



Incorporating estimands in the clinical trial protocol

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Agenda

- **Implementation of E9(R1)**
- **Example**
- **Relation of ICH E9(R1) to E6(R2), E3, E8 and E17**
- **Summary**

Implementation of ICH E9(R1)

- EWG propose to promote specification and possibly discussion of the estimand choice in the trial protocol.
 - ‘Front-end’: new protocol section on Estimands alongside Trial Objectives?
 - Needs to be up-front because of implications on trial design, patient follow-up, data collection etc.
 - ‘Back-end’: Revised section for Statistical Analysis.
- Should the trial protocol include a ‘justification’ for choice of estimand?

Example

1. OBJECTIVES

1.1 Primary

The primary objective of this study is to assess whether NEWDRUG in combination with chemotherapy improves progression-free survival (PFS) compared to chemotherapy alone as first-line therapy for metastatic colorectal cancer (mCRC).

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The primary estimand is the hazard ratio of PFS for all randomized patients regardless of treatment compliance or initiation of any other anticancer therapies for patients with previously untreated mCRC.

or

Example

1. OBJECTIVES

1.1 Primary

The primary objective of this study is to assess whether NEWDRUG in combination with chemotherapy improves progression-free survival (PFS) compared to chemotherapy alone as first-line therapy for metastatic colorectal cancer (mCRC).

The primary estimand for this study is defined by the following 3 components:

- Target population: patients with previously untreated mCRC
- Endpoint: progression-free survival (PFS)
- Measure of intervention effect: Hazard ratio of PFS for all randomized patients regardless of treatment compliance or initiation of any anticancer therapies.

Supportive Estimands

Supportive estimands will be considered, which will have the same endpoint as the primary estimand but the target population and measure of intervention will be defined as in the following table:

Estimand	Target Population	Measure of Intervention:	Details
Primary Estimand	patients with previously untreated mCRC	Hazard ratio of PFS for all randomized patients regardless of treatment compliance and initiation of anticancer therapies	Includes all randomized subjects including measurements collected after treatment discontinuation and after initiation of any anticancer therapy
Supportive Estimand 1	patients with previously untreated mCRC	Hazard ratio of PFS for all randomized patients regardless of treatment compliance but prior to initiation of any anticancer therapy	Includes all randomized subjects including measurements collected after treatment discontinuation but ignores measurements after initiation of another anticancer therapy
Supportive Estimand 2	patients with previously untreated mCRC with Biomarker X at baseline	Hazard ratio of PFS for all randomized patients regardless of treatment compliance or initiation of anticancer therapies for patients identified	Includes all randomized subjects identified with Biomarker X at baseline including measurements collected after treatment discontinuation and after initiation of any anticancer therapy

Impact of E9(1) to protocol writing

- **Synopsis**
 - New section on estimand(s) after objectives.
 - Statistical methods section – how to estimate estimand(s).
- **(new) Estimand Section**
 - Define the chosen estimand(s) of interest
- **Rationale for Study design, doses and control groups**
 - Justify choice of estimand(s)

Impact of E9(1) to protocol writing (cont.)

- **Study Design**

- Address implications of the chosen estimand(s) eg
 - Duration of follow-up

- **Subject enrolment, randomisation, restrictions, discontinuation and WITHDRAWAL**

- Procedures for confounding data eg rescue medication
- Procedures for discontinuation of IP –
 - Will patients be retained in the study for follow-up?
 - If retained in the study will full or partial data collection be required?

Impact of E9(1) to protocol writing (cont.)

- **Study assessments**
 - Impact on chosen estimand(s) on the study assessments
 - Assessments after IP discontinuation
- **Analysis section**
 - The chosen estimand(s) of interest
 - Analysis method(s) to estimate estimand
 - Sensitivity analysis aligned to estimands

Impact of E9(R1) on E9

- EWP plan to insert footnotes in E9 where the existing guidance is superseded by E9(R1)
- Major impact on:
 - Analysis sets, in particular on the per-protocol
 - Missing data
 - Sensitivity analysis
- ICH Steering committee have challenged the EWG to consider updating part(s) of E9

Relation of ICH E9(R1) to E6(R2), E3, E8 and E17

- Three types of observations
 - Parts of other ICH guidance documents where ‘estimand’ can be introduced
 - Text in other ICH guidance documents that needs to be read with an understanding of E9(R1)
 - Changes in methodological approach that impact the content of other documents

Summary

- ICH E9(R1) will have implications on how we design clinical trials, write protocols, conduct trials and perform statistical analyses
- Identification of estimand(s) at the design stage requires informed discussion with all stakeholders - clinical teams, regulatory agencies, payers, and patients
- Certain estimands may require innovative designs and/or endpoints - new statistical methodologies and new/updated clinical guidances?
- Deviations from the treatment policy estimand implied by the intention-to-treat principle should not be taken lightly, but adherence to the intention-to-treat principle to answer efficacy questions should not be done blindly

- ICH concept paper (2014) E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials
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- Little RJ, D'Agostino R, Cohen M, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med*, 367(14): 1355-1360.
- A structured approach to choosing estimands and estimators in longitudinal clinical trials. C. H. Mallinckrodt et al. *Pharmaceut. Statist.* 2012, 11 456–461
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- Choosing Appropriate Estimands in Clinical Trials. AK Leuchs et al. *DIA Therapeutic Innovation & Regulatory Science*. 2015
- Seeking harmony: estimands and sensitivity analyses for confirmatory clinical trials. Mehrotra et al. *Clinical Trials*. 2016 [Laymans summary]