Early Development

Estimands are in regular use for later phase studies
(particularly registrational studies)

Although ICH E9-R1 primarily focuses on randomized clinical trials, it stipulates that the same principles should be applied to all trials

The impression prevails that for early phase studies estimands are not needed or even do not bring any benefit

Background: Phase 1b/2 in clinical oncology

Early indicators of antitumor activity as measured by response rate e.g., ORR or DCR

Phase 1b/2 trials commonly evaluate the effect of a dose (identified as recommended doses for expansion as an outcome of Ph1a) in single arm expansion cohort(s)

Often multiple independent cohorts are run concomitantly to detect a signal of efficacy in different cancer types, lines of therapy, or biomarker defined sub-populations.

The primary goal is to identify early indicators of antitumor activity with binary response type endpoints

Stakeholders

While putting trial participant's interest first and before anything, early phase trials have two key stakeholders:

Sponsor

- to support the internal decision-making process regarding future development

Regulatory bodies

- Phase 1b trials (in Oncology) may become registrational if the positive treatment effect is so outstanding that it can justify
  - breakthrough designation
  - Priority Medicines (PRIME) designation

EDEN is advocating to employ estimand thinking

If this scenario manifests, it would be beneficial to have estimands documented in the protocol.

What is this?

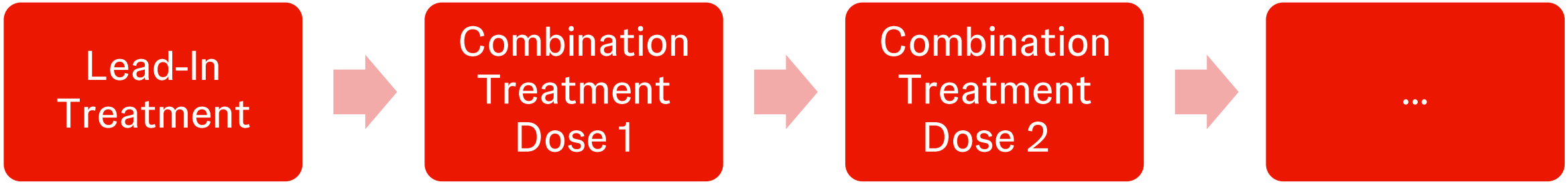
ICH E9(R1)
Training Material

Generic Case Example

1. Therapeutic setting and intent of treatment determining a trial objective
2. Identify intercurrent events
3. Discuss strategies to address intercurrent events
4. Construct the estimand(s)
5. Align choices on trial design, data collection and method of estimation
6. Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions
7. Document the chosen estimands

Identify Intercurrent Events

FIH study, including a lead-in treatment with one of the drugs



Clinicians' proposal: consider data after start of combination treatment and compare proportions of those who responded?

What would you say?

Intercurrent Event of ‘Failure to start combination treatment’

Focus on Clinical Question of Interest

Early Development is a screening process.

The focus of Early Development should be on the treatment regimen that we want to carry forward to Phase 2/3.

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The focus of Early Development should be on the treatment regimen that we want to carry forward to Phase 2/3.

What are we ‘actually’ interested in?

Let’s redefine the question.

Consider Strategies

Intercurrent Event of ‘Failure to start combination treatment’

Treatment Policy Strategy

Phase 1 focus should follow the intent-to-treat principle:

We should look at the treatment effect of the intention to start the combination treatment as defined in the study, regardless of if they actually received the combination treatment or if they ultimately received lead-in only.

Principal Stratum Strategy

Phase 1 should focus on at another target population:

We should focus on the strata of patients that tolerate lead-in treatment.

Clinical Question of Interest

Phase 3 study will also have Lead-In treatment

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Phase 3 study will not have Lead-In treatment

Phase 1 should focus on at another target population:

We should focus on the strata of patients that tolerate lead-in treatment.

Ultimate question was if Phase 3 study participants still receive Lead-In treatment, or was this a safety measure during FIH?

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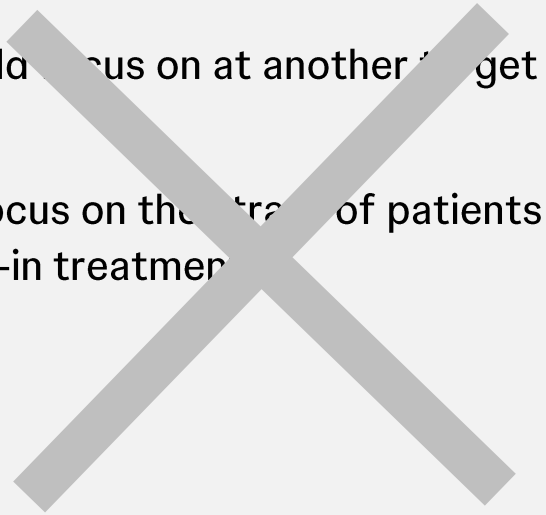

Ultimate question was if Phase 3 study participants still receive Lead-In treatment, or was this a safety measure during FIH?

Estimand Thinking > Estimand Framework

Could our team solve this question? Yes. One e-mail.

Have we used the estimand framework. No (sort of).

At least, in team discussions we've not used any of the terms:

- Intercurrent Event
- Estimand

But:

It gave us the right tools.

ICH E9(R1)
Training Material

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A plea for estimand focused discussions

Early development is not about documenting the treatment effect of interest.

Never stop there.

Always ask yourself:

How does the intercurrent event ‘actually’ effect the interpretation?

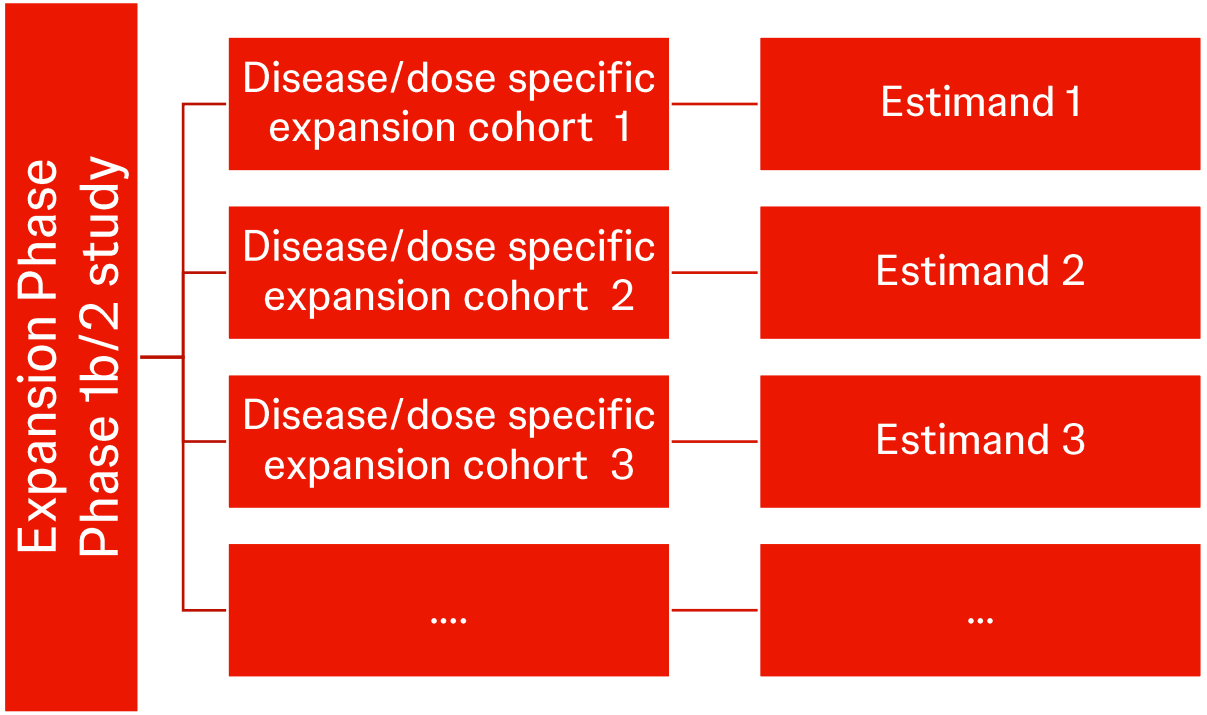
What is the relevance of these estimands regarding the global development program?

Consider all estimand attributes not only intercurrent events.

Specific Recommendations for Estimand Attributes

Target population

- The target population for response evaluation in Phase 1b/2 is typically defined as patients with a specific indication and therapy line.
- Multiple phase 1b/2 expansion cohorts should be viewed as multiple single treatment sub-studies and that estimands should be defined for each such sub-study separately
- We should not intermingle target population with the analysis set



Reference: Englert et al. 2023. Defining estimands for efficacy assessment in single arm phase 1b or phase 2 clinical trials in oncology early development. Pharmaceutical Statistics. Volume 22, Issue 5.

Specific Recommendations for Estimand Attributes

Treatment condition of interest

- The treatment condition attribute of the estimand should reflect the given intervention, combination of interventions, or sequence of interventions, which is administered during the study.
- We recommend using the time of first dose as landmark to define the start of the ‘treatment condition of interest’.
  - We argue that for most single-arm studies the primary research question is about what happens after actual initiation of treatment and not after the intention of treatment.
  - Even in special situations, like in CAR-T therapies, the treatment period for the assessment of efficacy will effectively start at the time of infusion of the CAR-T cells.

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Specific Recommendations for Estimand Attributes

Endpoints & population level summary measure

- We should stop describing ORR or DCR as study endpoints
  - They combine two attributes of the estimand: the endpoint (achieving a response) and the population-level summary measure (proportion of).
- Clear criteria what constitutes a response should be specified
  - Response assessment criteria used,
  - Confirmed vs. unconfirmed
  - Accepting different radio-imaging techniques or not, etc.
- If different clinical questions of interest are related on one endpoint, each clinical question of interest would need its own estimand.

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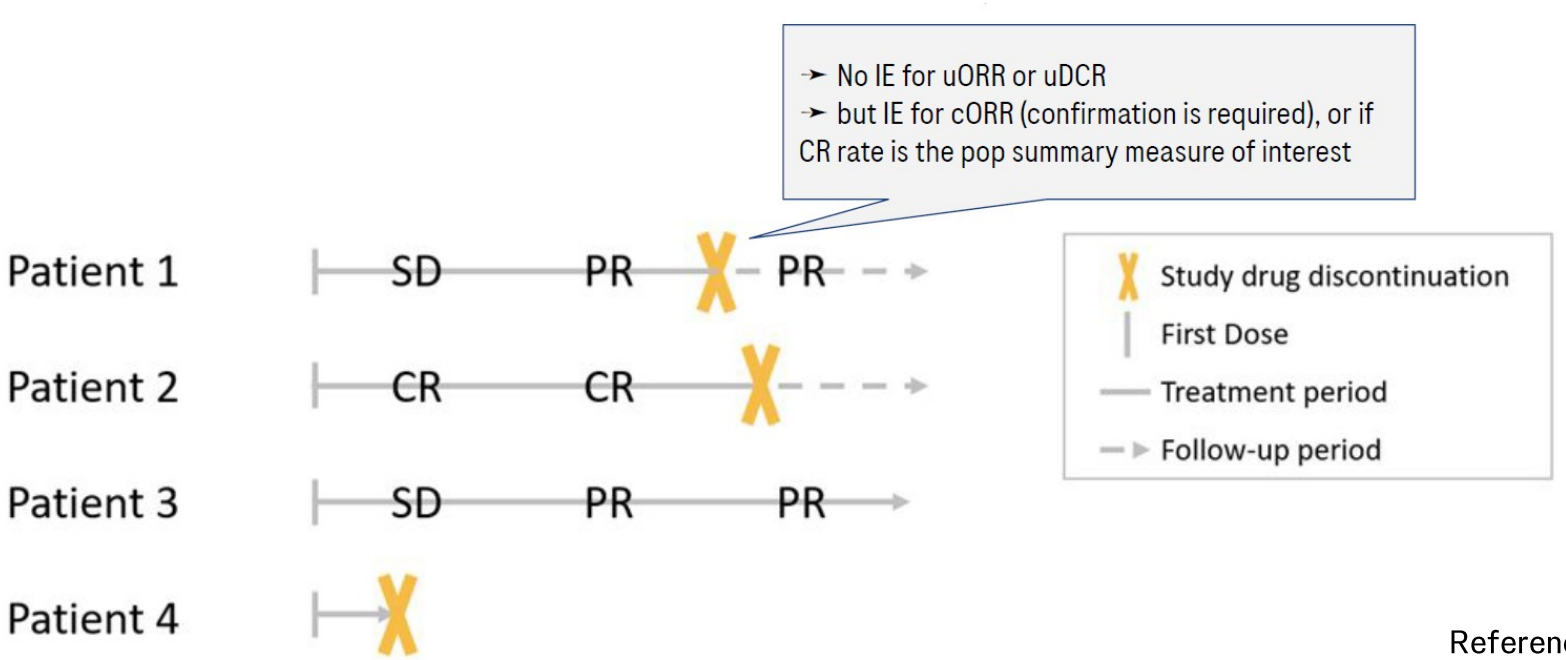
Specific Recommendations for Estimand Attributes

Intercurrent Events

- The ICH E9 (R1) definition of intercurrent events suggests that events occurring after the variable (endpoint) is observed do not qualify anymore.
- Requires a ‘By endpoint/summary measure’ assessment of intercurrent events



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Specific Recommendations for Estimand Attributes

Intercurrent Events

Frequently observed intercurrent events in early oncology trials include

- Treatment discontinuation due to AE
- Subsequent anti-cancer therapy
- Clinical progression
- Death
- Treatment adherence
- Surgery as intercurrent event
- Occurrence of neutralizing ADAs

- Withdrawal from the study
- Concomitant medications and supportive care

Multiple clinical question of interest, potentially study outcome dependent

Use specific categories not 'Treatment Discontinuation'

Pre-specification may be challenging

Not considered intercurrent events

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Pre-specification

In contrast to late clinical development where proof of concept have been established, early phase clinical trials are all about learning, mining, estimating and predicting.

It may not always be possible to prospectively define all the intercurrent events in a Phase 1b study protocol.

The strategy ultimately chosen may depend on other factors, including the outcome of the study itself.

Note on estimators.

Often easy if you have clarity on the clinical question of interest.

The analyzed variable is of binary nature and is summarized as proportions with one- or two-sided confidence intervals.

Pre-specified chosen strategies to handle intercurrent events determine how the numerator and denominator of the proportion will be calculated.

Case Example

Reference: Englert et al. 2023. Defining estimands for efficacy assessment in single arm phase 1b or phase 2 clinical trials in oncology early development. Pharmaceutical Statistics. Volume 22, Issue 5.

Small molecule oral kinase inhibitor: consistent inhibition of the target over time is essential to drive durable efficacy, and treatment interruptions or discontinuations are invariably followed by tumor escape and progression.

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Clinical development interest:

What is the probability of treatment success if we disregard outcomes after events that by themselves indicate treatment failure or intolerability?

Estimand Attribute	Description
Target Population	Patients with a specific cancer indication
Endpoint	Composite binary indicator of treatment success/failure, where success is defined as confirmed response per RECIST v1.1 as assessed by the investigator; [per RECIST v1.1 any response after first observation of radiographical progression is ignored. Thus, a while-on-treatment strategy is implied by this definition for the event of radiographical progression]
Treatment Condition of Interest	Investigational drug at the RDE in combination with standard of care. The treatment period starts at the first dose of study drug.
Population-Level Summary	Probability of treatment success [Measured by, for example, the proportion of subjects with a treatment success]
Intercurrent Events	**ICE Strategy**
Death	Composite, handled as failure. [even if a PR or CR was first confirmed at the same time as the death occurred, the subject will be considered as a non-responder]
Treatment discontinuation due to AE	While-on-treatment, data before event is included to determine success/failure
Subsequent anticancer therapy	

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Monoclonal antibody targeting an immune checkpoint molecule: anticancer immune response that will then persist beyond the duration of therapy.

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Individualized cancer vaccine: induce long-lasting immunologic effects that may synergize with subsequent lines of therapy

Clinical development interest:

What is the probability of treatment success when the current treatment is seen in the broad context of the intended treatment paradigm and where treatment effects after initiation of another treatment are of relevance?

Conclusion

Single-Arm Early Clinical Trials in Oncology

Centered on the clinical questions of interest, estimands will help in streamlining decision-making from early to late clinical development stage

Estimands should be defined with the intention to

- increase transparency in communication and reporting,
- align stat analysis with the clinical question of interest,
- strengthen interdisciplinary dialogue throughout the study.

Do we need Estimands in Early Phase?

Why jeopardize clarity, consistency, and coherency in early phase?

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Why jeopardize clarity, consistency, and coherency in early phase?

A holistic thinking process centered around the clinical question of interest and aligned estimands in early drug development will ensure that optimized estimands are carried forward to later stage studies.

Thank you

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If you have more questions, please contact:
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References

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