



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

Training Module 2.6 - Documenting estimands and sensitivity analysis

Addendum to ICH E9 – Statistical Principles for Clinical Trials

ICH E9(R1) Expert Working Group
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for Registration of Pharmaceuticals for Human Use

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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

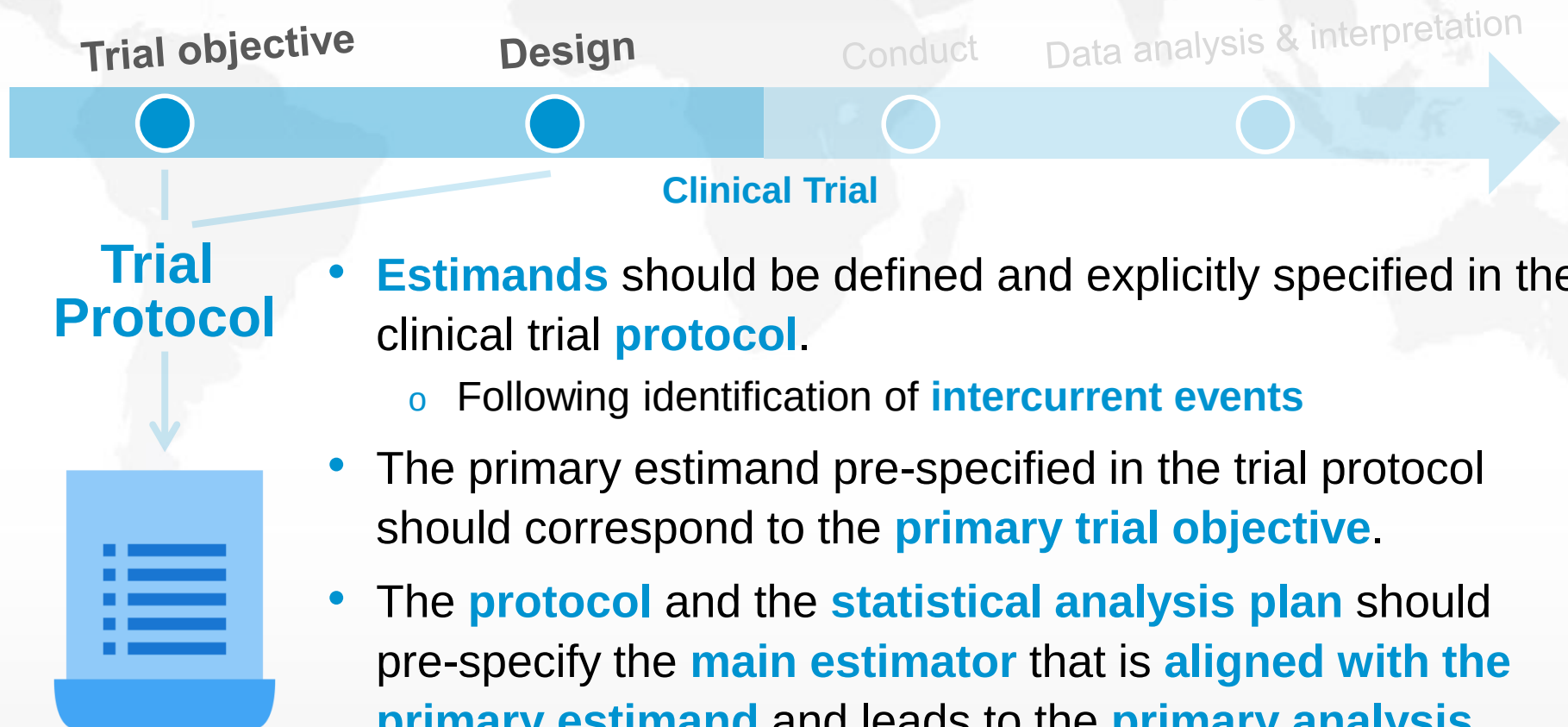
ICH E9(R1) – Table of Contents

- **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**Module 2.3**
- **A.4. Impact on Trial Design and Conduct** **Module 2.4**
- **A.5. Impact on Trial Analysis**
 - A.5.1. Main Estimation
 - A.5.2. Sensitivity Analysis
 - A.5.2.1. Role of Sensitivity Analysis
 - A.5.2.2. Choice of Sensitivity Analysis
 - A.5.3. Supplementary Analysis**Module 2.5**
- **A.6. Documenting Estimands and Sensitivity Analysis** **Module 2.6**
- **Glossary**

Outline of Module 2.6

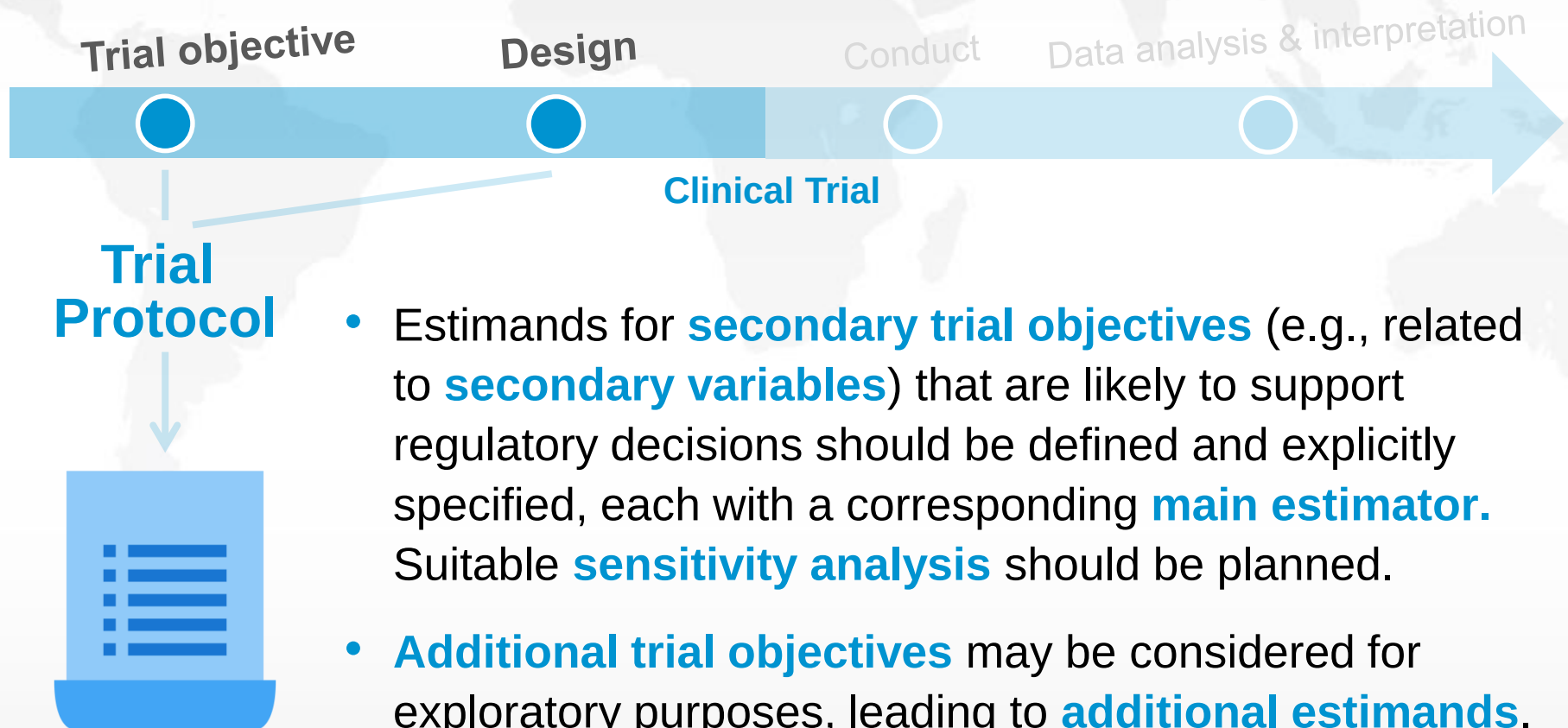
- Incorporating estimands and methods of estimation including suitable sensitivity analysis in the writing of a trial protocol and statistical analysis plan
- Reporting results in the Clinical Study Report
- Handling changes to an estimand

Incorporating estimands in protocol writing

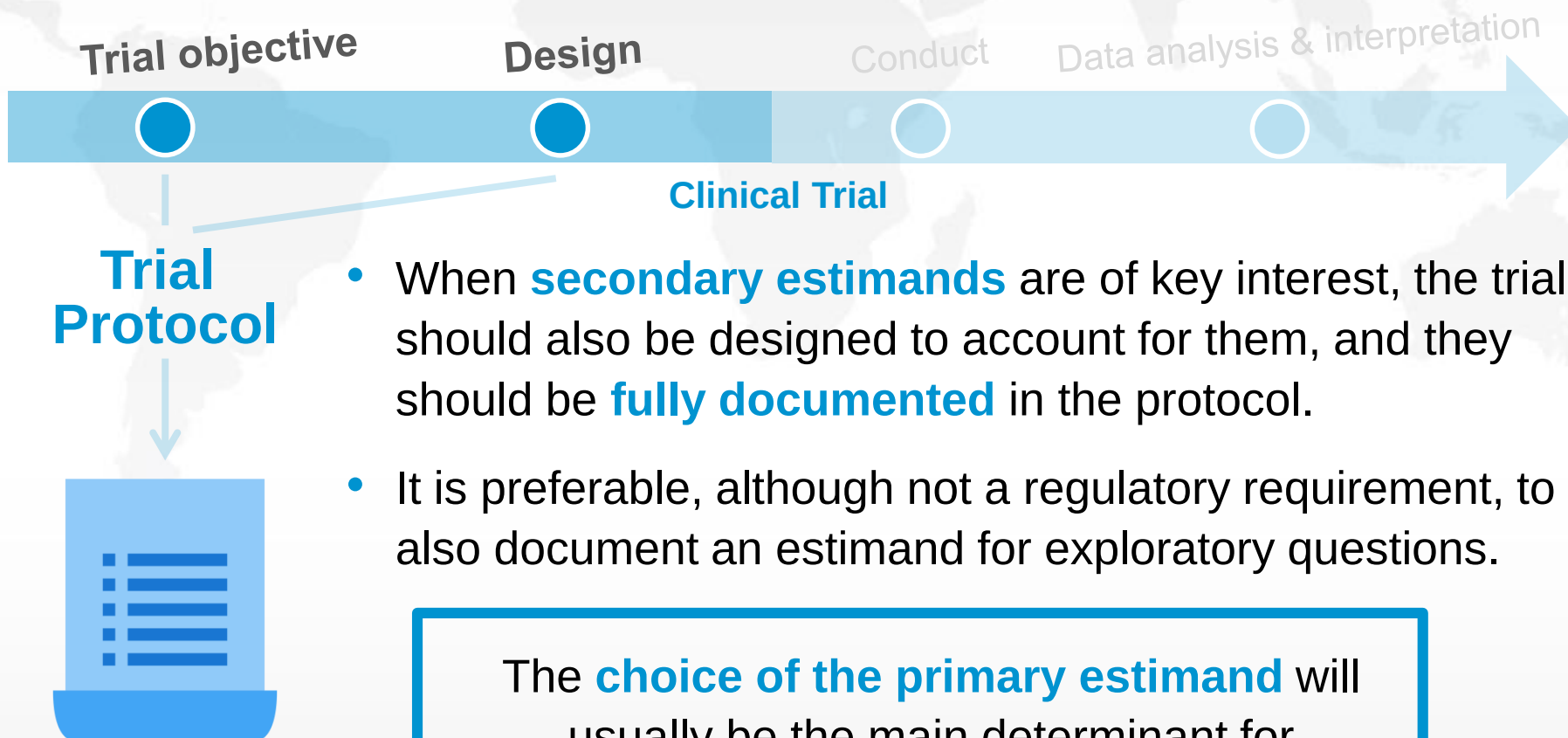


- **Estimands** should be defined and explicitly specified in the clinical trial **protocol**.
 - Following identification of **intercurrent events**
- The primary estimand pre-specified in the trial protocol should correspond to the **primary trial objective**.
- The **protocol** and the **statistical analysis plan** should pre-specify the **main estimator** that is **aligned with the primary estimand** and leads to the **primary analysis**. Suitable **sensitivity analysis** should be planned to explore the robustness under deviations from its assumptions.

Incorporating estimands in protocol writing



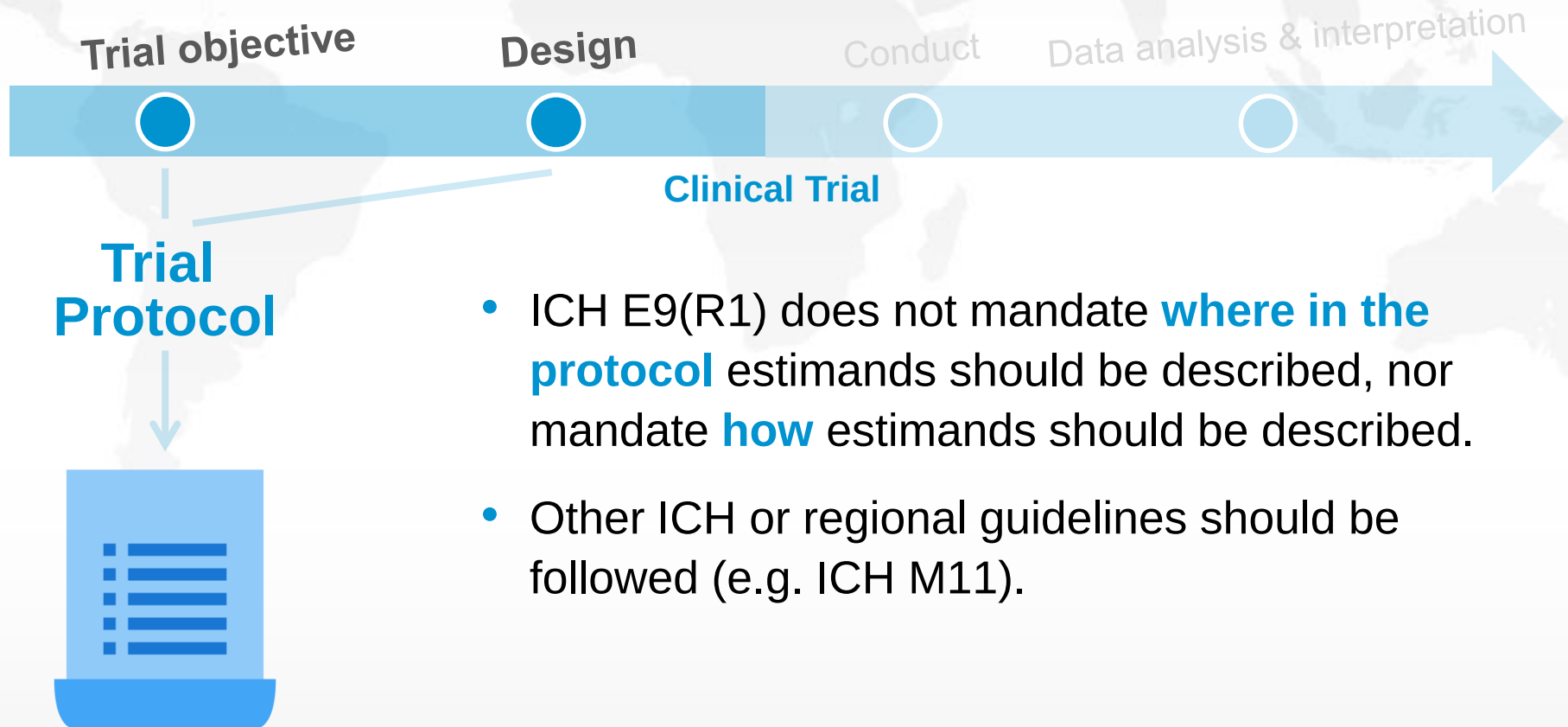
Incorporating estimands in protocol writing



Incorporating estimands in protocol writing

- The **trial analysis summarised in the protocol should be aligned with the primary estimand** with regards to (including but not limited to):
 - **Handling of intercurrent events**, for example:
 - Use of rescue medication;
 - Changes in permitted medications;
 - Switching treatments;
 - Discontinuing treatment;
 - Subject deaths.
 - The **selection of the data** to be included in the analyses.
 - **Details of the estimator**, including handling of missing data.
- Beyond these aspects, the conventional considerations for trial design, conduct and analysis remain the same.

Incorporating estimands in protocol writing



Incorporating estimands in the SAP

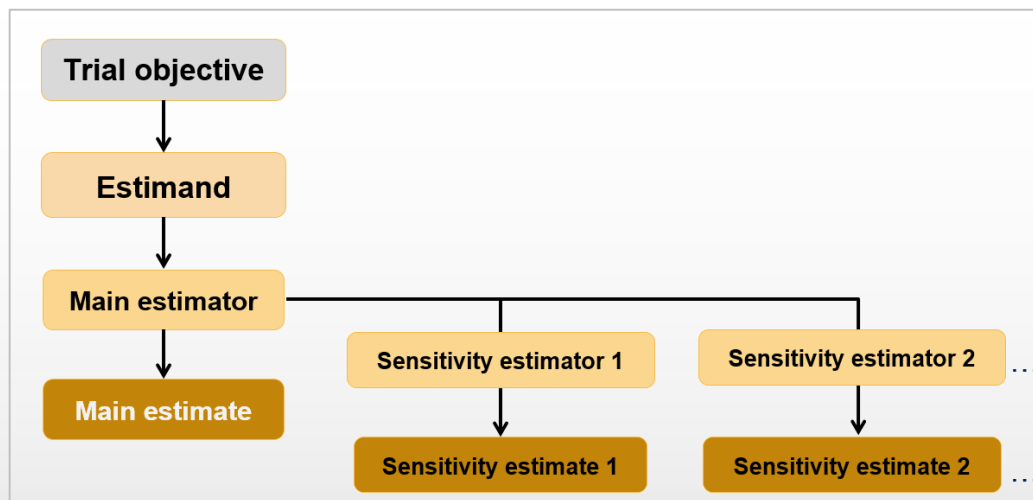


Trial Protocol

Statistical Analysis Plan



- Full details of the planned statistical analyses should align with the estimand(s) defined, and not the other way around!



Potential impact on study conduct



- All efforts should be made to **define** the primary estimand **before the beginning of the trial**, as changes to it would be problematic and reduce its credibility.
- The occurrence of anticipated intercurrent events should be **monitored during the study**.
- The impact of any **unanticipated intercurrent events** occurring and/or other study conduct issues possibly affecting the primary estimand should be evaluated.
- A change in the primary estimand would usually require a **protocol amendment**.

Data analysis and interpretation



- Results from the main, sensitivity and any supplementary analyses should be **reported systematically** in the clinical trial report, specifying whether each analysis was **pre-specified, introduced while the trial was still blinded, or performed post hoc**.
- Summaries of the **number and timings of each intercurrent event** in each treatment group should be reported.

Data analysis and interpretation



- For **intercurrent events that were not foreseen** at the design stage, and were identified during the conduct of the trial with no possibility to formally amend the estimand specified in the protocol, the sponsor should:
 - explain how the unforeseen intercurrent events were **handled for estimating treatment effects in the analysis**;
 - explain the **impact on what the revised analysis estimates** for the treatment effect (i.e. the **impact on the pre-specified estimand**).



Next module:

3. Generic example

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