Estimand in Hematologic Oncology Trials

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Presenting on behalf of Hematology Taskforce: Oncology Estimand Working Group

- Joint work with
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  - Hans-Jochen Weber (Novartis)
  - Emily Butler (GlaxoSmithKline)
  - Kaspar Rufibach (Roche)

Sun, S, Weber, H-J, Butler, E, Rufibach, K, Roychoudhury, S. Estimands in hematologic oncology trials. *Pharmaceutical Statistics*. 2021; 20: 793– 805. https://doi.org/10.1002/pst.2108

Challenges in Hematology Oncology

- Number of development programs in Leukemia, Multiple myeloma, and Lymphoma in recent years
- Uniqueness in endpoint, treatment strategy, and interpretation of treatment effect
- Includes broad disease population causes heterogeneous response based on genomic characteristics (large B cell lymphoma vs others)
- Challenging to summarize treatment effect:
  - Long term vs short term effect
  - Effect of induction vs maintenance
  - Responder vs non-responders

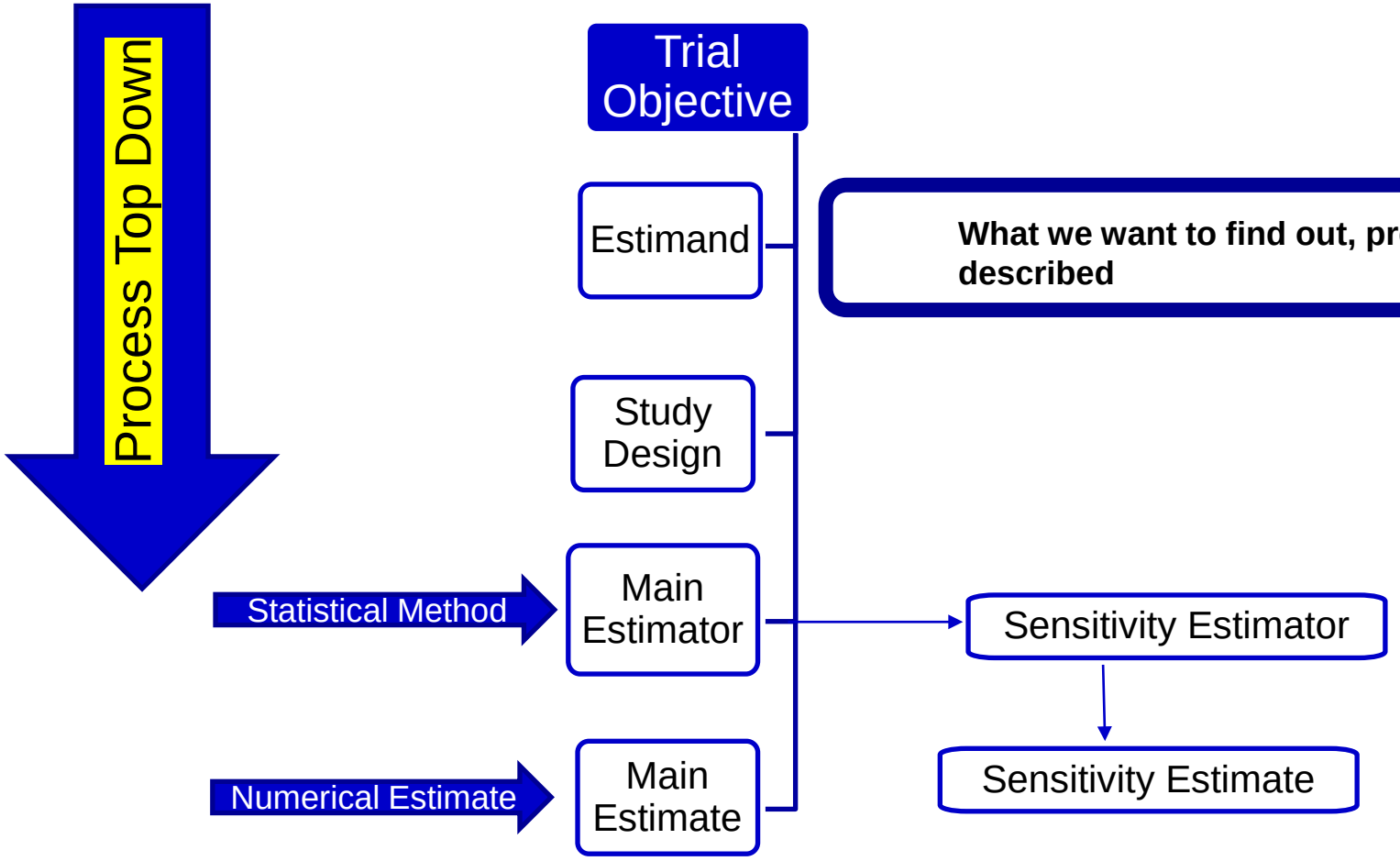
Example

Examples	Gallium Study	Multiple Myeloma Study	RATIFY Study
Treatment	Obinutuzumab vs Rituximab in combination with three backbone chemo	Drug X vs Placebo In combination with background therapy	Midostaurin vs Placebo in combination with chemo
Population	Advanced indolent non-Hodgkin's lymphoma	Diagnosed with multiple myeloma and eligible for high-dose therapy	First-line acute myeloid leukemia (AML) with a FLT-3 mutation
Induction and Maintenance Phase	**Induction:** Received Obinutuzumab or Rituximab + chemotherapy **Maintenance:** • Achieving response : continue the treatment until disease progression. • Stable disease (SD) : No further therapy	**Induction:** Patients have received drug X + background therapy or background therapy only. Followed by a stem cell transplant and consolidation phase **Maintenance:** Same as randomized until disease progression or unacceptable toxicity	Patients have received midostaurin or placebo along with chemotherapy for one cycle. If there are definitive evidence of clinically significant residual leukemia, a second cycle of same therapy continues. Induction phase is followed by 4 cycles of consolidation Patients who remained in remission entered a maintenance phase in which they received drug A or placebo.
Primary Endpoint	Progression-free survival	Progression-free survival	Overall survival
Sample Size (events)	1202	690	717

Questions of Clinical Interest

- **Key question**: Is the inclusion of experimental treatment/regimen to SOC improve risk of progression and/or death for patients over SOC
- Is the question above clear?
  - How to handle patients who had considered other anti-cancer therapy before progression?
  - How to handle treatment discontinuation
- Other clinical questions:
  - Impact of induction/consolidation phase and maintenance phase
  - Response in subgroups: e.g., achieved CR or PR in the induction phase.

What is an estimand?



- The estimator or summary measure should be able to provide clear answer to the quest of interest
- Any assumptions made should be explicitly stated, and sensitivity analysis should be used to assess the robustness of the results to the underlying assumptions.

Attributes of an Estimand

Detailed description of treatment including all components

Who to study

Endpoint for an individual trial participant

Treatment

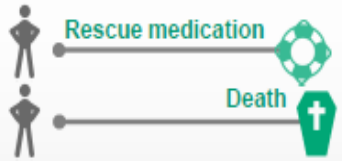
Treatments being compared

Population

Variable

Population-level summary

The description of an estimand will not be complete without reflecting how potential intercurrent events are addressed in the scientific question of interest.



Intercurrent Events and Missing Values

Estimand framework allows pre-specification of (some) intercurrent events and handling of intercurrent events

- Results thorough data collection and analytical methods or strategies to handle intercurrent events prior to unblinding

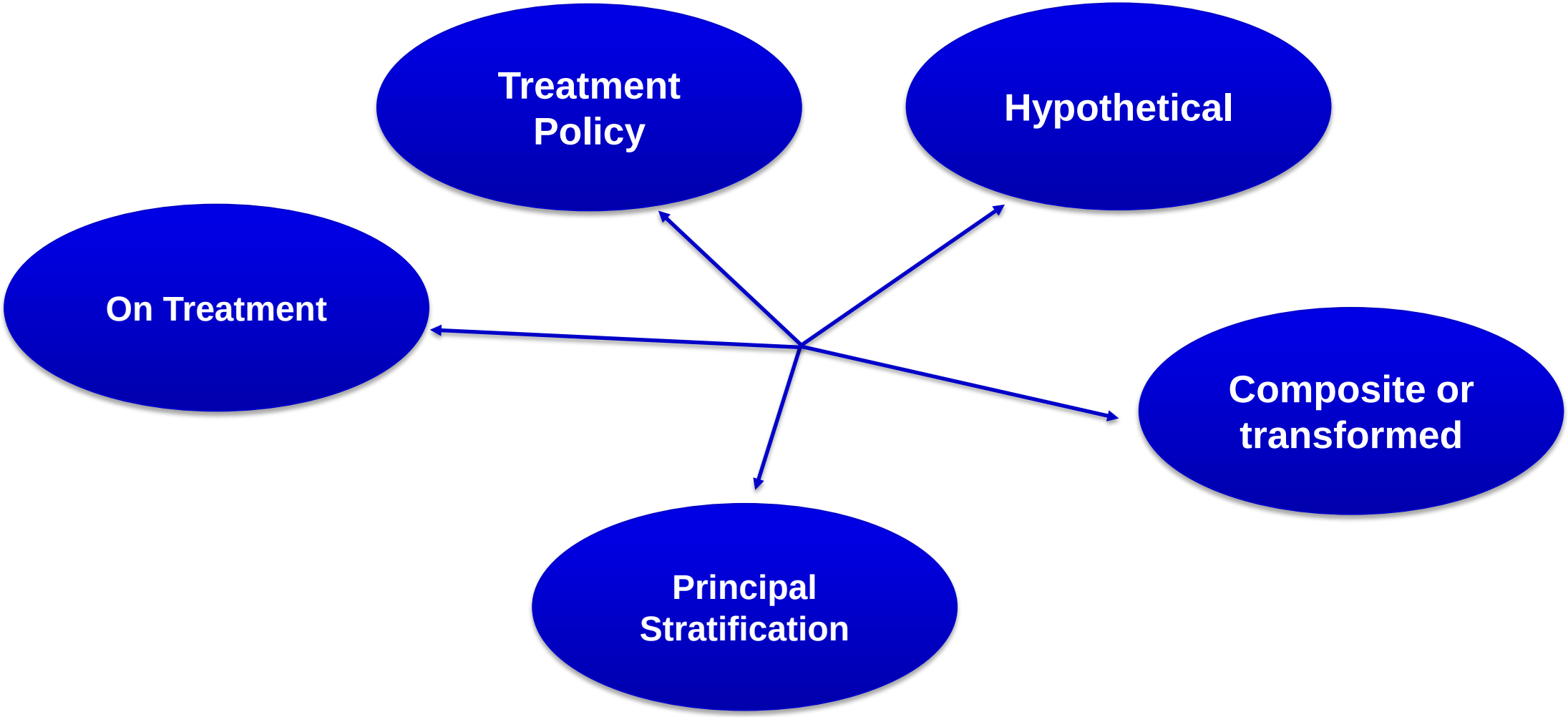
Missing data: *Meaningful data for analysis of an estimand but were not collected*

- After study withdrawal, after trial termination, due to missed visits or measurements

In an estimands framework, it is necessary to:

- Understand the **actual reasons** for intercurrent events
- Understand the **impact** these events might have on the interpretation of the actual data considering the research question
- **Pre-plan** for them in close cooperation among study team members of different disciplines

Strategies for Handling Intercurrent Events



Sensitivity Analysis vs Supplementary Analysis

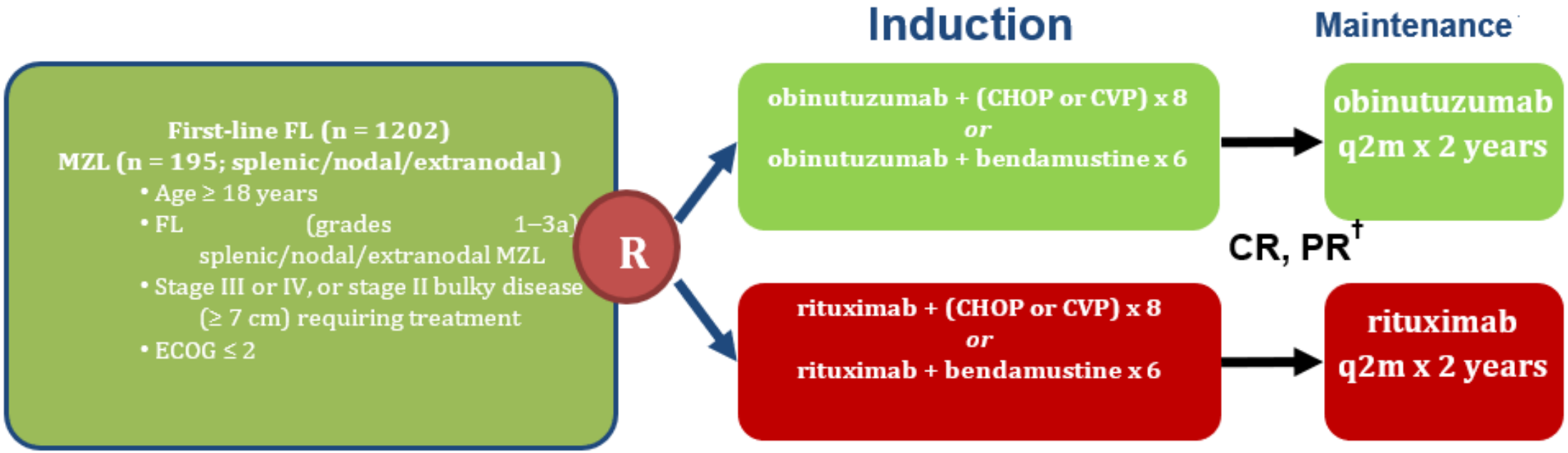
Sensitivity Analysis

A series of analyses targeting the same estimand, with differing assumptions to explore the robustness of inferences from the main estimator to deviations from its underlying modeling assumptions and limitations in the data

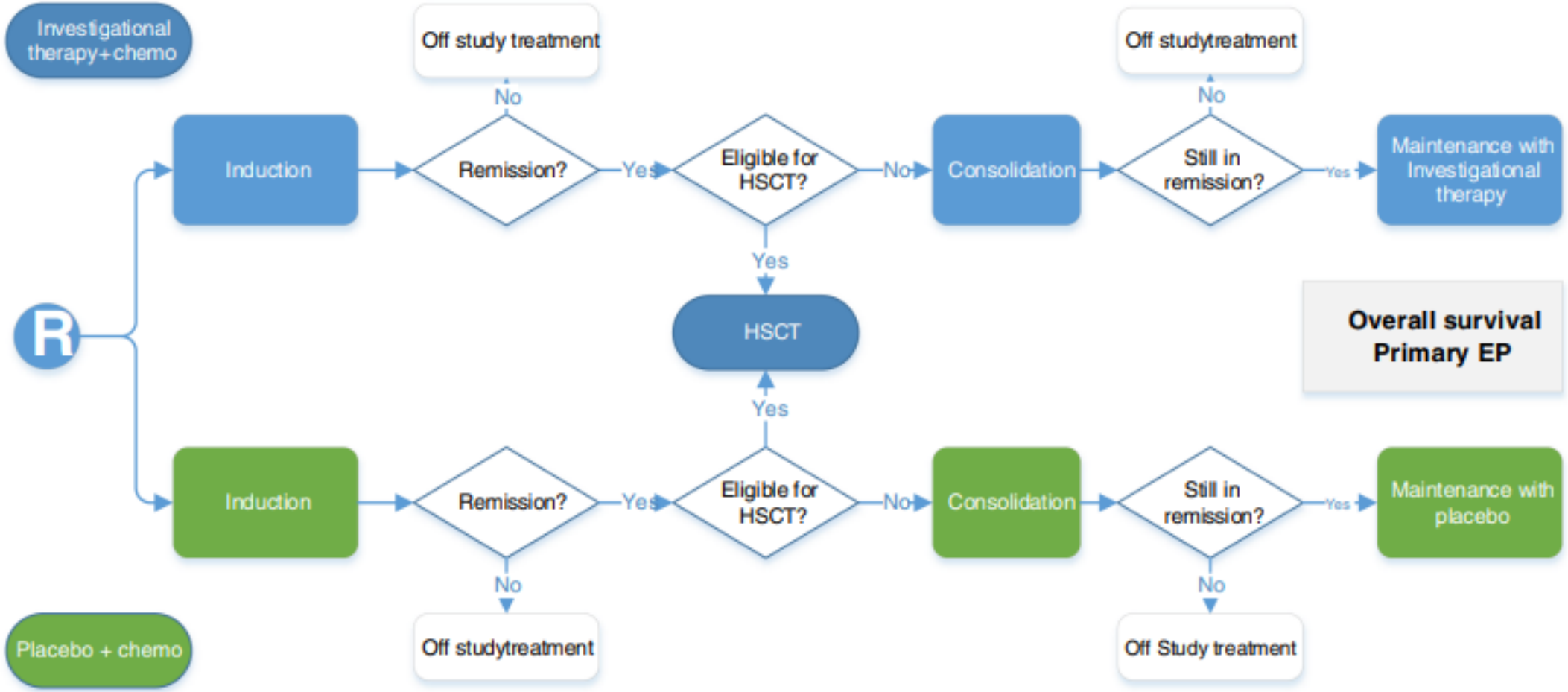
Supplementary analysis

A general description for analyses that are conducted in addition to the main analysis to provide additional insights into the understanding of the treatment effect. The term describes a broader class of analyses than sensitivity analyses. The need for, and utility of, supplementary analyses should be considered for each trial

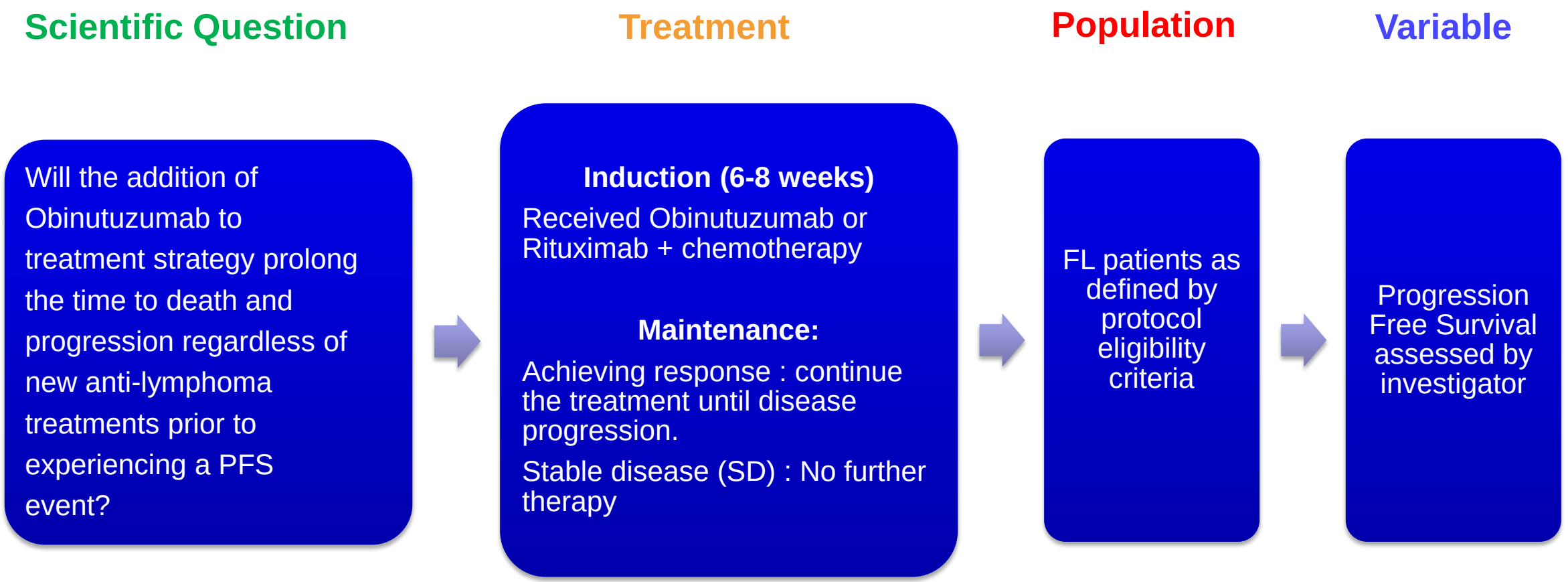
Example 1: Gallium Study



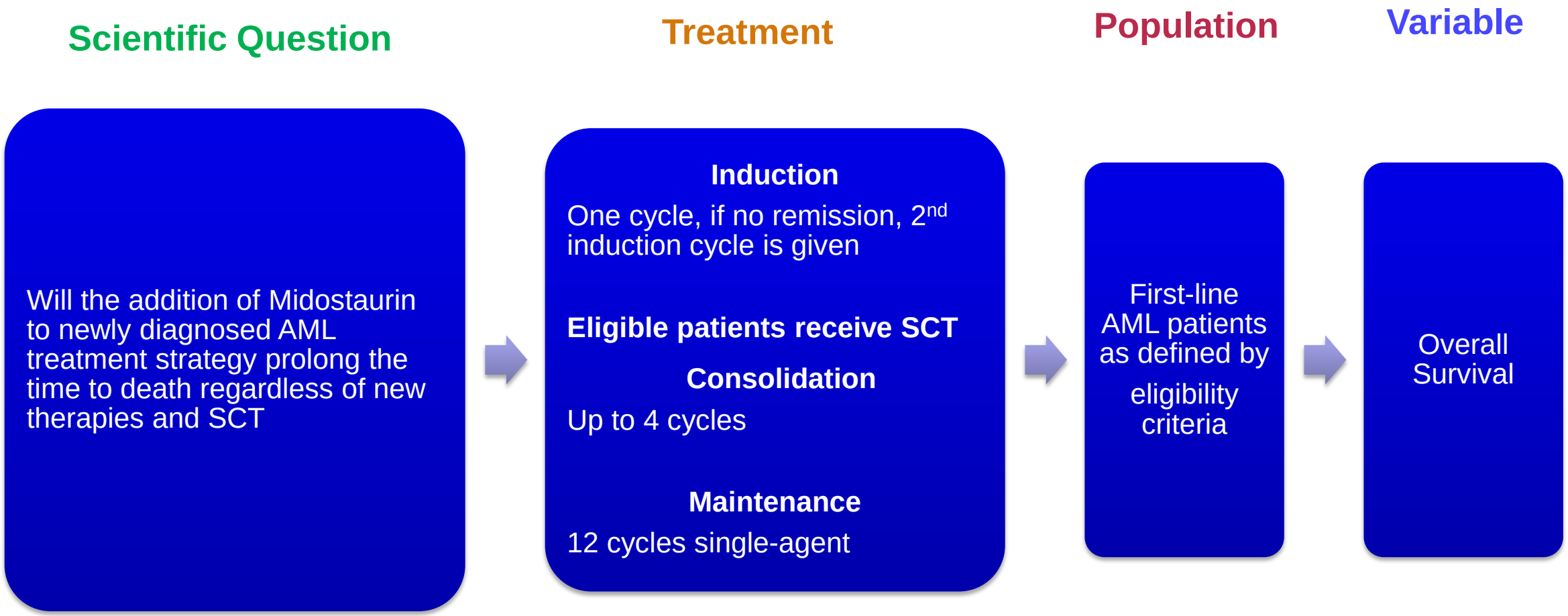
Example 2: RATIFY Study



Estimand Framework for Gallium Study



Estimand Framework for Ratify Study



Handling Intercurrent Events

Intercurrent event	Strategy addressing the event
Use of anti-multiple myeloma therapy prior to PFS events	**Treatment policy:** intercurrent event is ignored **Used for Gallium and Ratify studies**
Premature discontinuation of study medication	
Possible alternative	**Hypothetical:** Patients who received anti-cancer therapy are assumed to have the same risk as those who did not receive subsequent anti-cancer therapy

Summarizing Treatment Effect

- **Assumption:**
  - non-informative censoring (missing at random for missing disease assessment or after study withdrawal, loss to follow-up, etc)
  - proportional hazard (PH)

- **Analysis method:**
  - **Stratified Cox regression model (with stratification factors used in randomization) for without adjustment by other covariates**

Design Challenges

How to isolate the treatment benefit in each phase (FDA's concern)?

- Overall benefit may be driven by the induction phase only
- Re-randomization may be necessary to estimate the effect of maintenance

What is appropriate follow-up time?

Can HR capture the benefit of treatment?

- Constant proportional hazard at two treatment phases?
- Patients with stable disease won't get maintenance treatment

Common Sensitivity and Supplementary Analyses for Progression Free Survival

Sensitivity Analysis

- Stratified cox regression using PFS by independent review committee (IRC-PFS)
- Unstratified Cox regression
- Imputing informative censoring
- Censoring for 2 or more consecutive missing assessment

Supplementary Analysis

- Analysis using per protocol (PP) population
- Censoring at subsequent therapy
- Covariate-adjusted analysis

Common Sensitivity and Supplementary Analyses for Overall Survival

Sensitivity Analysis

- Imputing informative censoring
- Unstratified Cox regression

Supplementary Analysis

- Censor at subsequent anti-cancer therapy
- Rank preserving structural failure time (RPSFT) model
- Inverse probability censoring weighting (IPCW) analysis
- Two-stage approach

Violation of Proportional Hazard (PH)

For NPH, a single measure is often inadequate to summarize the treatment effect

- More than one clinical question or “estimand” need to be answered to understand treatment effect
- Traditional effect like HR and Median are often inadequate

Stepwise approach helps practitioners to provide appropriate summary

- Test for rejecting null
- Assessing PH assumption
- Choice of proper summary based on the variability of PH assumption

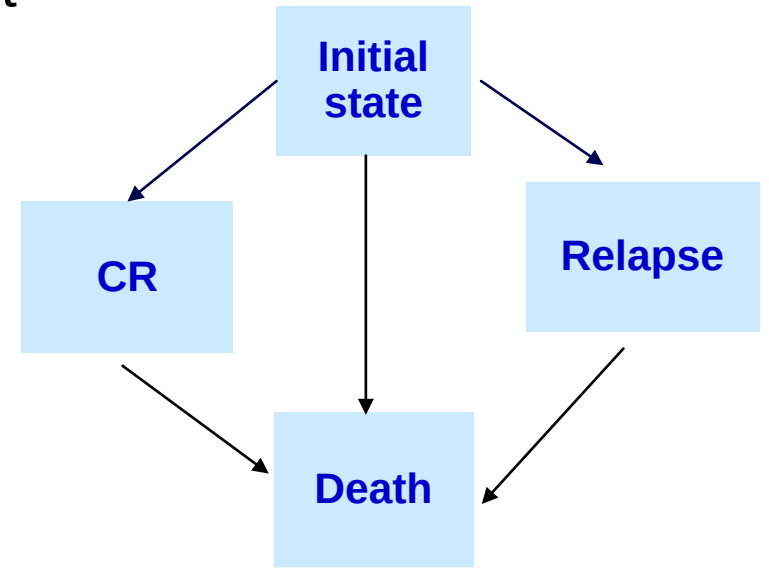
Flexible and interpretable measures are required for totality of evidence

NPH is often driven by heterogeneity of effect in disease specific subgroups

- Supplementary analysis are important to understand the treatment effect
- Requires appropriate methodology (principal stratification) for post-hoc subgroup analysis

Evaluating Stage-wise Effect

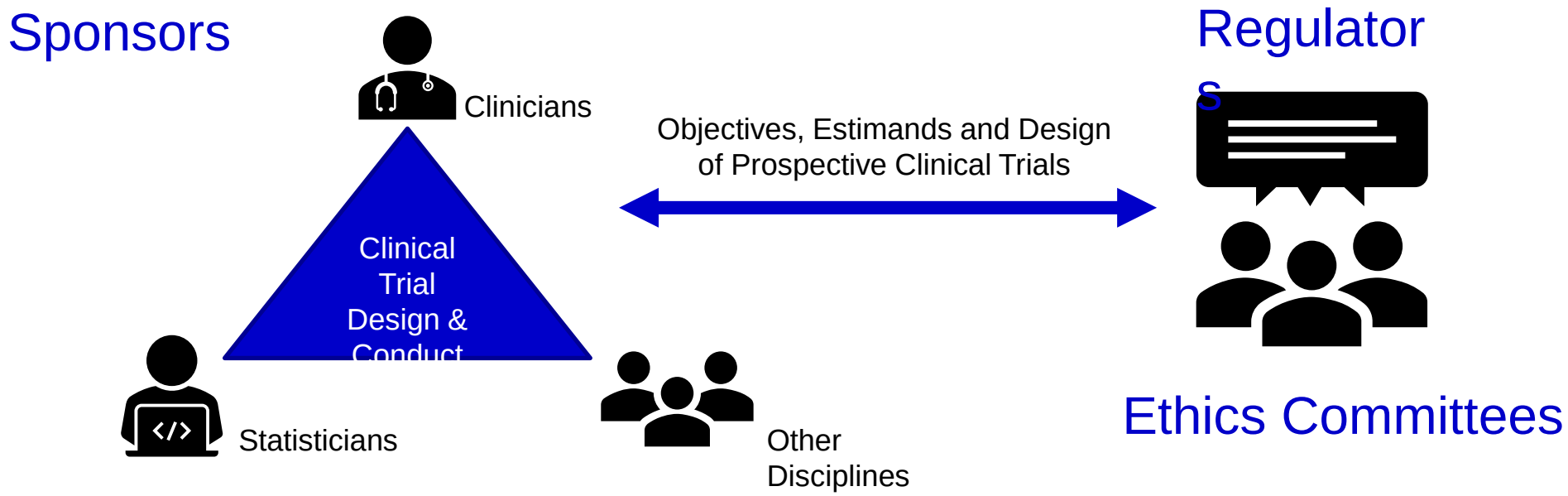
- Design with induction and maintenance phase
  - How to isolate the treatment benefit in each phase (FDA's concern)?
- Use of multistate survival model
  - Example: Considers complete remission as intermediate events to investigate the impact of the maintenance phase on the treatment effect
  - Other models are possible based on the design
  - Appropriate summary measures need to be chosen



Use of ***"While on treatment strategy"***

Multi-disciplinary Collaboration is the Key to Success

It is a multi-disciplinary undertaking and should be the subject of discussion between sponsors and regulators



Conclusion

- The estimand framework lends itself to a more transparent way of specifying each objective of a trial and ensuring alignment with the selected estimator/analysis method
- Detailed pre-specification of sensitivity and supplementary analyses are required
- Estimand(s) need to be included in the study protocol and statistical analysis plan (SAP) for the study
- To assess the contribution of each treatment phase of a sequential treatment strategy requires further work

Thank You