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

A plea for introducing estimand focused discussions to early development acknowledging similarities and differences as compared to late development.

Johnson&Johnson

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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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Baseline

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

Baseline

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Do we need Estimands in Early Phase?

It's not the first time I have heard this question. And not only related to early development.

Estimand Addendum Framework

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.

TABLE 1 Illustrations of objectives and corresponding potential ORR estimands with strategies to address ICEs

Objective	To determine the objective response rate of investigational drug regimen in combination with or on top of standard of care in patients with a specific cancer indication.		
Clinical question	What is the probability of treatment success if we discontinue comes after events that indicate treatment intolerability?	What is the probability of treatment success in the current treatment period and line of therapy, with the understanding that the treatment may be discontinued early?	What is the probability of treatment success when the current treatment is seen in the context of the treatment paradigm and effects of another treatment relevance?
Estimand label	Estimand Example	Estimand Example 2	Estimand Example 3
Target population	Patients with a specific		
Endpoint	Composite binary indicator success/failure, where success is RECIST v1.1 as assessed by (per RECIST v1.1 any radiographical progression is ignored while-on-treatment event of radiographical progression)		confirmed response per first observation of implied by this definition for the
Treatment condition(s)	Investigational drug at the RDE in combination		treatment period starts at the first dose of study drug.
Population-level summary	Probability of treatment success (Measured by, e.g.,		of subjects with a treatment success)
	ICE strategy		
ICE (Death)	Composite, handled as failure. (even if a first co		(Disease related death is included as part of RECIST v1.1 definition progression.)
ICE (Treatment discontinuation due to AE)	While-on-treatment, data befo event is included to deter success/failure	nent Policy, data before and after the event is included to determine success/failure	nt Policy, data before and vent is included to cess/failure
ICE (For selected prohibited medications)			Hypot ry. (e.g., multiple can be used to determi lure after the use of the medication)
ICE (Subsequent anticancer therapy)	While-o ent, data before event is included to determine success/f ure		Treatment Policy, data b and after the event is included to determine success/failure

I will not talk about this (sort of)

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

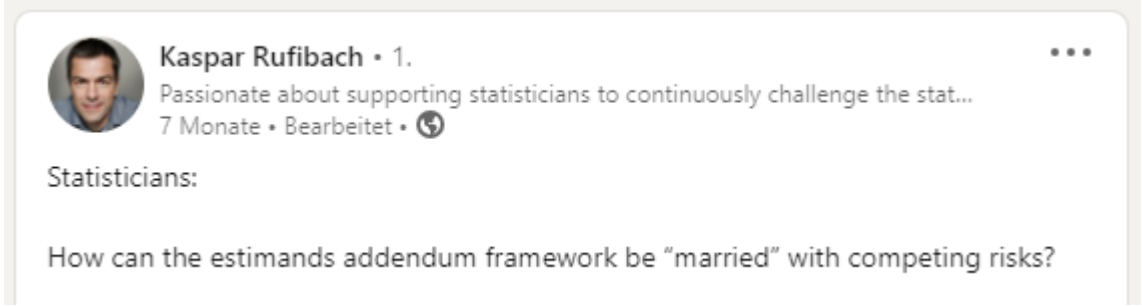
Regulatory bodies

- 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

?

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

Estimand Addendum Framework?



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Statisticians:

How can the estimands addendum framework be “married” with competing risks?

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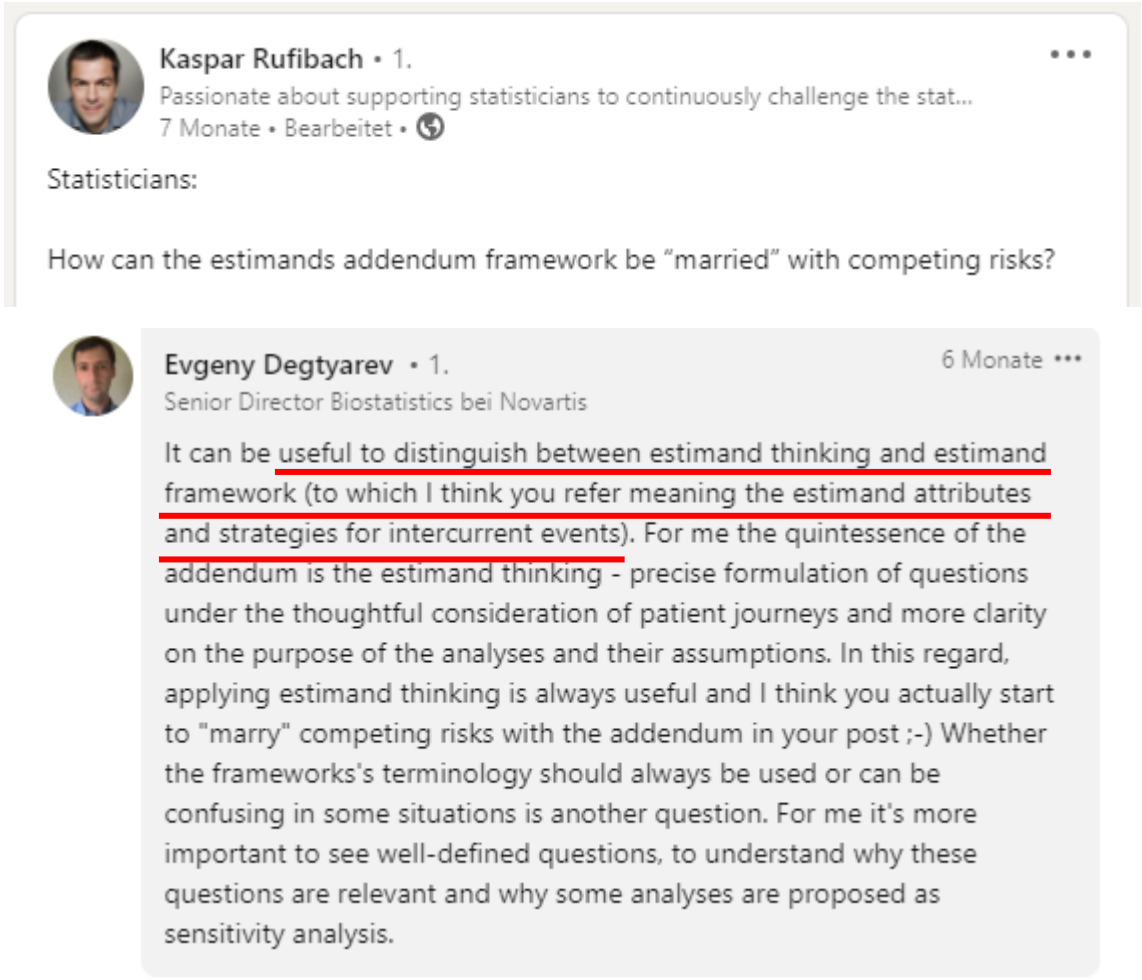

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Statisticians:

How can the estimands addendum framework be “married” with competing risks?

Evgeny Degtyarev • 1.
Senior Director Biostatistics bei Novartis
6 Monate

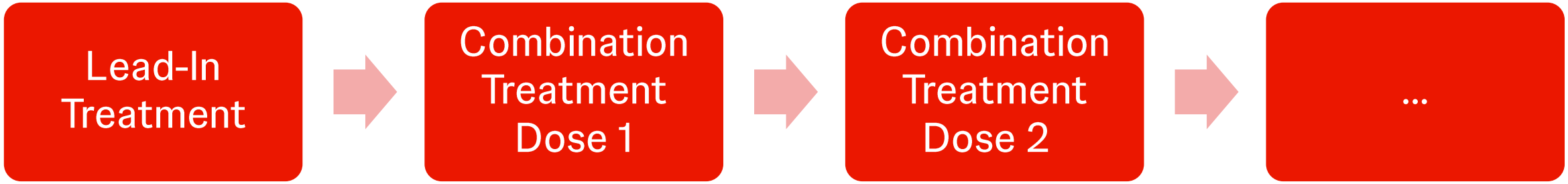
It can be useful to distinguish between estimand thinking and estimand framework (to which I think you refer meaning the estimand attributes and strategies for intercurrent events). For me the quintessence of the addendum is the estimand thinking - precise formulation of questions under the thoughtful consideration of patient journeys and more clarity on the purpose of the analyses and their assumptions. In this regard, applying estimand thinking is always useful and I think you actually start to "marry" competing risks with the addendum in your post ;-) Whether the frameworks's terminology should always be used or can be confusing in some situations is another question. For me it's more important to see well-defined questions, to understand why these questions are relevant and why some analyses are proposed as sensitivity analysis.

What is this?

Let me explain.

Combination Product Development

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?

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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What are we ‘actually’ interested in?

Let’s redefine the question.

Clinical Question of Interest

Phase 3 study will also have Lead-In treatment

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.

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?

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 (also not in this presentation, so far):

- Intercurrent Event
- Estimand

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But:

It gave us the right tools.

Let me explain.

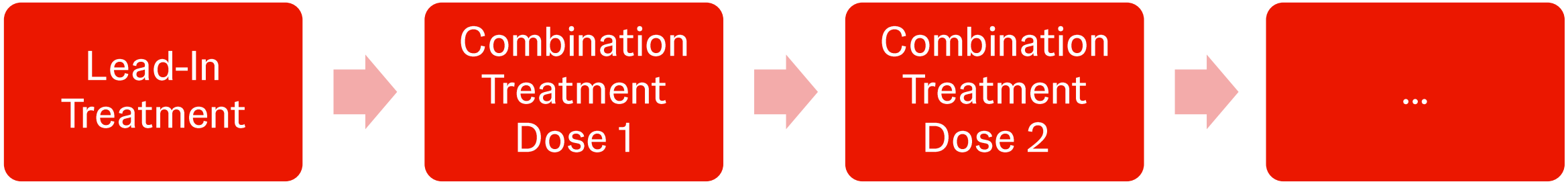
ICH E9(R1)
Training Material

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

Combination Product Development

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



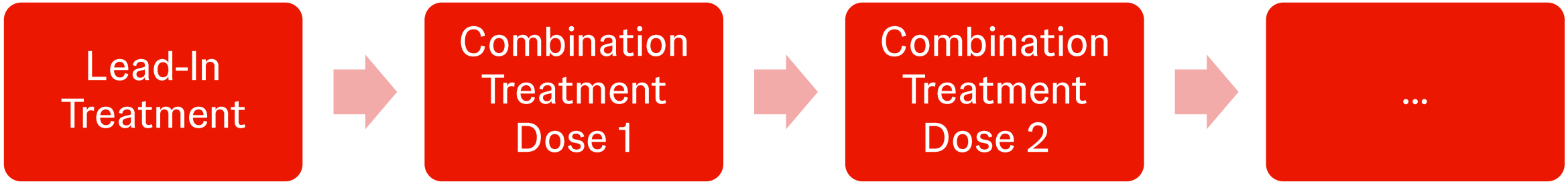
Definition of Intercurrent Event

Intercurrent events Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

Intercurrent events definition, ICH E9(R1) addendum

Identify Intercurrent Events

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



Intercurrent Event of ‘Failure to start combination treatment’

Definition of Estimand

Estimand A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.

Estimand definition, ICH E9(R1) addendum

Consider Strategies

Intercurrent Event of ‘Failure to start combination treatment’

Treatment Policy Strategy

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

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Principal Stratum Strategy

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A plea for estimand focused discussions

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Never stop there.

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Always ask yourself:

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

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

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Estimands are a tool for better clinical development

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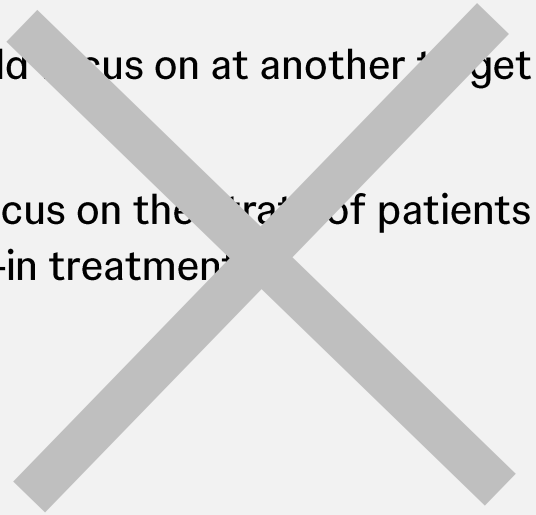

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Further Examples

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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Success prior to start of subsequent anticancer therapy, treatment discontinuation due to AE and use of prohibited medications

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Success prior to start of subsequent anticancer therapy, regardless of treatment discontinuation due to AE and use of prohibited medications

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

Clinical development interest:

Success defined regardless of start of subsequent anticancer therapy and treatment discontinuation due to AE.

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 ICEs determine how the numerator and denominator of the proportion will be calculated.

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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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