Estimands in oncology early clinical development

Assessing the impact of intercurrent events on the dose-toxicity relationship

Stefan Englert

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Early development estimand nexus (EDEN) working group

- Francois Mercier
- Victoria Homer
- Junxian Geng
- Hongtao Zhang
- Natalia Kan-Dobrosky
- Anja Victor

Disclaimer

- Stefan Englert is an employee of Janssen Germany.
- All opinions and information in this presentation are these of the authors and do not necessarily reflect the views of Janssen Germany.

Agenda

01 **Introduction**

02 **Estimands in a dose-escalation study**

03 **Estimator Considerations**

04 **Discussion & Recommendations**

Introduction & Background

- Estimands are in regular use for later phase studies (particularly registrational studies)
- Although E9-R1 primarily focuses on randomized clinical trials, it stipulates that the same principles could be applied to single arm trials, such as dose escalation trials in oncology
- The impression prevails that for early phase studies estimands are not needed or even do not bring any benefit
- EDEN is advocating to employ estimands thinking already in early oncology studies and is giving examples for implementation

Dose escalation studies in oncology

- Aim to
  - characterize the dose-toxicity relationship and determine MTD for a new therapeutic agent
  - select one or several dose(s) (and/or dosing regimen) to test in the next step of drug development
- Phase Ia trials can be thought of as being adaptive (dose escalation and de-escalation) and iterative (multiple cohorts), and will in the following be refer to as adaptive dose escalation (ADE) trials
- The objective is usually set broadly e.g., 'to assess safety and tolerability of the investigational medicinal product' and several estimands will qualify to address it
- In this talk we limit the considerations to the objective of ADE trials to ascertain the MTD.

Clinical Trial Objective and Target of Estimation

Objective

- to determine an MTD

a dose

Target of decision
(not directly estimated)

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Estimated Quantity

- a probability of DLT

a treatment effect

Target of estimation

(subject to estimand's definition)

Intercurrent events in ADE trials

Categories with standard examples

1. Treatment discontinuation before the end of the DLT assessment period for reasons other than toxicity
   - Progression prior to end of DLT observation
2. Treatment discontinuation before the end of the DLT assessment period due to non-DLT AE
   - Grade 2 AE, where Grade 3 event would qualify for DLT
3. Temporary Treatment interruption or dose modification during the DLT assessment period to mitigate toxicity or tolerability issues
   - Investigator suspends drug due to undesirable drug-related events

Illustration of strategies considered

ICE strategy	*Targeted clinical question*
ICE: Treatment discontinuation during the DLT-AP for reasons other than toxicity	
Treatment policy	What is the probability of DLT irrespective of the participant discontinuing treatment?
Composite	What is the probability of DLT or treatment discontinuation?
Hypothetical	What would be the probability of DLT, had treatment discontinuation not occurred?
While on-treatment	What would be the probability of DLT, before treatment discontinuation occurs?
Principal stratum	What would be the probability of DLT, in the strata of participants who would not experience treatment discontinuation?

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ICE strategy	*Targeted clinical question*
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Estimator Considerations

1. Hypothetical strategy
   (implementation challenging in ADE trials given limited sample size and lack of prior data)
   - **TITE-BOIN approach:** the potential outcome of the patient is imputed using single mean imputation based on the elapsed time during the DLT assessment period until an ICE occurs
   - **Bayesian data augmented CRM (DA-CRM)**: uses the Bayesian data augmentation approach to iteratively impute the missing toxicity outcomes and to sample from the resulting posterior distribution

2. While on-treatment strategy
   (will require methods that incorporate a time-to-event element)
   - **TITE-CRM:** a weight is allocated to each patient which is equal to 1 if the participant has a DLT and otherwise which is proportional to the elapsed time during the DLT assessment period
   - **TITE-EWOC**, or exponential working model by Andrillon *et al.* or incorporating pseudo-pharmacokinetic data by Gunhan *et al.*
   - Or treat ICE and DLT as mutually exclusive. In this case, a competing risk approach could also be appropriate.

Illustration of strategies considered

ICE strategy	*Targeted clinical question*	
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Composite	What is the probability of DLT or treatment discontinuation? *The targeted question is not clinically relevant*	Not applicable
Hypothetical	What would be the probability of DLT, had treatment discontinuation not occurred? *The targeted question is clinically relevant*	Possible, e.g. using TITE-BOIN or DA-CRM
While on-treatment	What would be the probability of DLT, before treatment discontinuation occurs? *The targeted question is clinically relevant*	Possible, e.g. using TITE-CRM or TITE-EWOC
Principal stratum	What would be the probability of DLT, in the strata of participants who would not experience treatment discontinuation? *The targeted question is clinically relevant*	Difficult

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Shaded rows identify strategies addressing sensible clinical question and for which estimators are readily available.

Discussion & Recommendation

- Clear specification of estimands in the early phase setting will have positive implications for late phase
- It is crucial to pay more attention to the design and conduct of phase 1 dose escalation trials
- Historically, ICEs in Phase 1a ADE oncology trials have been handled using a replacement approach, i.e., replacing participants who experience the ICE. We recommend against this strategy.
- Strategies addressing sensible clinical question for which estimators are readily available should be used as appropriate
  (or new strategies may be invented that will best fit the clinical setting)

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