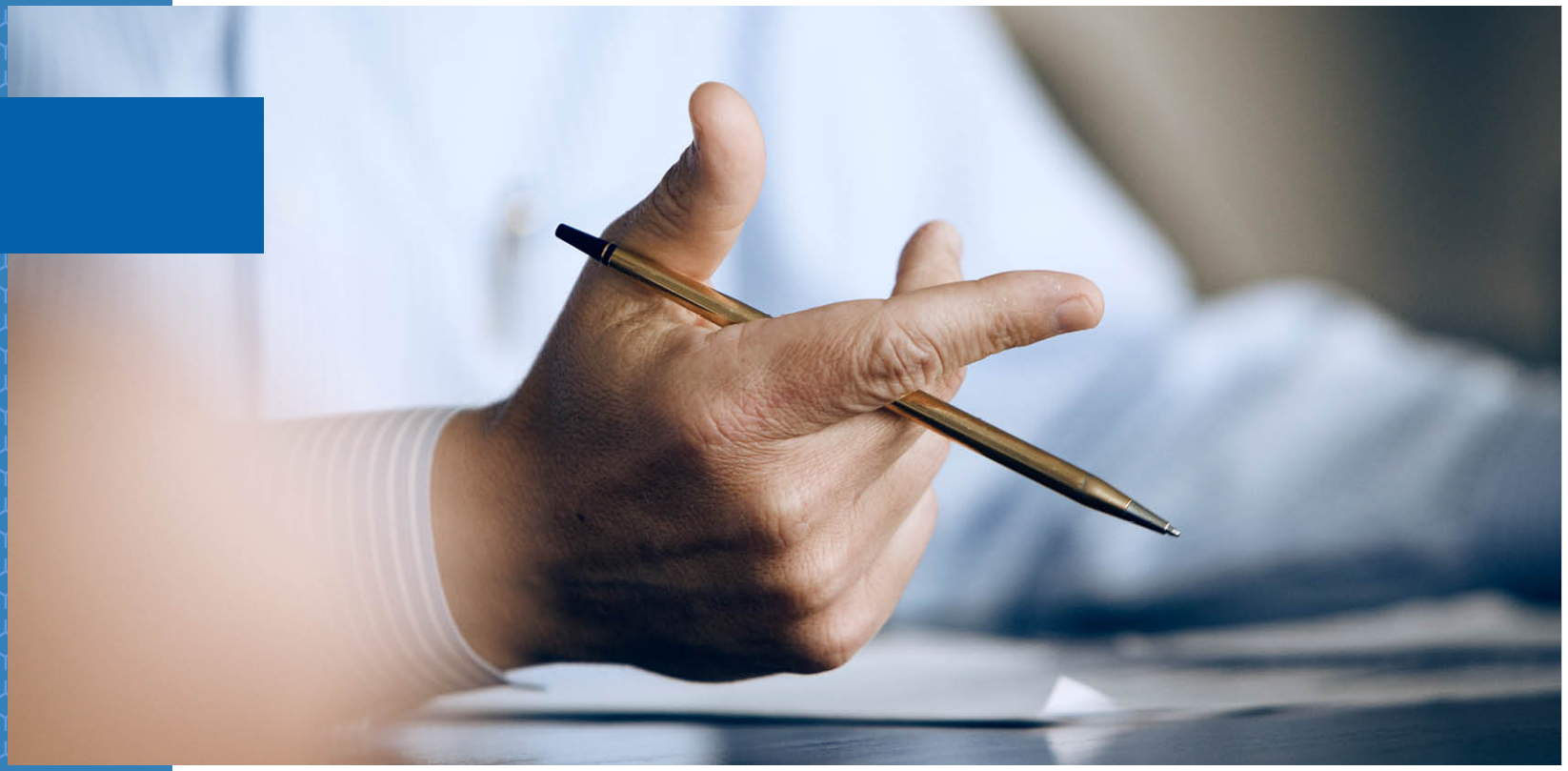

Need for Treatment strategy as an estimand attribute – A case study of CAR-T in lymphoma

Emmanuel Zuber
on behalf of Novartis Team

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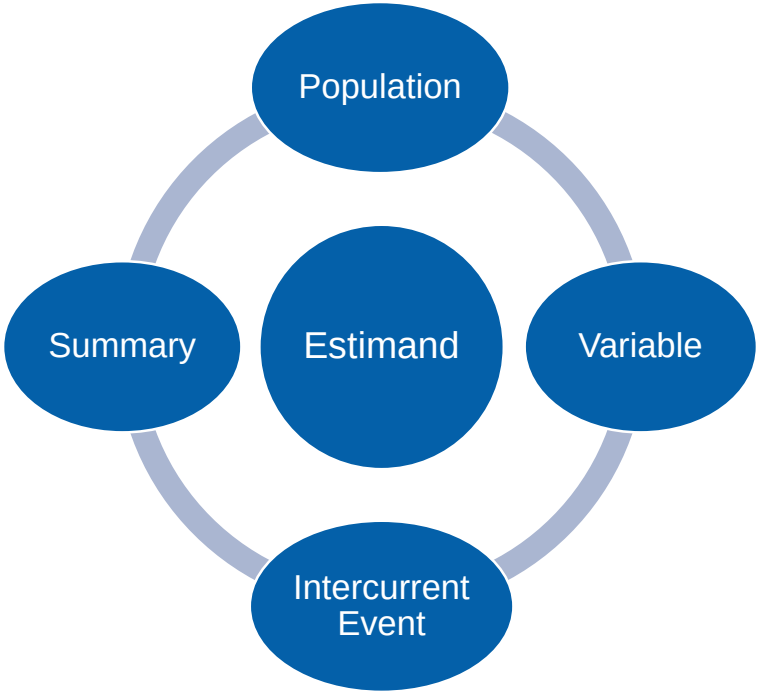
What is the Estimand framework

ICH E9 Addendum

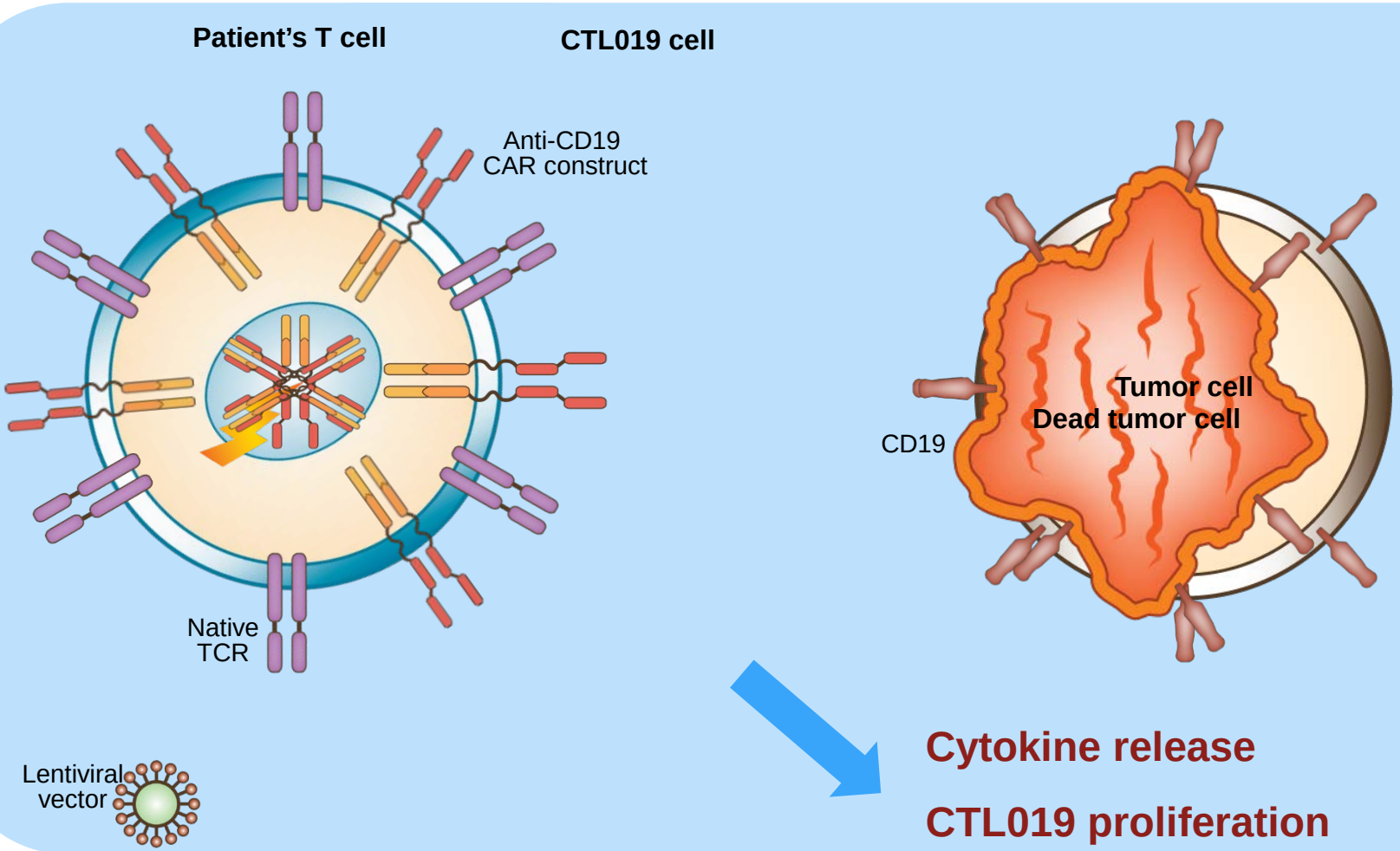
- A structured **framework** that translates the **trial objective** into a precise definition of the **treatment effect** that is to be estimated

- It aims to **facilitate the dialogue** between disciplines involved in clinical trial planning, conduct, analysis and interpretation, as well as **between sponsor and regulator**, regarding the treatment effects of interest that a clinical trial should address



Kymriah (CTL019) – Chimeric antigen receptor T cell (CAR-T) therapy

A living drug designed to target CD19+ B cells



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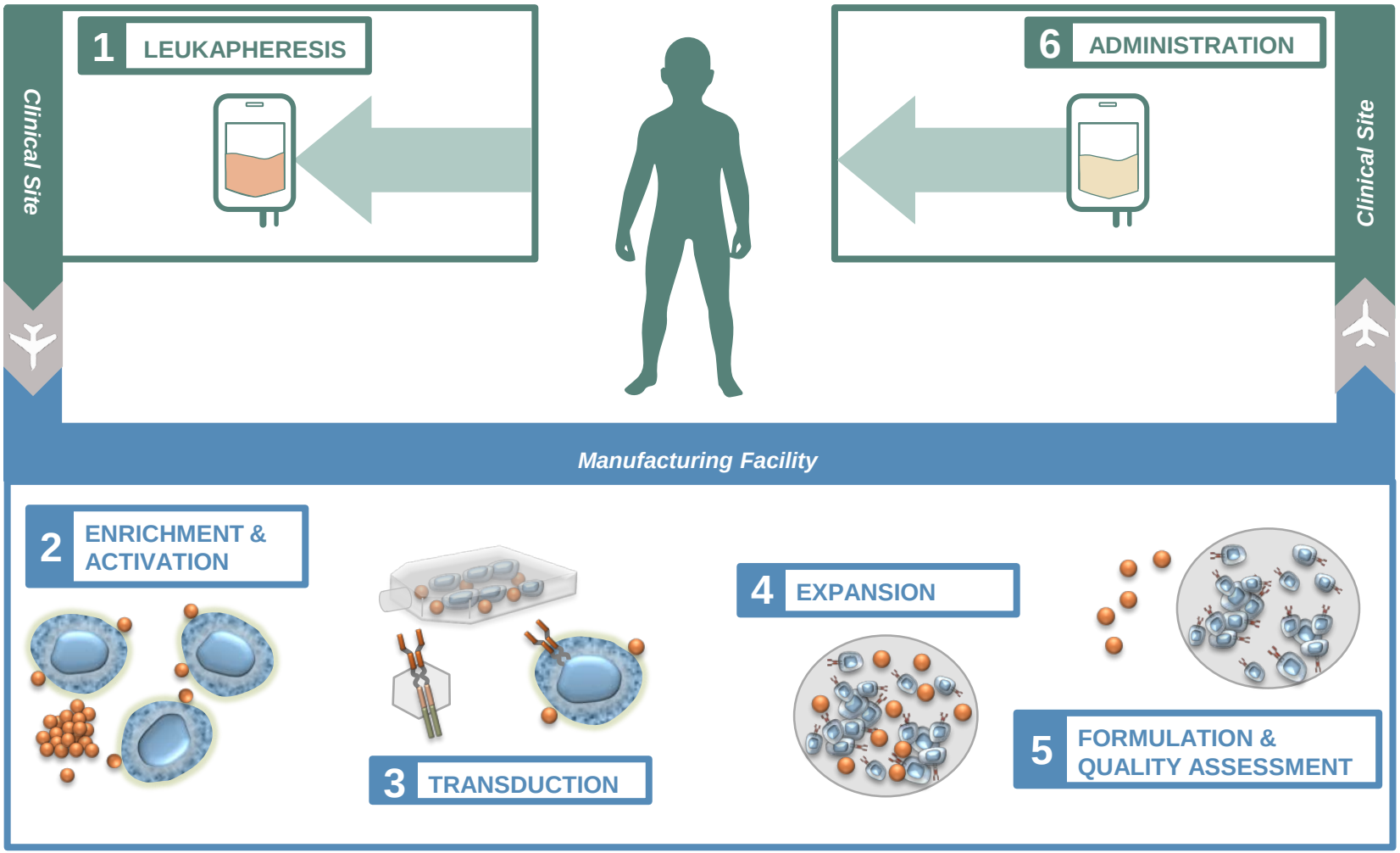
CAR-T Cell Manufacturing process



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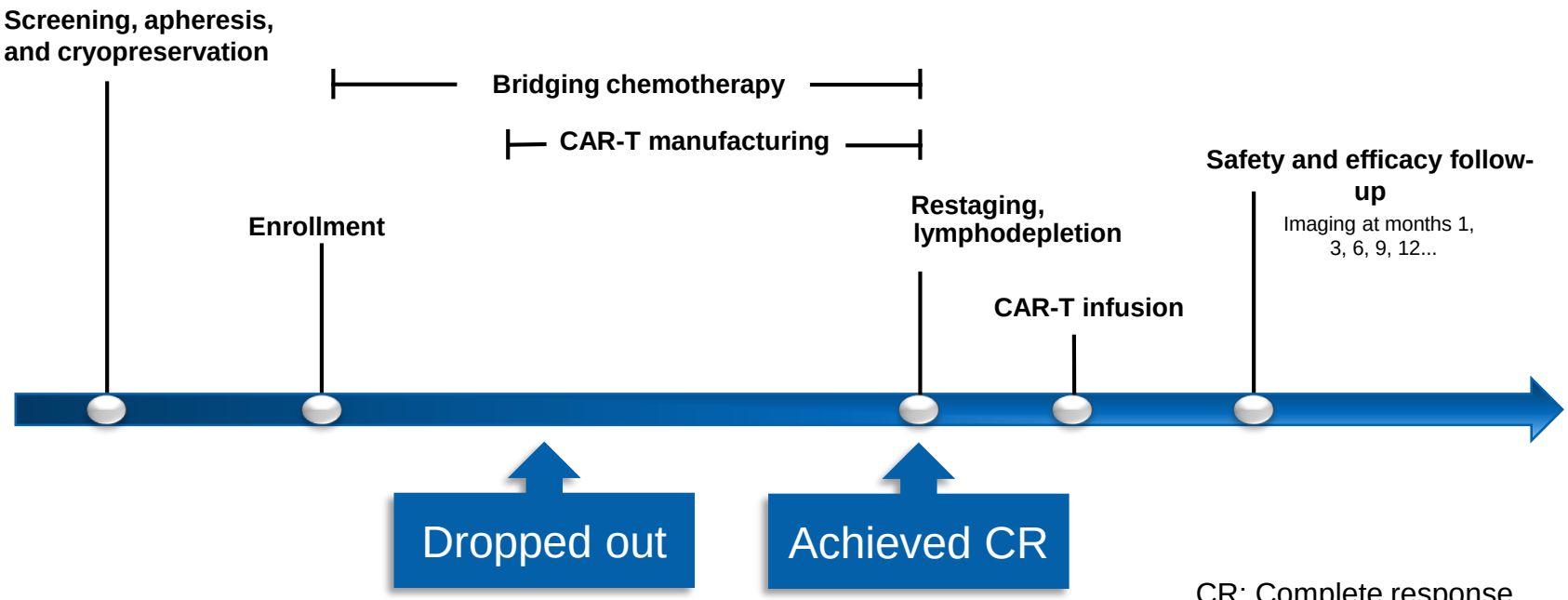
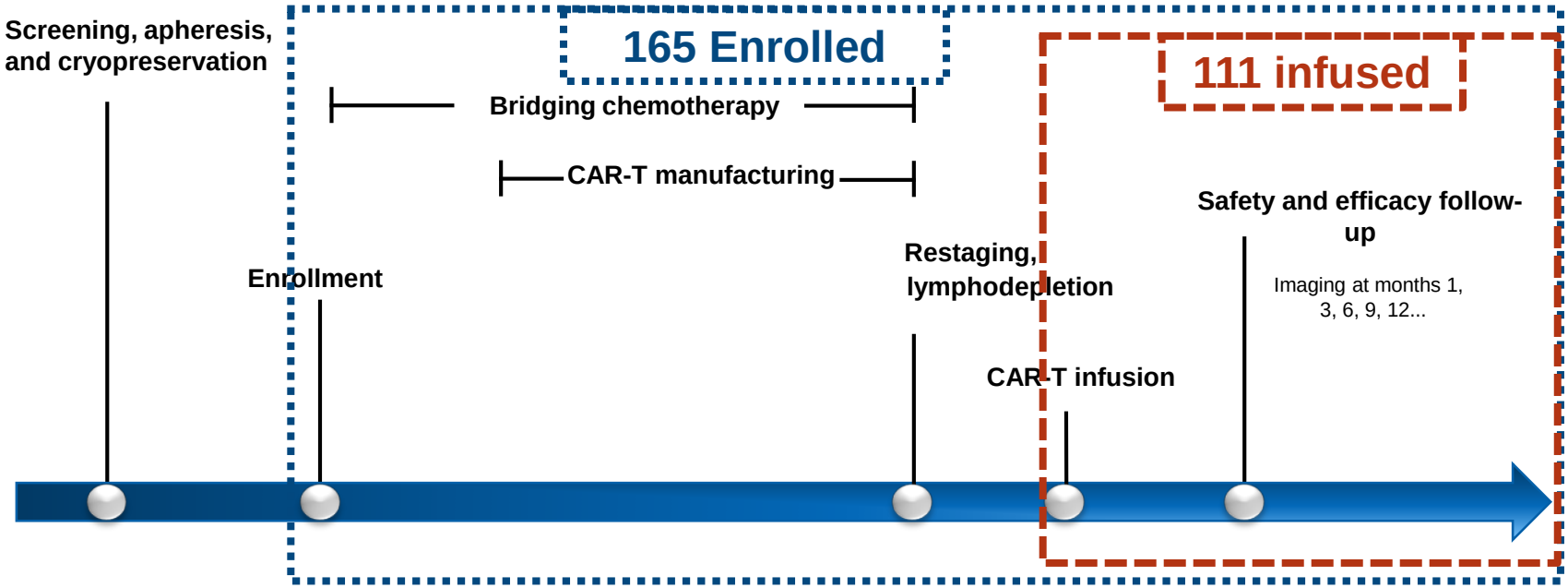
Motivating example: Pivotal Phase II Single Arm Study

- Adult relapse or refractory diffuse large B cell lymphoma (DLBCL) patients after 2 systematic therapies
- Primary endpoint: Overall Response Rate (ORR) <u>in All Infused Patients</u>



CR: Complete response

What is the treatment effect of interest?



- **CAR-T infusion? (Infused set)**
- **Bridging chemo followed by CAR-T infusion? (Enrolled set)**

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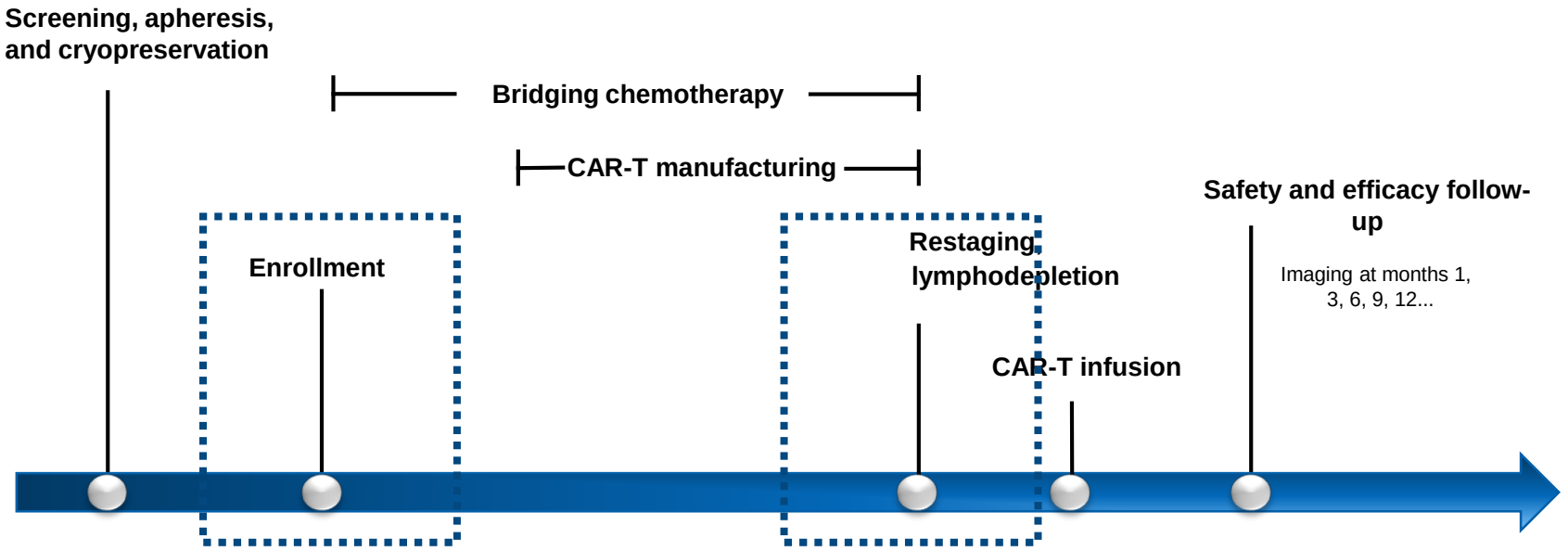
What is the proper baseline?



- Timing of baseline?
- Evidence of disease at baseline?
  - At enrollment, all patients had disease
  - Some patients may have transient response to bridging chemotherapy prior to CTL019 infusion

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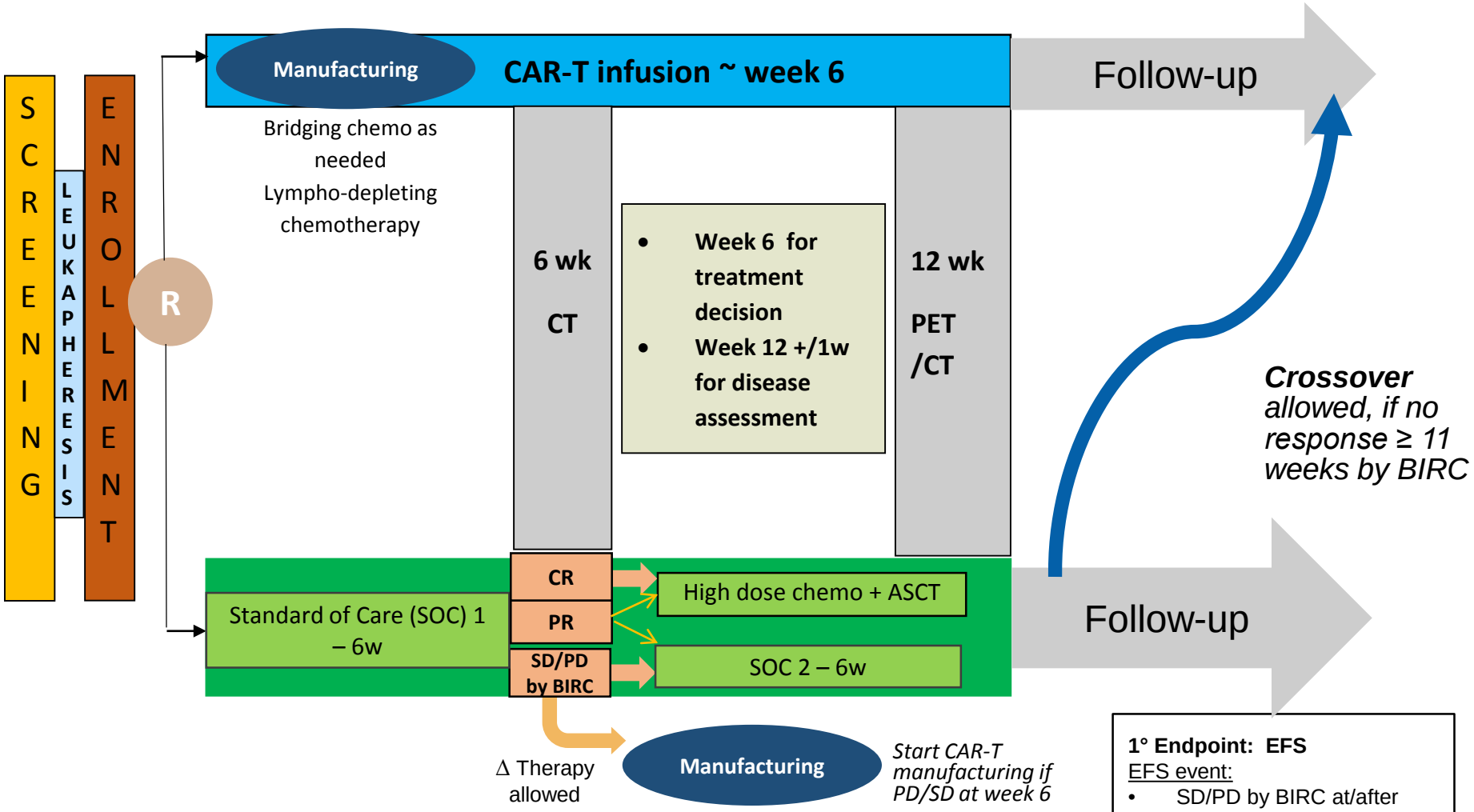
Regulatory feedback during Kymriah approval process

- EMA: Focused on enrolled patients with evidence of disease at enrollment
  - Sensitivity analyses performed using **all enrolled patients regardless of disease status prior to CAR-T infusion** for all relevant endpoints

- FDA: Focused on infused patients with evidence of disease prior to infusion
  - Retrospectively identified **sub-group among infused patients**
    - Excluded patients without documented disease after bridging and prior to CAR-T infusion

CAR-T Phase III study design

Earlier line; patients eligible for allo stem cell transplant (ASCT)



Questions to be addressed

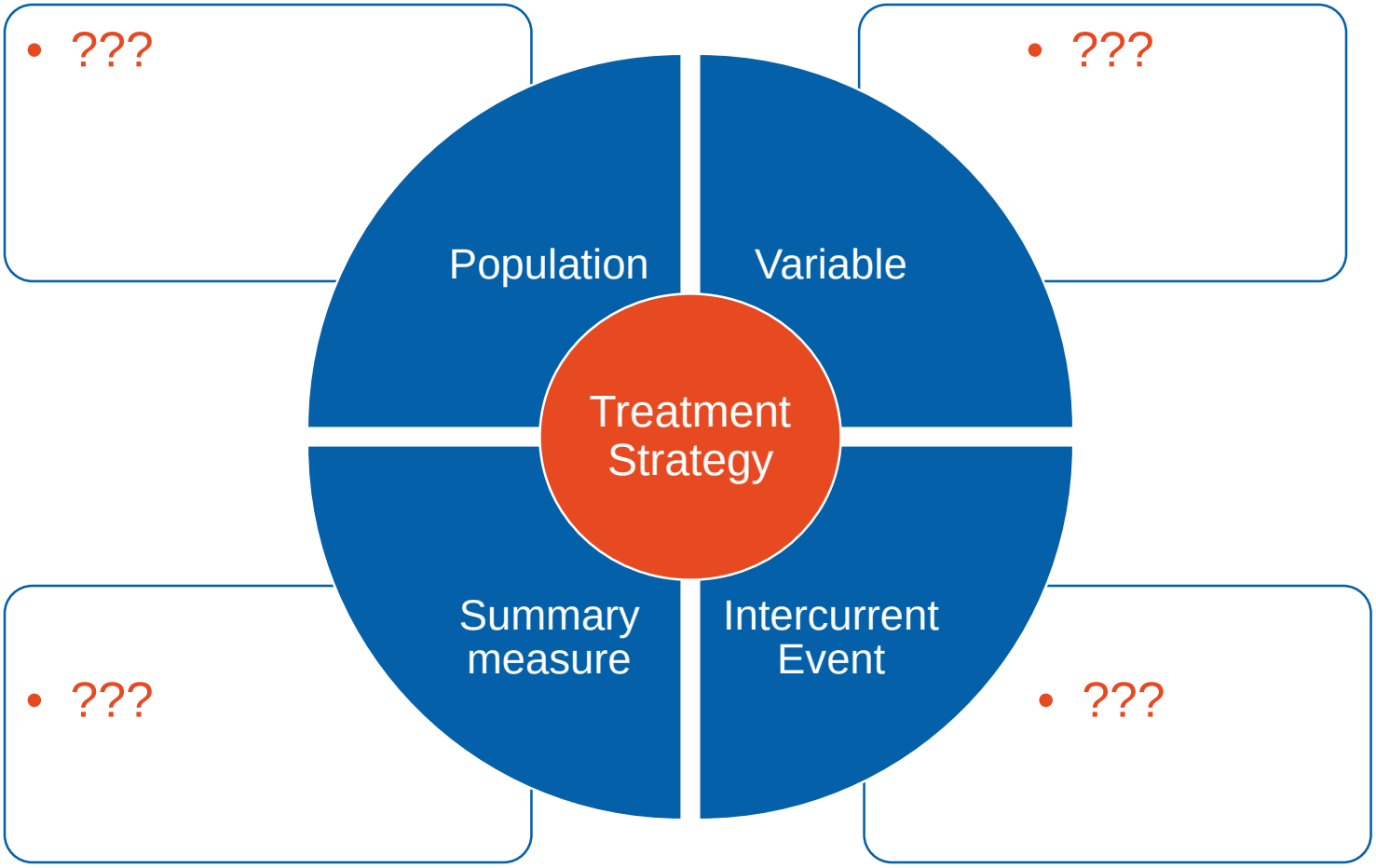
- What is the scientific objective?
- What is the treatment effect of interest?
  - Entire strategy or only CTL infusion?
  - What is the right timing of randomization?
- What are the intercurrent events and how to handle them?
- How to test for the presence of a treatment effect and measure its size?

Challenges in defining the treatment effect

- CAR-T treatment not readily available at randomization:
  - Patients in CAR-T arm need to wait, and may take bridging therapy
  - Tumor may progress or respond to bridging therapy, before receiving CAR-T
  - Manufacturing process may fail and patients may not receive CAR-T
  - Delayed treatment effect and possible curative effect are expected: highly non-proportional hazards
- SOC is a complex treatment algorithm:
  - Possibly involving several lines of treatment, including ASCT or not
  - Decisions made based on tumor response to different treatment courses
  - In contrast, CAR-T is a single infusion, regardless of response to bridging therapy
- Crossover needs to be allowed:
  - CAR-T approved in US & EU in patients after 2 or more lines of treatment
  - No other available option for patients failing SOC

Estimand

Defining treatment strategy is a critical step to define other estimand attributes!



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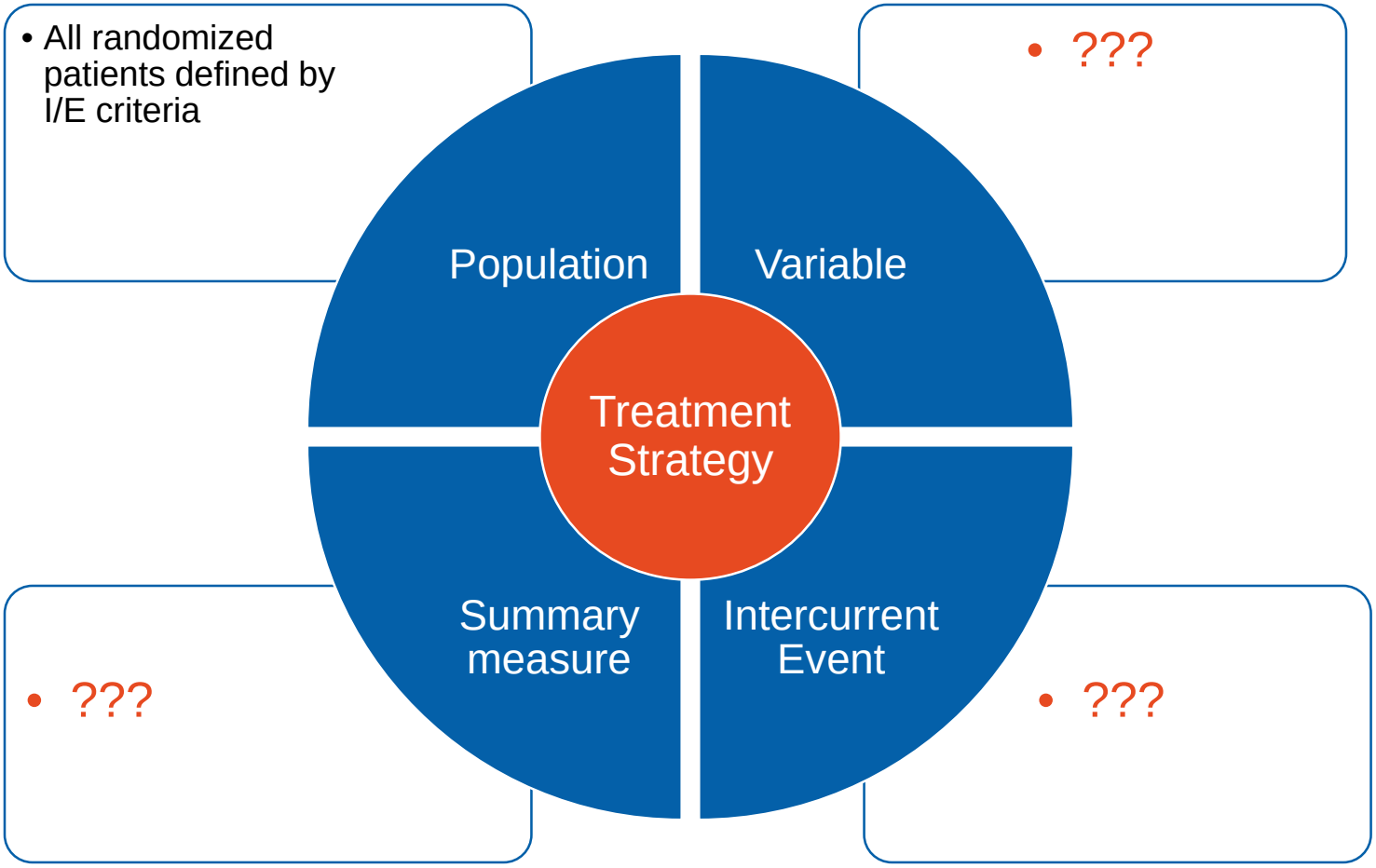
Complex treatment strategies

- **CAR-T strategy:**
  - CTL019 after optional bridging chemotherapy and lymphodepleting chemotherapy
- **SOC strategy:**
  - Standard of care chemotherapy followed by transplant (ASCT) if eligible
- Patients may not receive final treatment in both arms!!

Population:

All randomized patients regardless of receiving final treatment (CAR-T or ASCT)

Estimand



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Primary endpoint

Event-free survival (EFS):

- Composite event of disease progression / stable disease at or after 11 weeks post randomization; or death at any time
  - Disease progression prior to week 11 is not the final outcome of the treatment strategy

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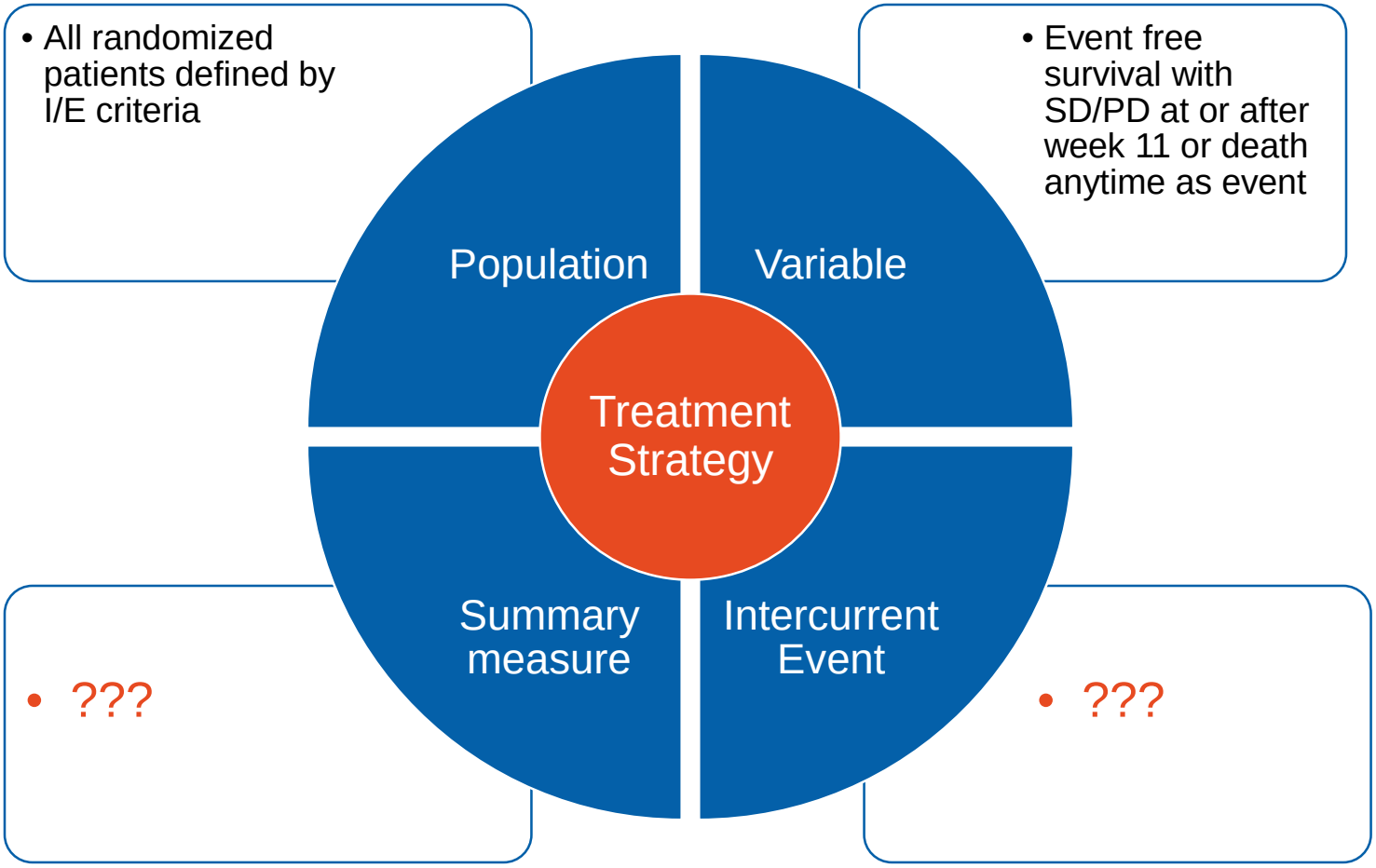

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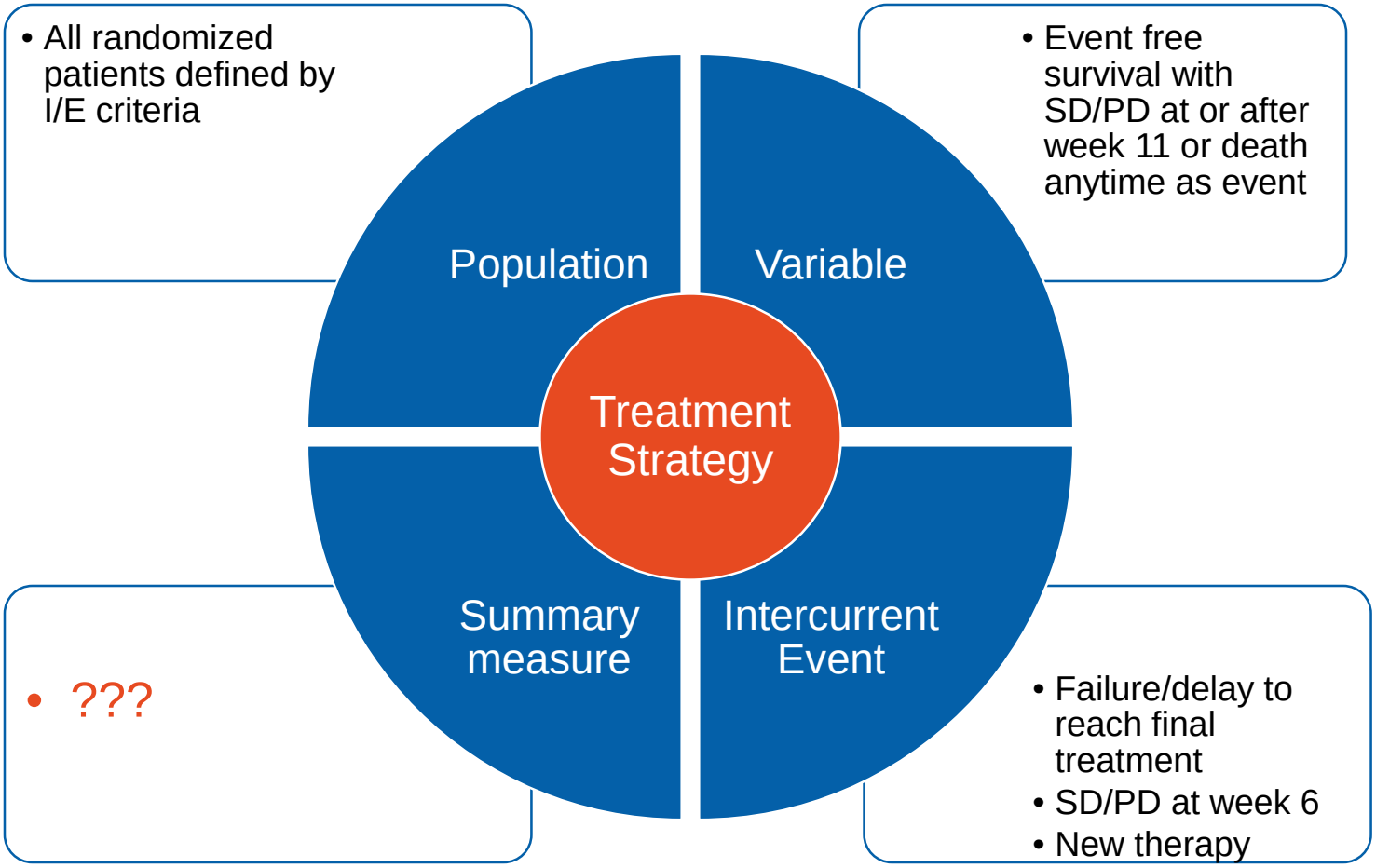
Intercurrent events

Intercurrent event	Handling strategy	Justification
Manufacturing failure in CTL019 arm, or failing to receive SCT in SOC arm	**Treatment policy:** Ignore, and follow patients until events or end of follow-up	Intrinsic to treatment strategy
New cancer therapy before observing event	**Hypothetical:** Censor	Not part of treatment strategy
SD/PD at Week 6	**Treatment policy:** Ignore, and follow patients until events or end of follow-up	Only used for treatment decision for SOC arm. Not used for CTL019 arm.

Estimand



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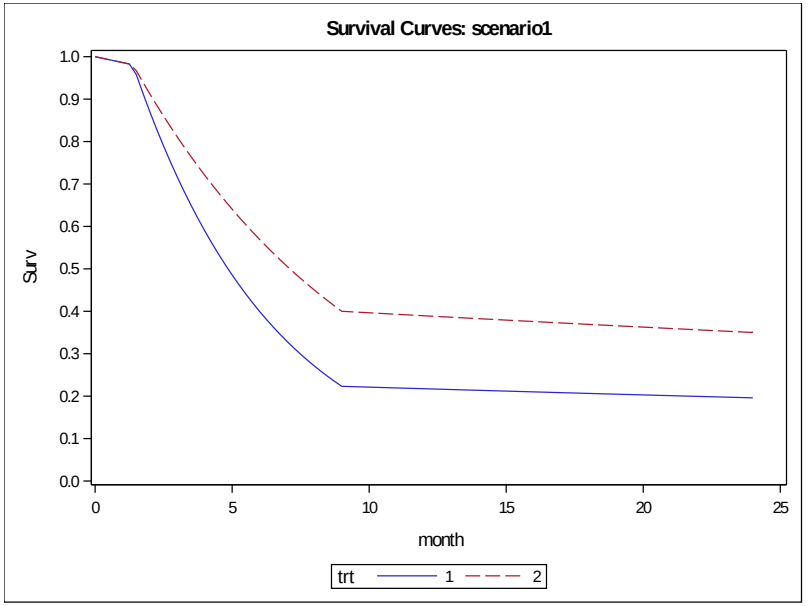
Summary measures

Challenge:

Non-proportional hazards

- Both arms are on a very similar treatment before CTL is available (in case of bridging therapy).
- Plateauing after ~9 month



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Estimation of treatment effect

Which one (or which ones) should be of interest?

- Cox HR
- Weighted HR
- Piecewise HR
- Difference in restricted mean survival time
- Difference in milestone survival
- Difference in median survival
- Other?

Hypothesis testing

What is the primary focus?

Focus on the comparison during all periods after randomization

- Regular log-rank test
- Weighted log-rank tests (e.g. Fleming-Harrington)
- Max combo tests

More focus on comparison during periods where differences are expected

- Piecewise weighted log-rank test (e.g. assigning 0 weight during period there is no difference expected)

Both can be of interest!!

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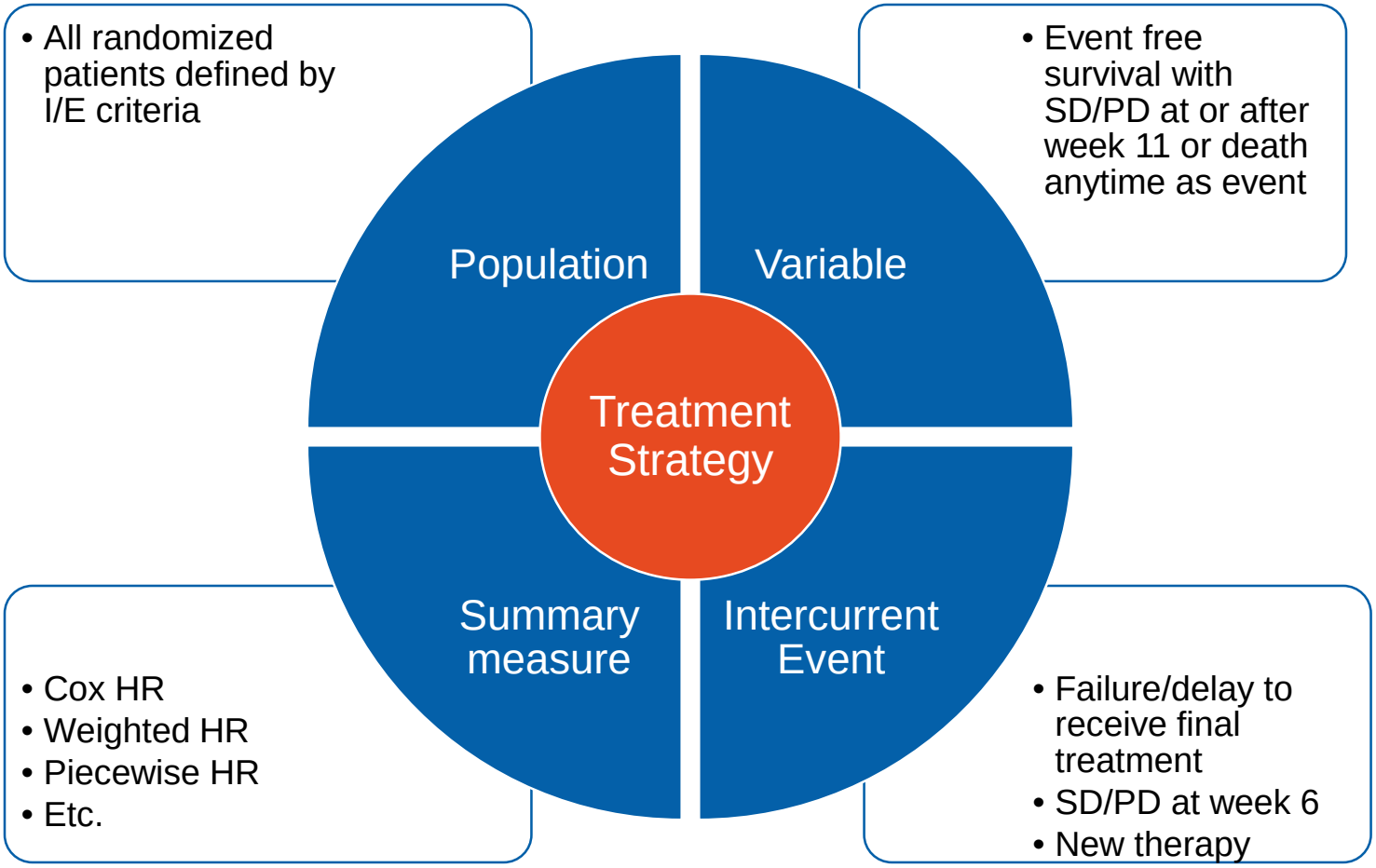
• All randomized patients defined by I/E criteria
• Event free survival with SD/PD at or after week 11 or death anytime as event
Population
Variable
Treatment Strategy
Summary measure
Intercurrent Event
• Cox HR
• Weighted HR
• Piecewise HR
• Etc.
• Failure/delay to receive final treatment
• SD/PD at week 6
• New therapy

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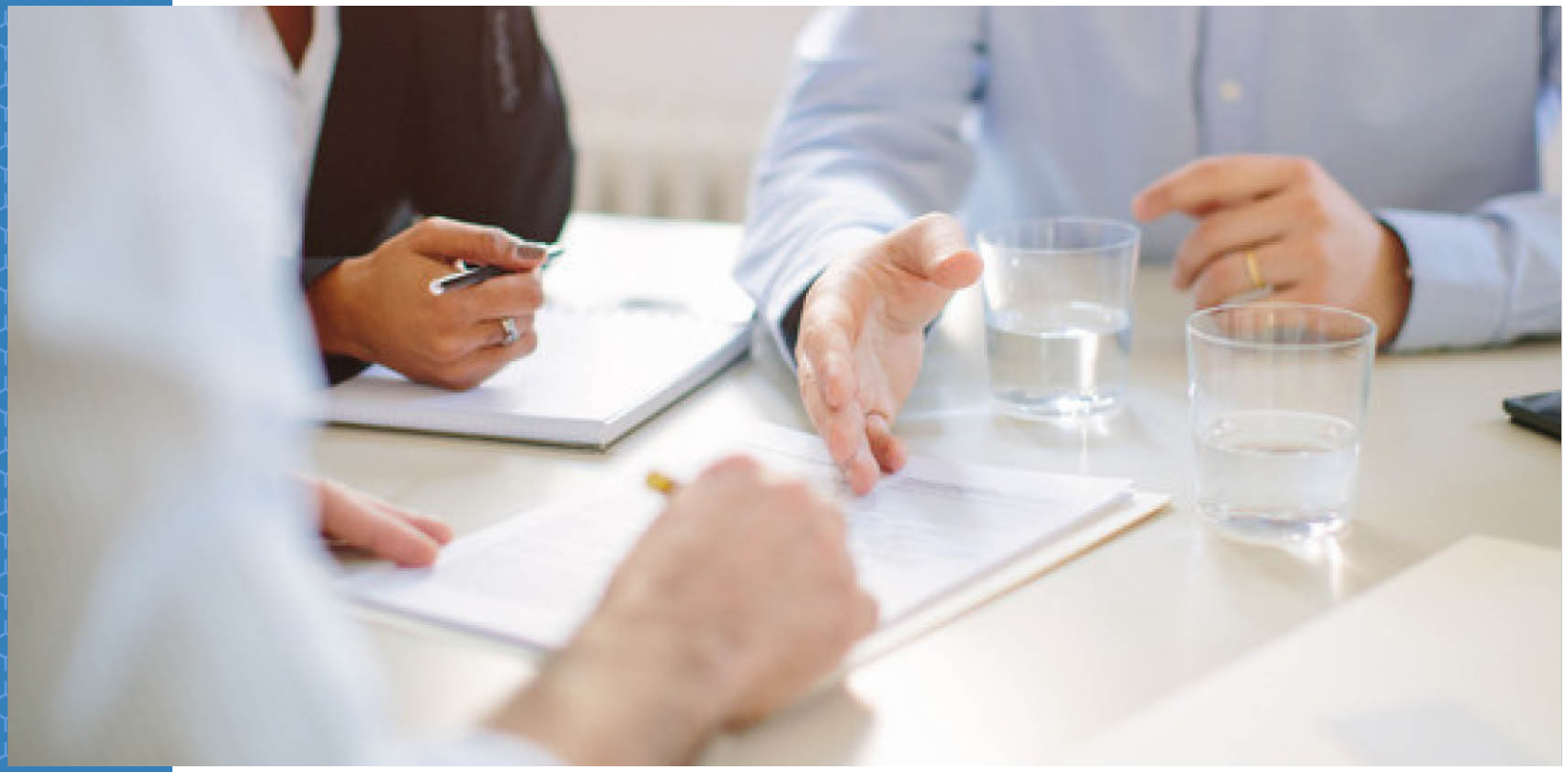

Thank you

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