



ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials

Training Module 2.2 – Framework

Addendum to ICH E9 – Statistical Principles for Clinical Trials

ICH E9(R1) Expert Working Group
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International Council for Harmonisation of Technical Requirements
for Registration of Pharmaceuticals for Human Use

Disclaimer

This presentation includes the authors' views on theory and practice regarding estimands and sensitivity analysis in clinical trials.

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Introduction note

These slides were produced as training material to accompany the ICH E9(R1) addendum.

The intention is to support the scientific community in the comprehension of a new framework to define estimands based on the trial objective and considering intercurrent events. For this purpose, most of the content of this addendum is presented in a practical fashion, accompanied by examples dealing with estimands and sensitivity analysis in clinical trials, based on the experience of Expert Working Group members.

The training material is divided in three main modules: module 1 (summary), module 2 (comprehensive slide deck) and module 3 (generic example). Module 2 is composed by 6 submodules that correspond to sections A.1 to A.6 of the addendum.

Training modules

- Module 1: Summary
- Module 2: Comprehensive slide deck
 - Module 2.1: Introduction
 - **Module 2.2: Framework**
 - Module 2.3: Estimands
 - Module 2.4: Impact on trial design and conduct
 - Module 2.5: Impact on trial analysis
 - Module 2.6: Documenting estimands and sensitivity analysis
- Module 3: Generic example

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- **A.1. Purpose and Scope** **Module 2.1**
- **A.2. A Framework to Align Planning, Design, Conduct, Analysis and Interpretation** **Module 2.2**
- **A.3. Estimands**
 - A.3.1. Intercurrent Events to be Reflected in the Clinical Question of Interest
 - A.3.2. Strategies for Addressing Intercurrent Events when Defining the Clinical Question of Interest
 - A.3.3. Estimand Attributes
 - A.3.4. Considerations for Constructing an Estimand
- **A.4. Impact on Trial Design and Conduct** **Module 2.4**
- **A.5. Impact on Trial Analysis**
 - A.5.1. Main Estimation
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 - A.5.2.1. Role of Sensitivity Analysis
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- **A.6. Documenting Estimands and Sensitivity Analysis** **Module 2.6**
- **Glossary**

Module 2.3

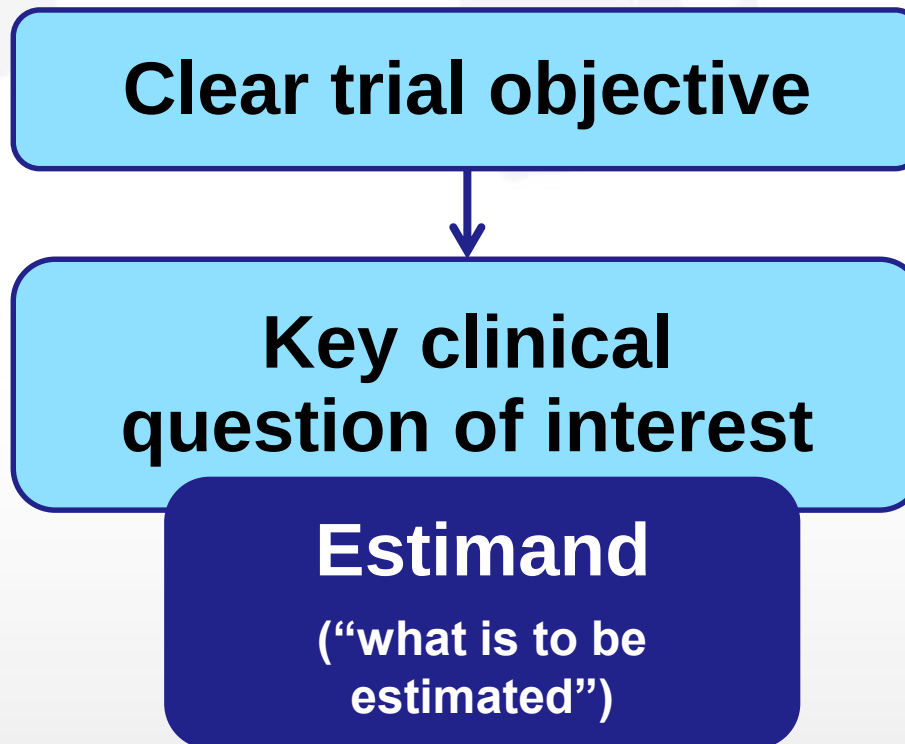
Module 2.5

Outline of Module 2.2

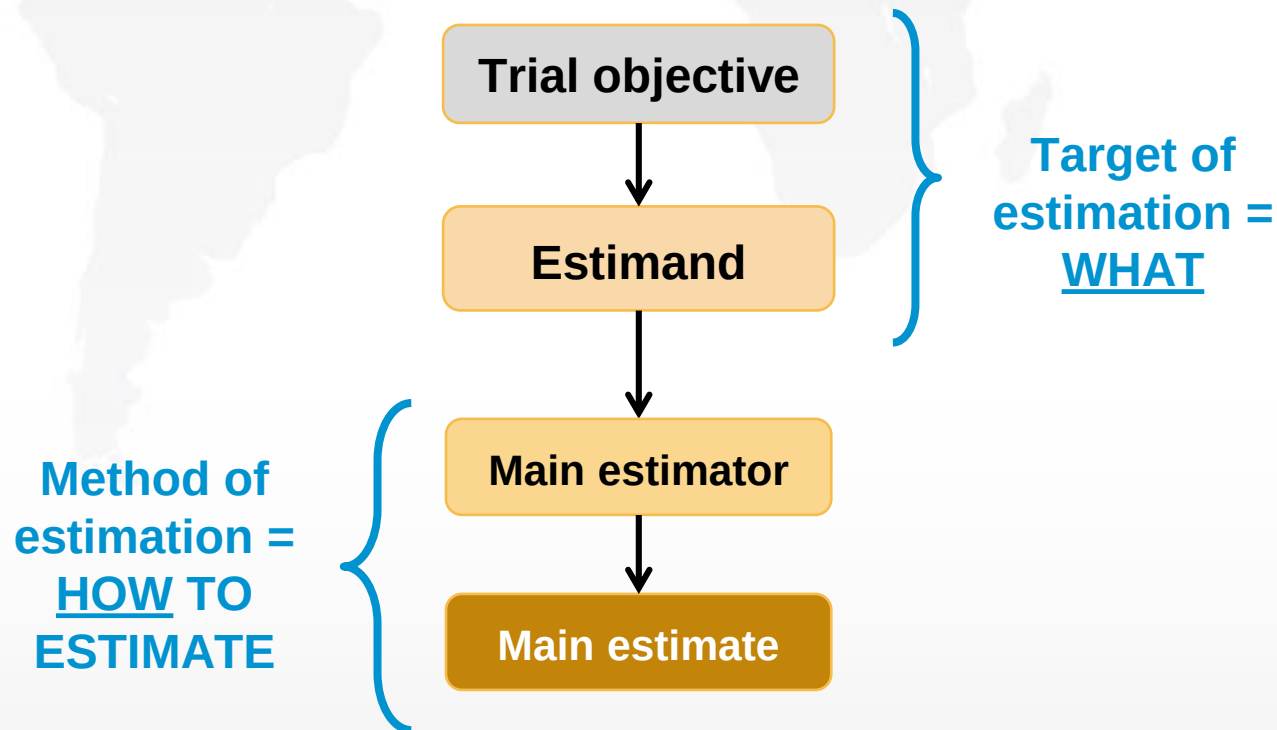
- A new framework for clinical trials
- Alignment between trial objective, design, planning, conduct, analysis and interpretation
- How this framework can improve discussions between sponsors and regulators on the suitability of designs and the interpretation of results

A “new” framework

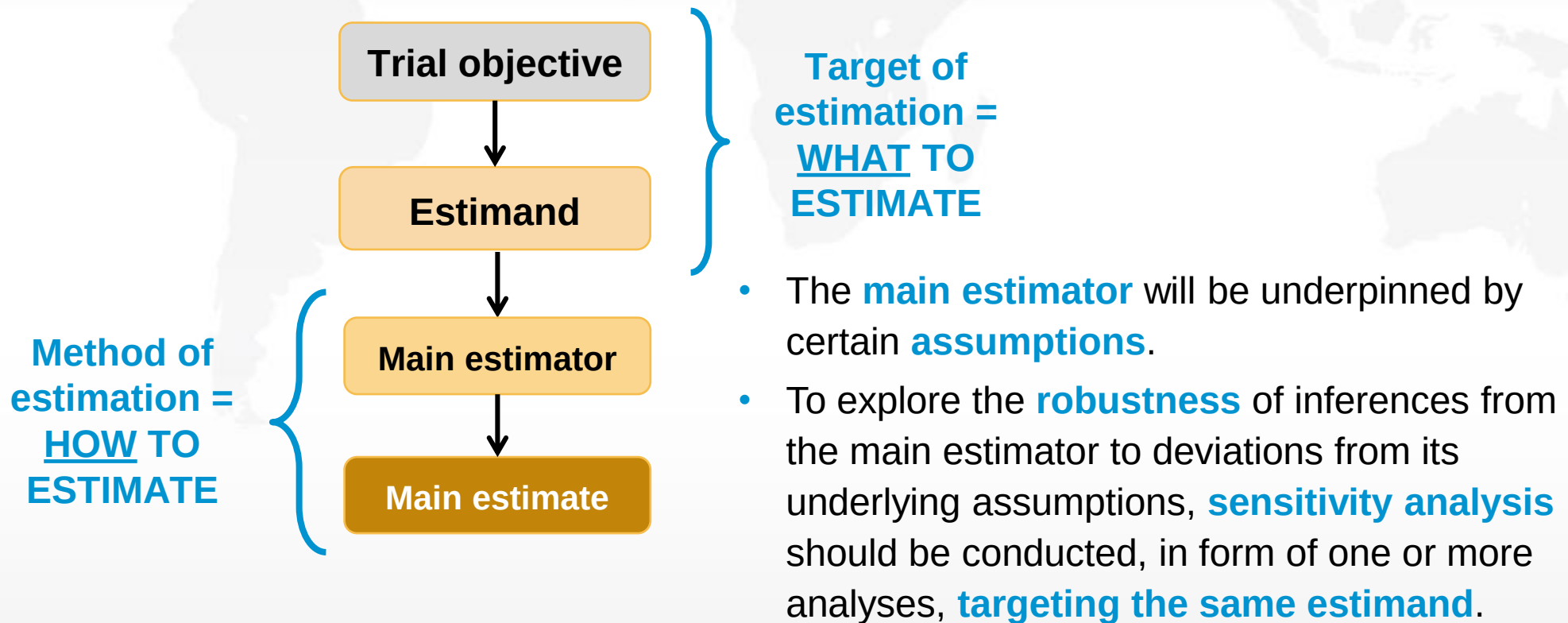
Clear trial objectives should be translated into key clinical questions of interest by defining suitable estimands.



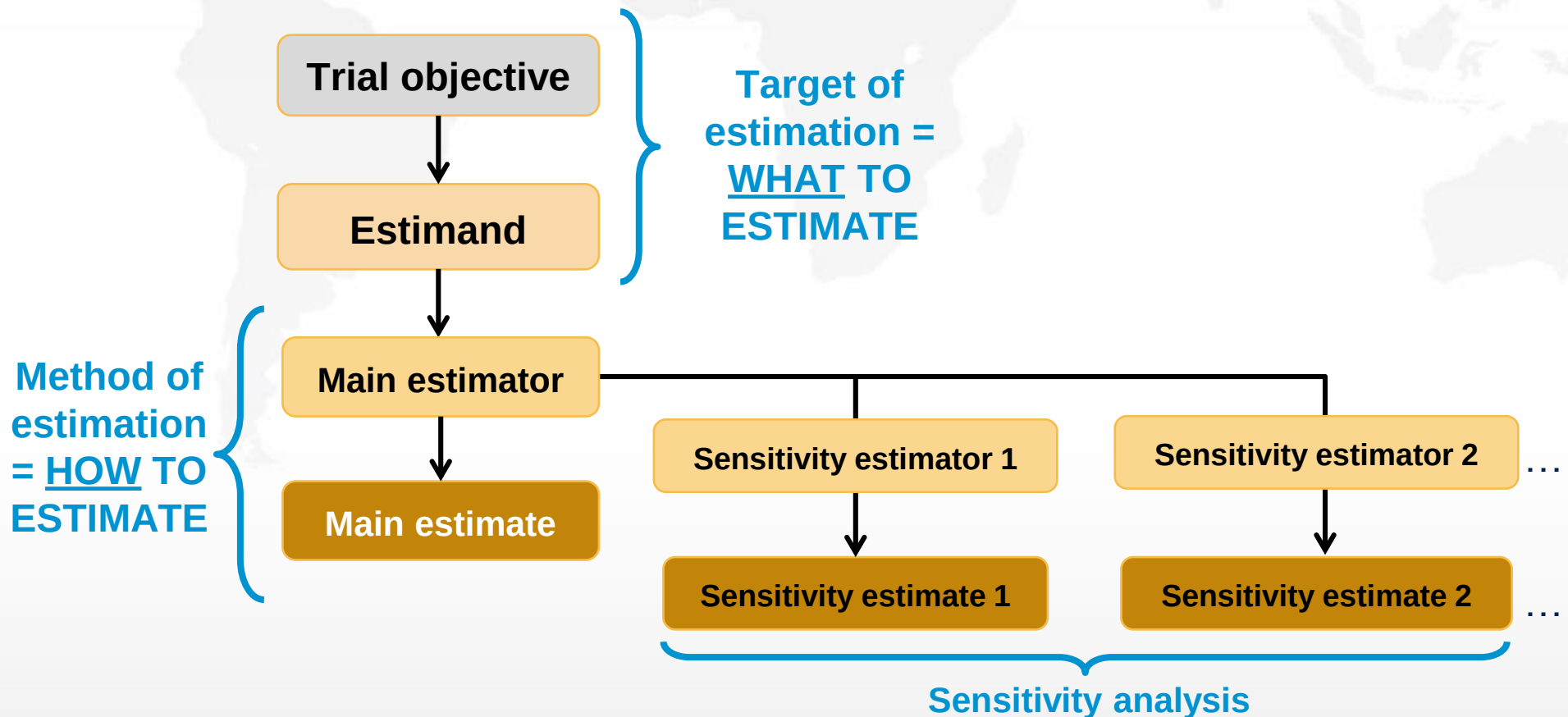
Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective



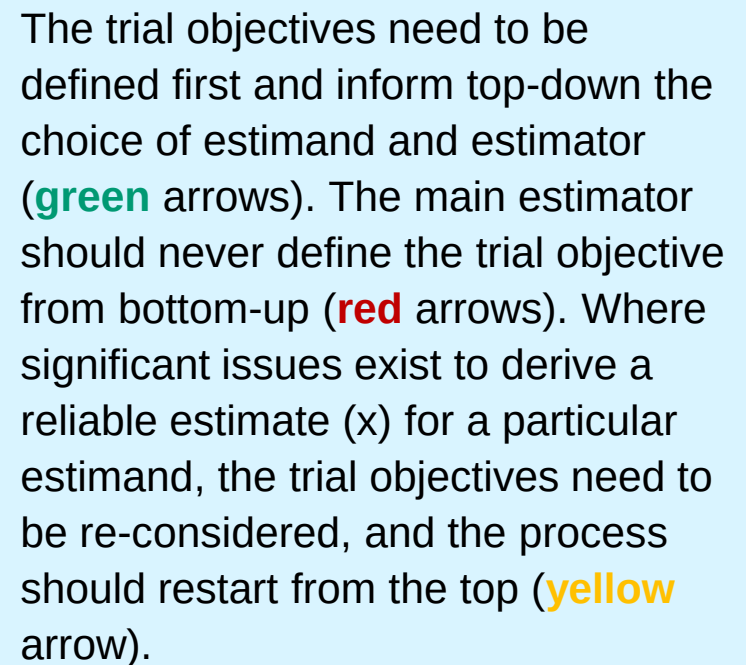
Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective



Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective



Trial planning should proceed sequentially. The trial objective should determine the choice of estimands and the estimands should determine the choice of estimators, not the reverse.



A new framework



Appropriate estimands
will be the main determinant
for aspects of trial design,
conduct and analysis.

A new framework

A common language and common understanding of this framework will help **sponsors planning trials** and **regulators in their reviews**, enhancing the **interactions** between these parties when discussing the suitability of designs, and the interpretation of results, to support drug licensing.



Next module:

2.3. Estimands

**Description, strategies and construction
of estimands**