Introduction to Estimands

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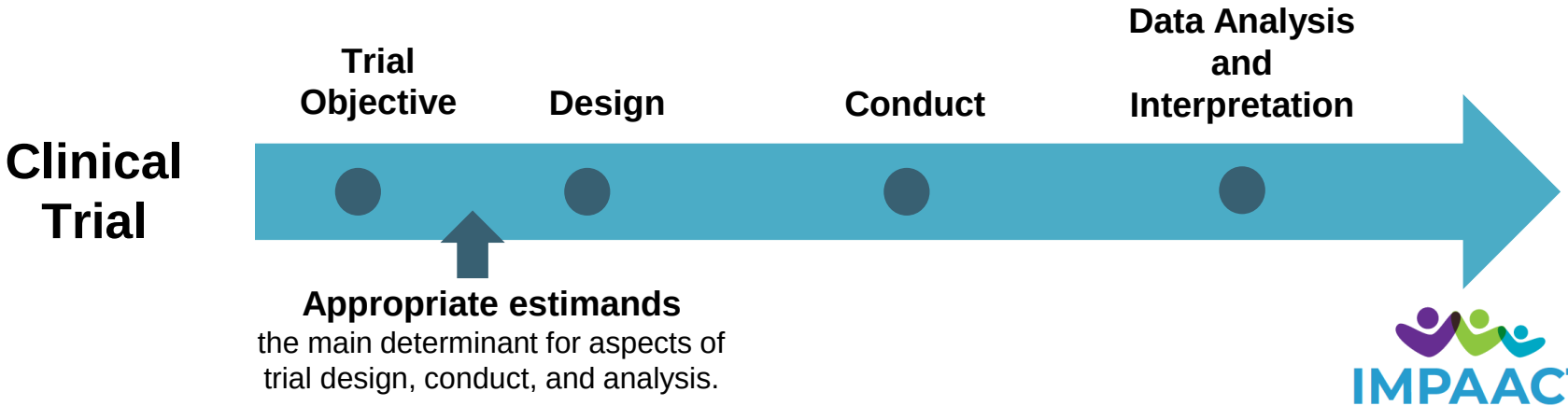
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

ANNUAL MEETING
2022

Today's Goal

- To provide an overview of International Council for Harmonisation (ICH) E9(R1) (or Estimand framework)
- By the end of the presentation, Study Teams should have a basic understanding of the concepts and be comfortable integrating them into the clinical trial design and protocol development process



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https://database.ich.org/sites/default/files/E9%28R1%29%20Training%20Material%20-%20PDF_0.pdf

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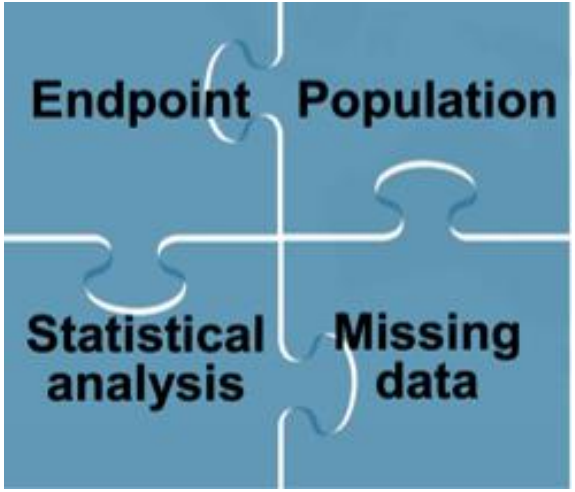
Concerns with Current Practice*

- Targets of estimation not clearly stated in the protocol and SAP
- Choices made for missing data handling and statistical analysis are not consistent with the targets of estimation



*Pre-ICH E9(R1)

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Background

2010

NRC

A NRC (US) expert panel published a report on "**The Prevention and Treatment of Missing Data in Clinical Trials**"

2017

ICH

Issued a draft addendum to ICH E9 (Statistical Principles for Clinical Trials) that aligned with the panel recommendations entitled **Estimands and Sensitivity Analyses**

2019

ICH

Finalized the addendum (November)

2020

EMA

Endorsed the addendum (February)

2021

FDA

Endorsed the addendum (May)

SDAC

estimands will be added to the statistical analysis plan (SAP) for all new and ongoing studies

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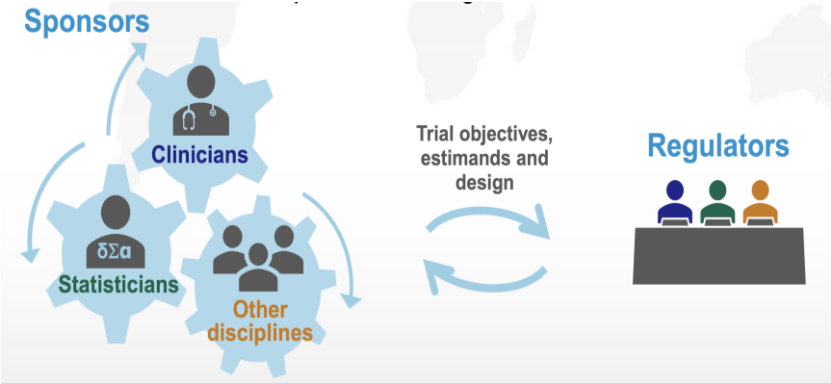
A.6. DOCUMENTING ESTIMANDS AND SENSITIVITY ANALYSIS

A trial protocol should define and specify explicitly a primary estimand that corresponds to the primary trial objective.

Source: ICH E9(R1)

The construction of estimands is a **multi-disciplinary undertaking** and should be the subject of discussion between study teams, sponsors, regulators, and the community



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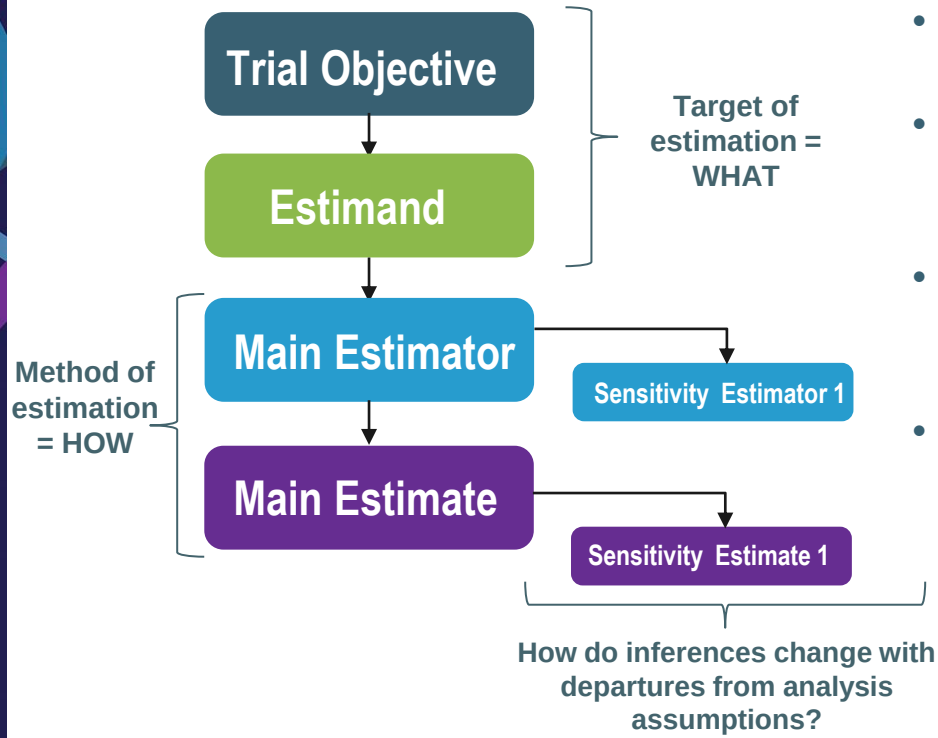
ICH E9(R1) presents a structured framework to align the target of estimation, method of estimation, and sensitivity analysis for a given trial objective



- **Trial objective** reflects clinical question of interest
- **Estimand** defines the target of estimation for the objective (i.e., “what is to be estimated”)
- **Estimator** represents the analytic approach from which the **Estimate** is derived
- **Sensitivity analysis** explores the robustness of inferences from the main estimator to deviations from its underlying assumptions

Image and text from: 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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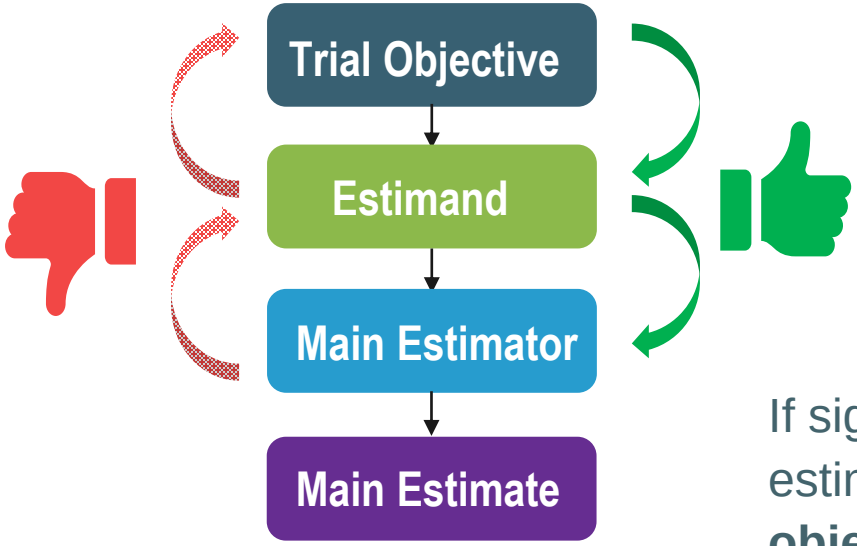
The trial objective should determine the choice of estimand and the estimand should determine the choice of estimator



If significant issues exist to derive a reliable estimate for a particular estimand, the **trial objectives need to be re-considered**

Image and text from: 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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IMPAACT 2032: Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States

- **Design:** Phase IV, prospective, open-label, non-randomized, opportunistic study in hospitalized pregnant and non-pregnant women
- **Primary Objective 2:** To describe the clinical and laboratory safety outcomes through 4 weeks post-infusion and during delivery in pregnant women receiving RDV as part of clinical care
  - **Outcome Measure:** Occurrence of maternal renal adverse event of any grade through 7 days post-last infusion

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An estimand (i.e., “what is to be estimated”) is defined through the specification of 5 attributes

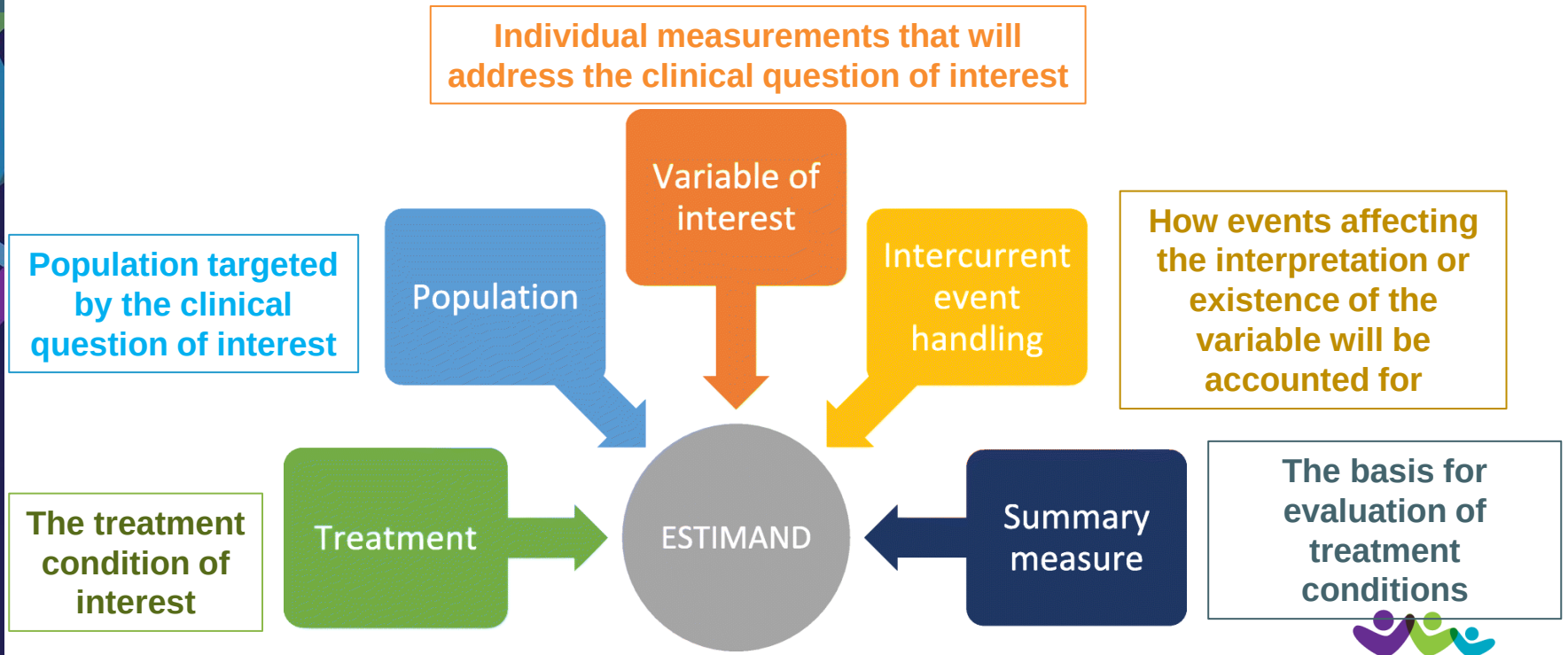

Image from: What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials? Lawrance et al. 2020

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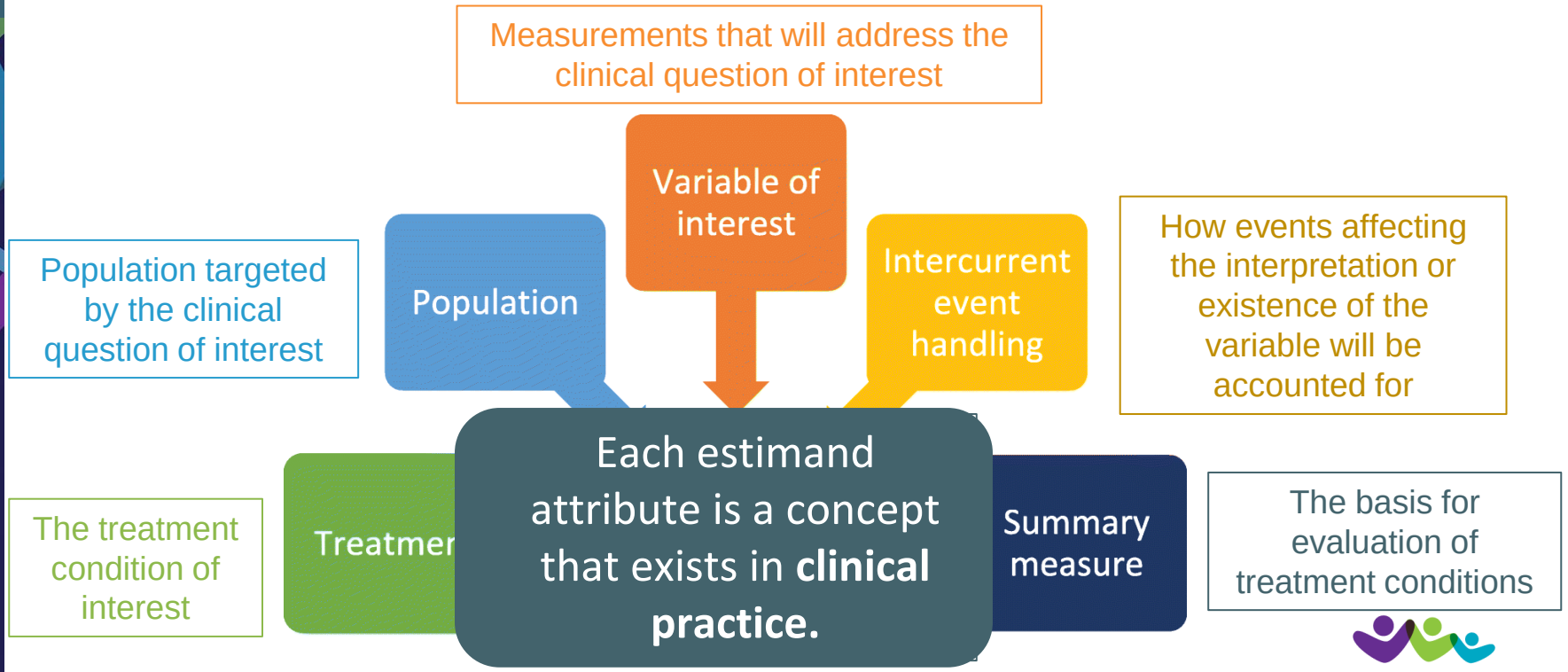

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The **treatment condition** of interest and the alternative treatment condition to which comparison will be made (if applicable)

Treatment

- Individual treatment
  - *IMPAACT 2032: Remdesivir*
- Combinations of treatments administered concurrently
  - *IMPAACT 2017: two long-acting drugs, Cabotegravir plus Rilpivirine*
- Overall regimen involving a sequence of interventions
  - *IMPAACT 2039: One arm will receive a sequence of a 2-vaccine regimen, followed by 2 bNABs, followed by IMAP*
- No treatment

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The **population** targeted by the clinical question of interest

Population

- The people in whom the treatment is intended to be used in clinical practice
- Most of the time **represented** by the enrolled trial population
  - *IMPAACT 2035: Pre-adolescents living with and without HIV*
- May be a subgroup of the enrolled population
  - *IMPAACT 2032: Hospitalized pregnant women who received any amount of RDV for treatment of COVID-19*

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The **variable** required **for each individual** to address the clinical question of interest

Variable

- Measurements taken or functions of a measurement
  - *HIV-1 in plasma (copies/mL)*
  - *IMPAACT 2008: Change of HIV-1 DNA concentration from baseline to week 14*

- Quantities related to observed events
  - *IMPAACT 2032: Occurrence of maternal renal AE of any grade through 7 days post-last infusion*

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Intercurrent Events (ICE) are events occurring after treatment initiation that affect either the **interpretation or the existence** of the measurements associated with the clinical question of interest.

Intercurrent event handling

The **occurrence of ICEs is not limited to the trial setting**; they are all events that may occur when the intervention is taken in clinical practice

ICE examples

- Terminal events (e.g., death, pregnancy loss)
- Use of rescue medication
- Discontinuation of medication due to toxicity/lack of efficacy

Non-ICE examples

- Loss to follow-up
- Study withdrawal (not related to study drug)
- Administrative censoring (e.g., a study site is defunded)

- A trial will typically be faced with more than one type of ICE
- The ICEs for consideration will depend on therapeutic setting and trial objective

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Five strategies to handle intercurrent events

Strategy	Definition	Example (rescue medication)
Treatment Policy	**ignores** the ICE with respect to variable assessment and analysis	Ignores use of rescue medication
Composite	incorporates the ICE into the **definition of the variable** component of the estimand	Occurrence of an event or use of rescue medication
While on Treatment	determines which **measurements over time may contribute** to definition of the variable component of the estimand; i.e., restricts the observation time of interest to that before occurrence of the ICE	Censors individual at time of rescue medication
Principal Stratum	potential for ICE occurrence or absence **contributes to the definition of the target population** component of the estimand	individuals who did not use a rescue medication
Hypothetical	inference under the **counterfactual** where the ICE did not occur	Imputes data for visits after the rescue medication

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Intercurrent Events (ICE) are events occurring after treatment initiation that affect either the **interpretation or the existence** of the measurements associated with the clinical question of interest.

Intercurrent event handling

Choice of intercurrent event handling can affect other attributes of the estimand – population, variable, analysis summary

- *IMPAACT 2032*
  - *ICE: Maternal death for any reason*
  - *Strategy: Composite* (**incorporates** the ICE into the definition of the variable component of the estimand)
  - *Variable: Occurrence of maternal renal AE of any grade **or death (for any reason)** through 7 days post-last infusion*

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The population-level **summary measure** forms the basis for evaluation of treatment conditions

Summary Measure

- Mean, proportion, or hazard rate
  - *IMPAACT 2032: Probability of renal AE or death*
- In the case of treatment comparisons, difference in means, difference in proportions, or a hazard rate
  - *IMPAACT 2010: Difference in proportion of participants with viral suppression*

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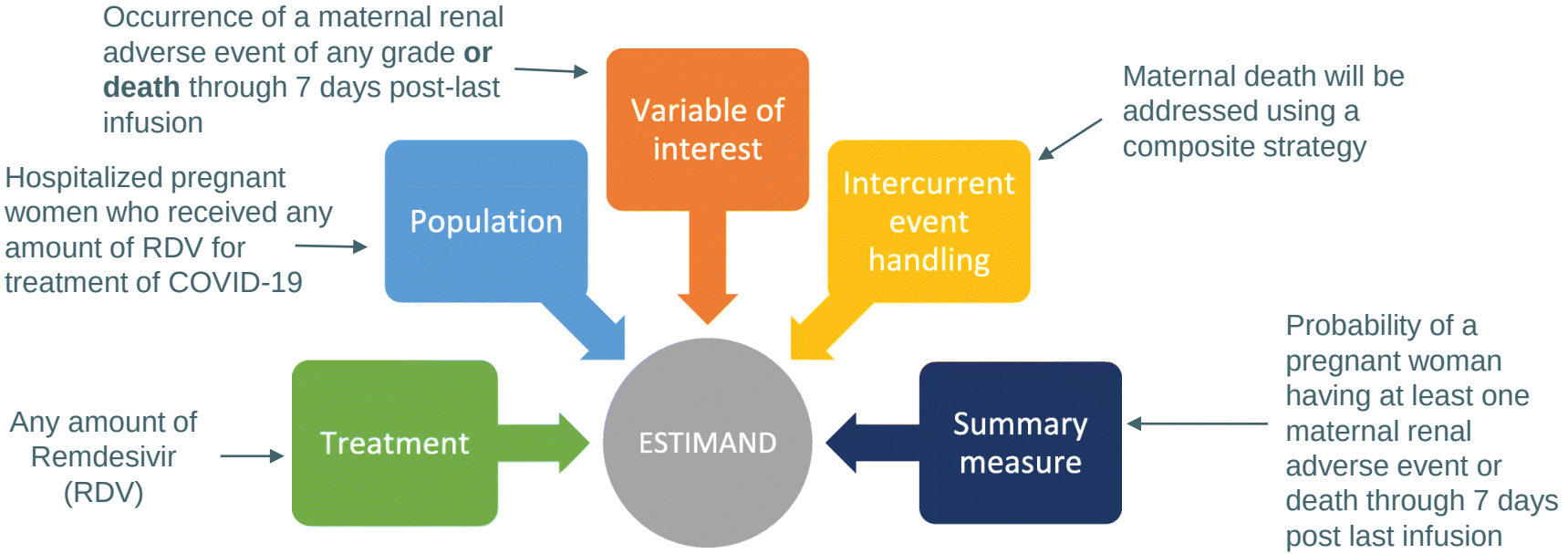
Primary Objective 2: To describe the clinical and laboratory safety outcomes through 4 weeks post-infusion and during delivery in pregnant women receiving RDV as part of clinical care



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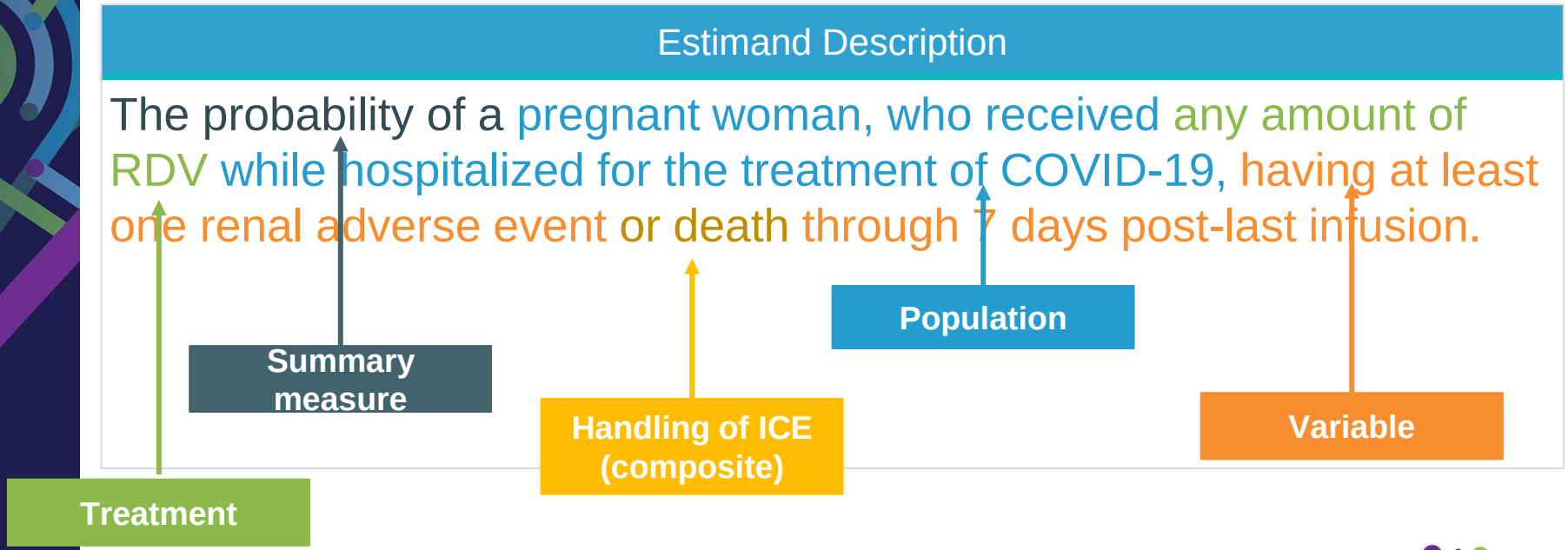

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Sensitivity versus Supplementary Analysis

- **Sensitivity analyses** target the same estimand to explore the robustness of inferences from the main estimator to deviations from its underlying assumptions and data limitations

- **Supplementary analyses** are conducted in addition to the main and sensitivity analysis to provide additional insights into the understanding of the treatment effect
- May target a different estimand, or the same estimand with a different analytical approach

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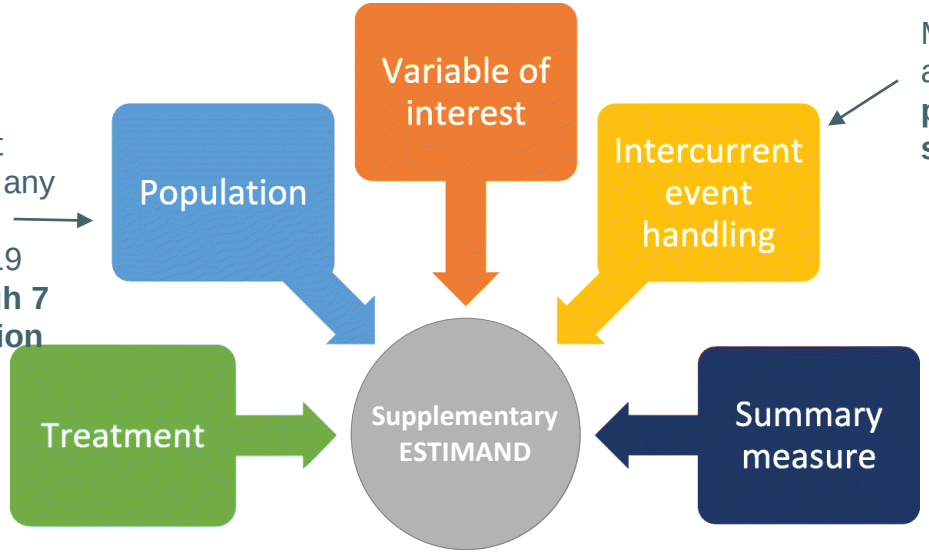
Primary Objective 2: To describe the clinical and laboratory safety outcomes through 4 weeks post-infusion and during delivery in pregnant women receiving RDV as part of clinical care

Hospitalized pregnant women who received any amount of RDV for treatment of COVID-19 **and survived through 7 days post-last infusion**



Maternal death will be addressed using a **principal stratum strategy**

Image from: What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials? Lawrance et al. 2020

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Primary Objective 2: To describe the clinical and laboratory safety outcomes through 4 weeks post-infusion and during delivery in pregnant women receiving RDV as part of clinical care

Primary Estimand Description	Supplementary Estimand Description
The probability of a pregnant woman, who received any amount of RDV while hospitalized for the treatment of COVID-19, having at least one renal adverse event **or death** through 7 days post-last infusion.	The probability of a pregnant woman, who received any amount of RDV while hospitalized for the treatment of COVID-19 **and survived through 7 days post-last infusion**, having at least one renal adverse event through 7 days post-last infusion.

Handling of ICE (composite)

Handling of ICE (principal stratum)

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Estimands in IMPAACT Protocols

SECTION 2.0: OBJECTIVES AND ESTIMANDS

Primary objective: To describe the clinical and laboratory safety outcomes through 4 weeks post-infusion and during delivery in pregnant women receiving RDV as part of clinical care

- ***Estimand:*** *The probability of a pregnant woman, who received any amount of RDV while hospitalized for the treatment of COVID-19, having at least one renal adverse event or death through 7 days post-last infusion*

Table: Attributes defining the estimand for the primary objective

Treatment	Any amount of Remdesivir (RDV)
Population	Hospitalized pregnant women who received any amount of RDV for treatment of COVID-19
Variable	Occurrence of a maternal renal adverse event of any grade or death through 7 days post-last infusion
Handling of intercurrent events	Maternal death will be addressed using a composite strategy
Summary measure	Probability of a pregnant woman having at least one maternal renal adverse event or death through 7 days post last infusion

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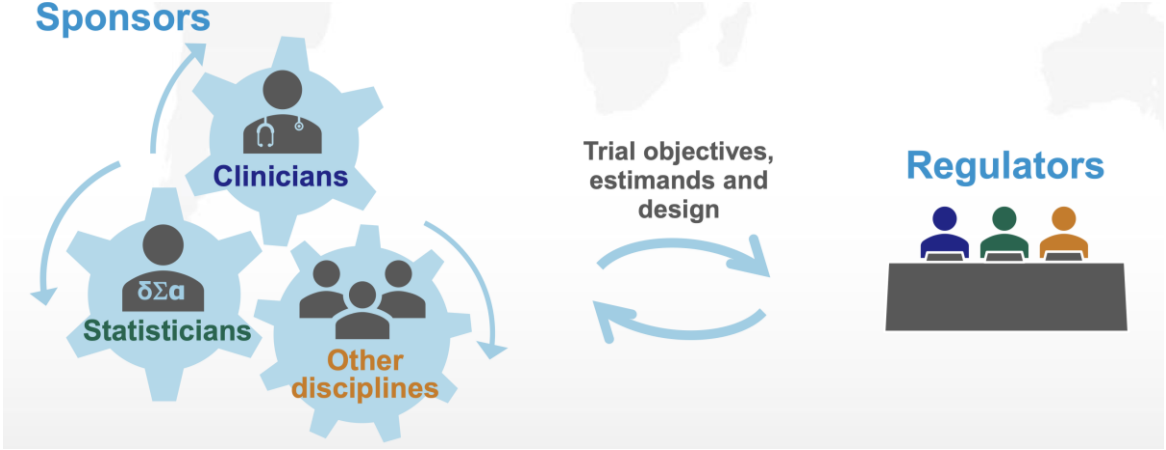

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THANKS!

Any questions?

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Acknowledgments

IMPAACT 2032 Protocol Team

CBAR Estimands Working Group

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Additional Reading

- ICH materials
  - https://www.ich.org/page/efficacy-guidelines
  - Original ICH E9(R1) document
  - Extensive training slide deck
- Other references:
  - Little et al. The Prevention and Treatment of Missing Data in Clinical Trials. *NEJM.* 2012
  - Mehrotra et al. Seeking harmony. Estimands and sensitivity analyses for confirmatory clinical trials. *Clinical Trials.* 2016
  - Lawrance et al. What is an Estimand & how does it relate to quantifying the effect of treatment on –reported quality of life outcomes in clinical trials. *Journal of Patient Reported Outcomes*. 2020
  - Kang et al. Incorporating estimands into clinical trial statistical analysis plans. *Clinical Trials.* 2022