Background on estimands and why they are important

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PAGE 2018 - Montreux
May 30th, 2018

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‘Guiding star’ of pharmaceutical statistics

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Current *Step 4* version

dated 5 February 1998

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Draft ICH E9 (R1) – the addendum

E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

For questions regarding this draft document, contact (CDER) Thomas Permutt 301-796-1271 or (CBER) John Scott 240-402-8779.

ICH E9(R1)

臨床試験のための統計的原則　補遺

臨床試験における estimand と感度分析

(案)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 August 2017
EMA/CHMP/ICH/436221/2017
Committee for Human Medicinal Products

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

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So what is an estimand?

- Represents **WHAT** is most important to estimate in order to address the scientific question of interest
- An estimator represents **HOW** to estimate the estimand
- The revision of the ICH E9 was triggered by concerns that we often focus on the HOW rather than on the WHAT
  - The WHAT is sometimes implicitly driven by the HOW
- ICH E9 (R1) aims to re-assign primacy to the question we ask, not the methods by which we answer them (see also Sheiner (1991), Box (1976))
- ICH E9 (R1) introduces a new framework to better align the WHAT and the HOW

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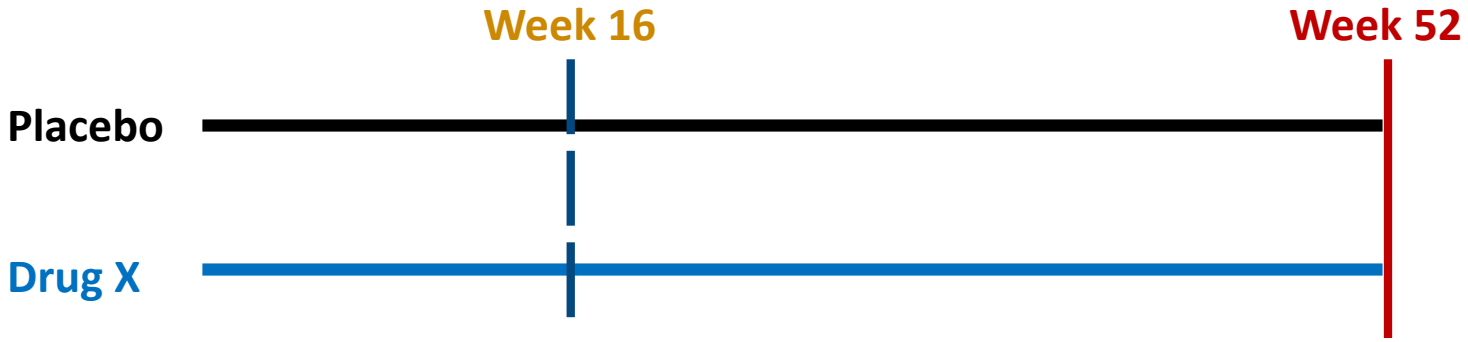
Example for illustration

- Randomized, double-blind, placebo-controlled Phase III study
- Compare a biologic Drug X versus Placebo in the treatment of an inflammatory disease
- Clinical measurement of interest: continuous symptom score at week 52



- **Patients are allowed to switch to rescue therapy (essentially Drug X itself) after week 16 if symptoms are not controlled**
- **Many Placebo patients are expected to switch to Drug X after week 16**
- **No deterministic rule for switching to rescue**
- **Patients are followed up beyond switching**

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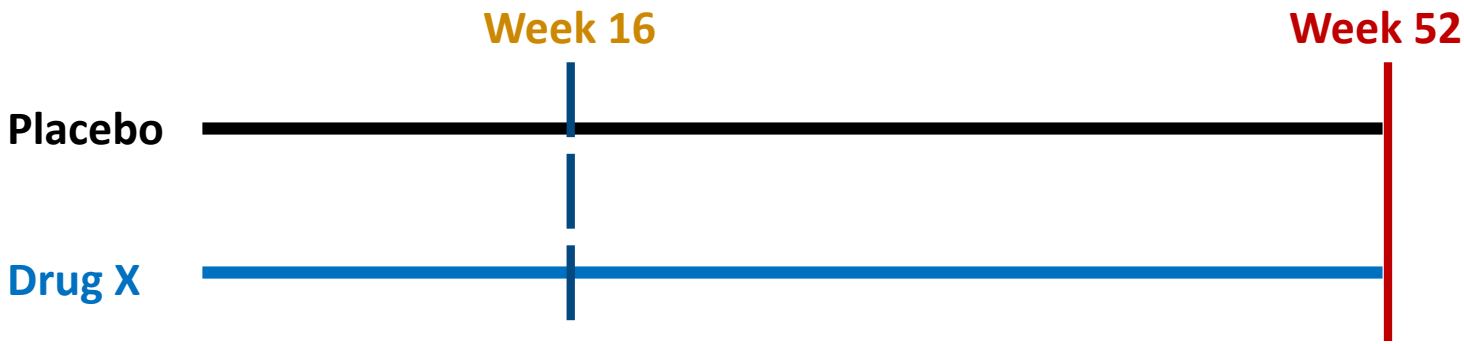
Trial objectives

Objective according to the protocol:

"To demonstrate that the efficacy of Drug X at Week 52 is superior to Placebo based on the change from baseline in the continuous symptom score."



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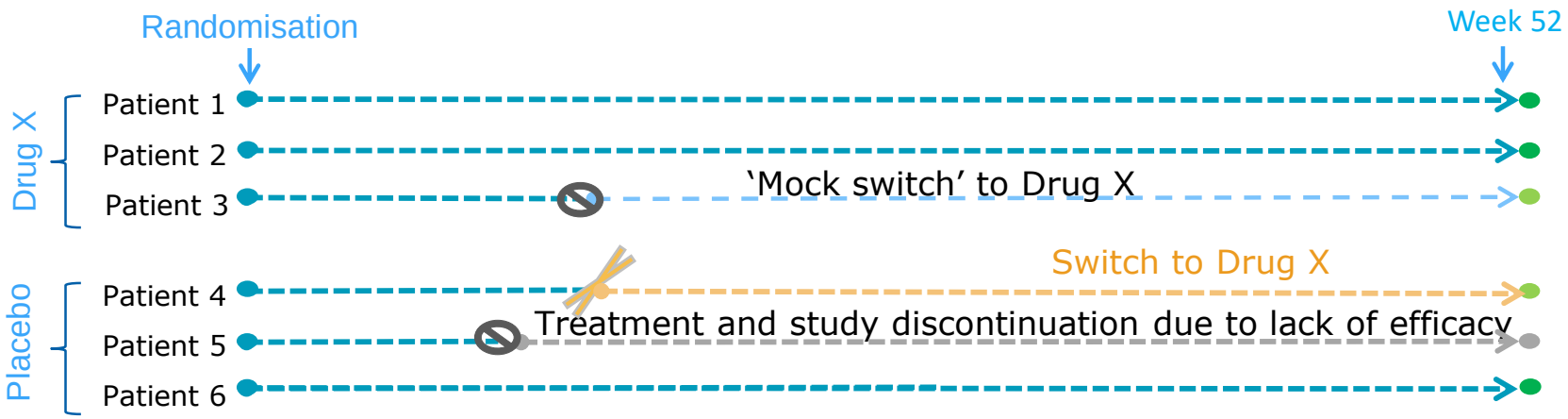
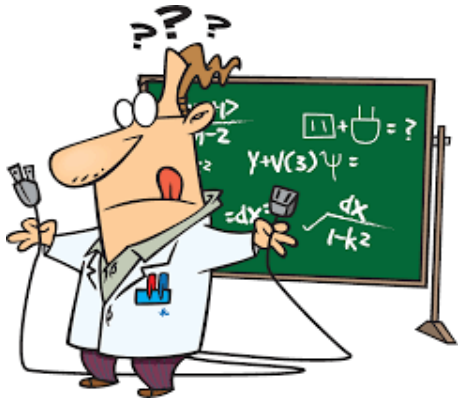
Is this objective precise enough?



These events are not captured in the objectives!



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Objective leaves room for ambiguity on the estimand (the WHAT)

Drug X is superior to Placebo in the situation...

- where we assign the trts to patients, regardless of whether they actually take their assigned trt or not?
- where all patients had remained on the randomized trt throughout 52 weeks?
- where the patients that switch to rescue are considered trt failures?
- where we compare the effect only in patients that would not switch to rescue regardless which trt they are randomized to?

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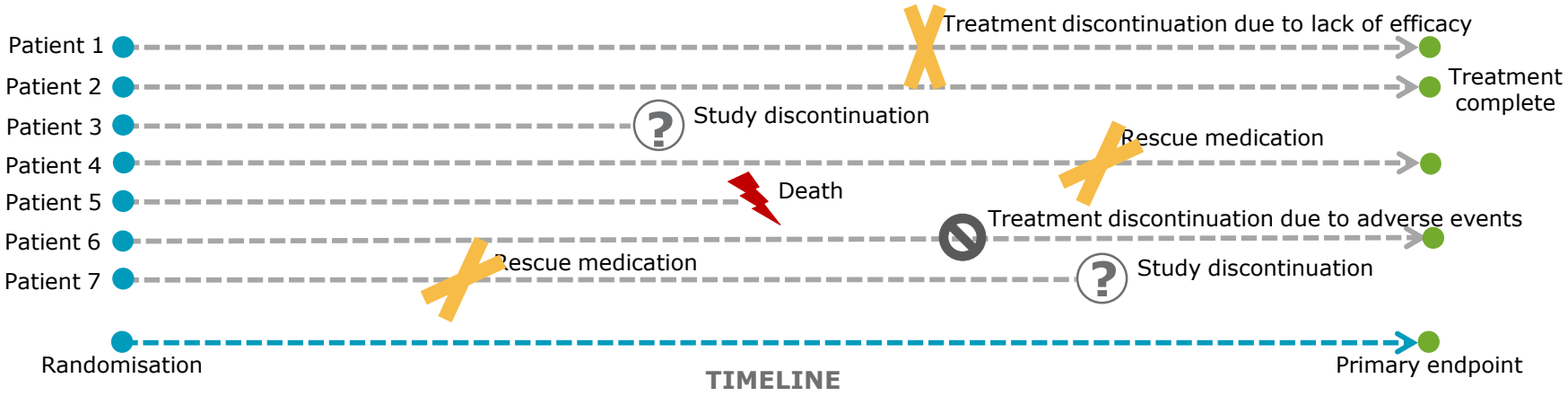
A lot of this boils down to:

- How do we account for events that occur after randomization
  - E.g. study treatment discontinuation due to AE or LoE, intake of concomitant medication, intake of rescue medication, death etc.



- Such events are called intercurrent events in the draft addendum

Intercurrent events

- These events may themselves be informative about some effect of the treatment
  - e.g. when a patient takes rescue or an alternative medication due to lack of efficacy or safety issues
- In the past, intercurrent events were often treated as a nuisance
  - Often ‘mislabelled’ as missing data and handled implicitly through the ‘HOW’
- ICH E9 (R1) clarifies that intercurrent events are not a nuisance – rather they offer a relevant perspective on the disease status and/or the treatment effects

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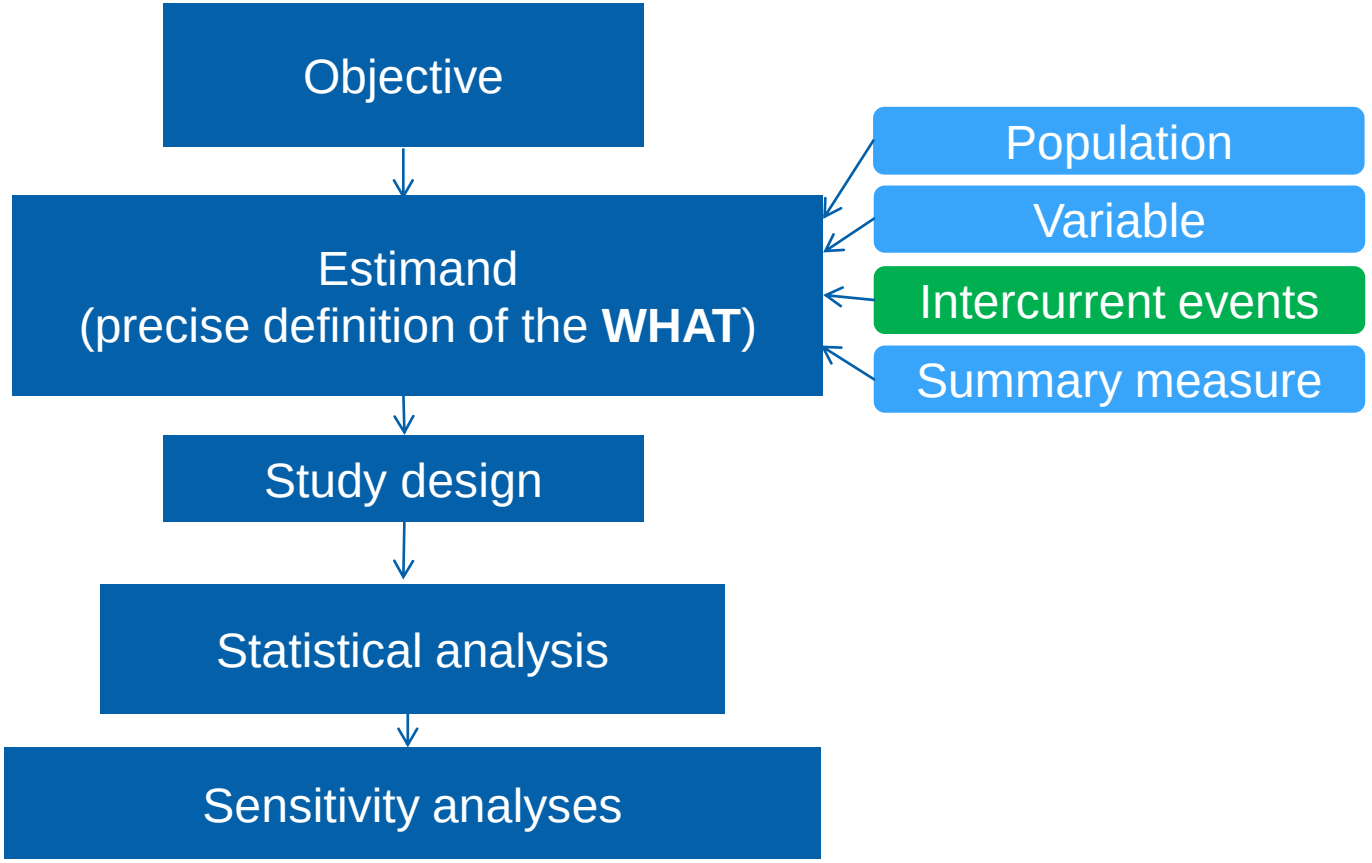
Framework presented in the ICH E9 (R1)



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How does this fit with current practice?

- Since the 1990s the intention-to-treat (ITT) approach has been the ‘steadfast beacon in the foggy vistas of biomedical experimentation’ (Efron (1998))
- ITT= ‘the effect of assigning a trt’, intercurrent events are ‘ignored’
- ITT approach also known as ‘de facto’, ‘effectiveness’, ‘use-effectiveness’ etc.

- Discussions around ICH E9 (R1) have re-emphasized that often other effects than ITT are of interest to patients, clinicians and various other stakeholders (see also Sheiner (2002), Keene (2011))

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Quantitative scientists play a key role in:

- Moderating the discussion with the different stakeholders (clinicians, regulators, payers, patients)
- Designing studies that allow targeting clinically meaningful estimands
- Assessing alternatives to the ITT effect that can be estimated reliably
  - When we deviate from ITT the quantitative methods usually become more complex and rely on assumptions that cannot be verified from the data (Sheiner (2002), Nedelman et al. (2007))
  - Increasing importance of causal inference framework and methods
  - Sensitivity analyses are a crucial component of the quantitative approach

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What is this changing for us?

- Estimand framework offers a language to have informed discussions with regulators and other key stakeholders to harmonize trial objectives (the WHAT)
- Estimand choice impacts trial design and conduct
- New designs, endpoints and quantitative methods may be needed to address the estimands of interest
  - ITT may no longer be the approach of main interest
- Quantitative scientists have the opportunity to
  - facilitate the discussion and choice of meaningful estimands
  - raise important questions and
  - develop targeted designs and appropriate analyses
- Health authorities are already adopting the estimand framework as shown by recent feedback

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Health authority feedback

- **Project A** – EMA feedback on an oncology study
  - "The scientific question (**estimand**) that is intended to be addressed by the primary analysis should be explicitly defined and discussed."
- **Project B** – FDA feedback on a Cushing's disease study
  - "We are interested in estimating the treatment effect based on the intent-to-treat (de facto) **estimand**. The analysis for xxx should account for missing data in a fashion consistent with what the measurement would have been, had it been measured."
- **Project C** – EMA feedback for a chronic pain study
  - "Please provide an extended discussion on appropriate **estimands** and how they are supposed to be estimated"
- **Project D** – FDA feedback for two asthma studies
  - "If you propose an alternative **estimand,** you should justify that it is clinically meaningful and can be estimated with minimal and plausible assumptions."
- **Project E** – FDA feedback on an Alzheimer's disease study
  - "Please clarify the **estimand** of primary interest and justify the suitability…"

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Avoid ‘cookbookery’

Box (1976)

“The tendency to force all problems into the molds of one or two routine techniques, insufficient thought being given to the real objectives of the investigation or to the relevance of the assumptions implied by the imposed methods.”

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Thank you

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References

(**Akacha & Kothny, 2017):** Akacha, M. & Kothny, W. Opinion paper on estimands: Opportunities and challenges. Clin. Pharmacol. Ther. 102, 894-896 (2017).

(Efron, 1998): Forword – Limburg Compliance Symposium. Stat. in Med.17, 249 -250 (1998).

(ICH, 1998): International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials E9. <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf>. Accessed June1, 2015.

(ICH, 2017): International Conference on Harmonisation. Draft ICH E9 (R1) Technical Document: Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials. <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/08/WC500233916.pdf>. Accessed on 18 Sep 2017.

(Keene, 2011): Keene, O.N. Intent-to-treat analysis in the presence of off-treatment or missing data. Pharm. Stat. 10, 191–195 (2011).

(Nedelman et al., 2007): Nedelman, J.R., Rubin, D.B. and Sheiner, L.B. Diagnostics for confounding in PK/PD models for oxcarbazepine. Stat. in Med.26, 290 -308 (2007).

(Ruberg & Akacha, 2017): Ruberg, S.J. & Akacha, M. Considerations for evaluating treatment effects from randomized clinical trials. Clin. Pharmacol. Ther. 102, 917-923 (2017).

(Sheiner, 1991): Sheiner, L.B. The intellectual health of clinical drug evaluation. Clin. Pharmacol. Ther. 50, 4-9 (1991).

(Sheiner, 2002): Sheiner, L.B. Is intent-to-treat analysis always (ever) enough? J. Clin. Pharmacol. 54, 203-211 (2002).

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