DESIGN AND ANALYSIS CONSIDERATIONS OF CAR-T STUDY

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DISCLAIMER

THE PRESENTATION REFLECTS THE VIEWS OF THE AUTHOR AND SHOULD NOT BE CONSTRUED TO REPRESENT FDA'S VIEW OR POLICIES

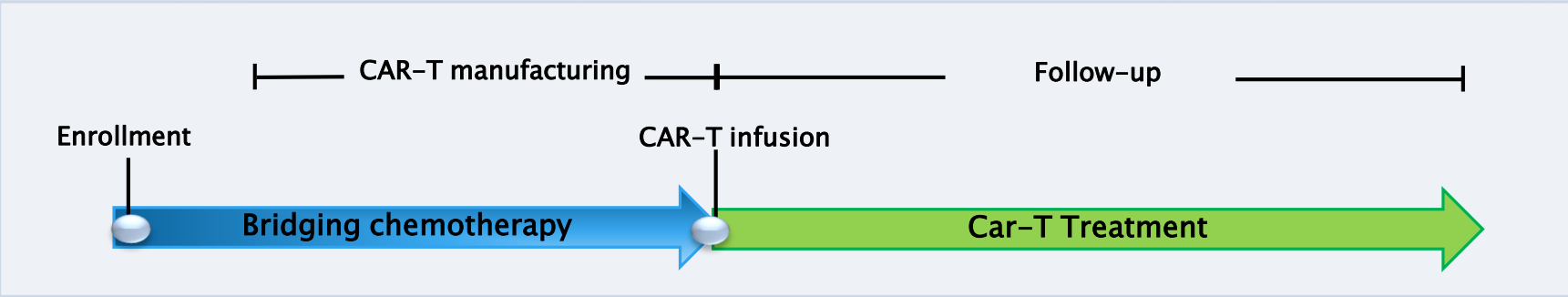
OUTLINE

- UNIQUE FEATURES OF CAR-T PRODUCT
- STATISTICAL CHALLENGES ON DESIGN AND ANALYSIS OF CAR-T STUDY
  - RANDOMIZED, CONCURRENT-CONTROLLED DESIGN SETTING
  - TIME-TO-EVENT ENDPOINTS

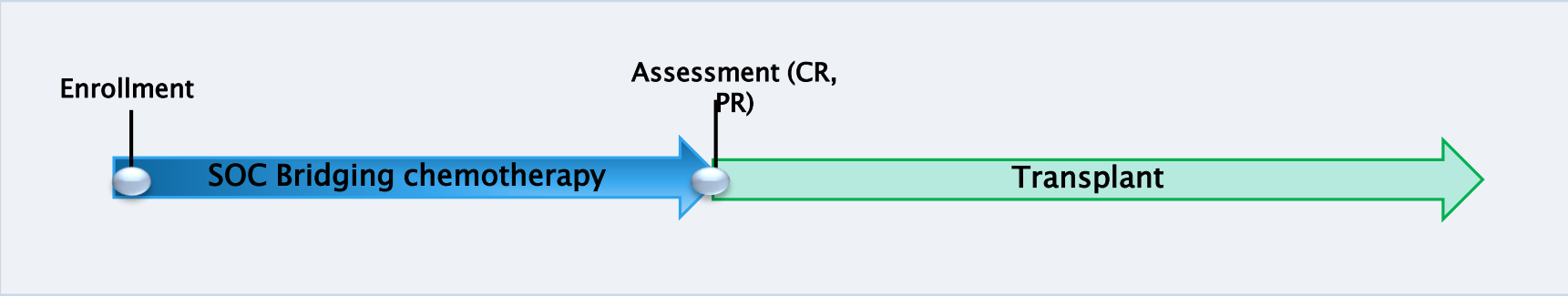
UNIQUE FEATURES

UNIQUE FEATURES

- CAR-T: MANUFACTURE



- STANDARD OF CARE (SOC):

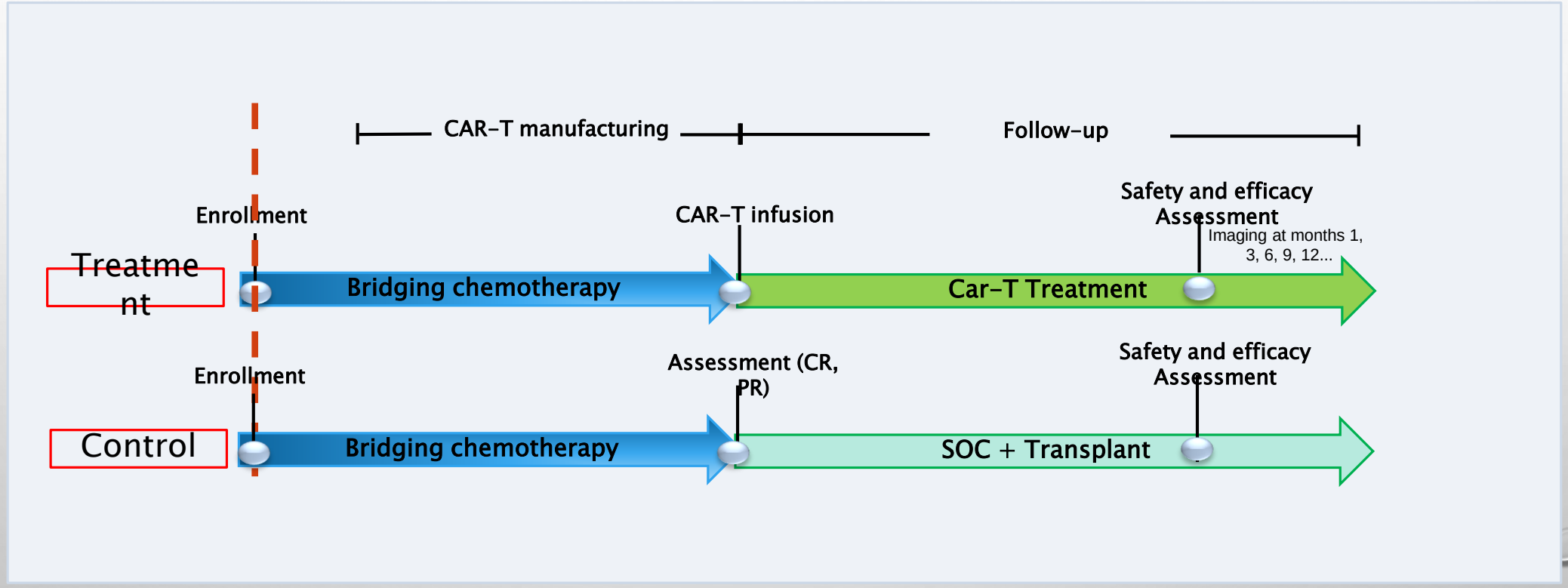


STATISTICAL CHALLENGES

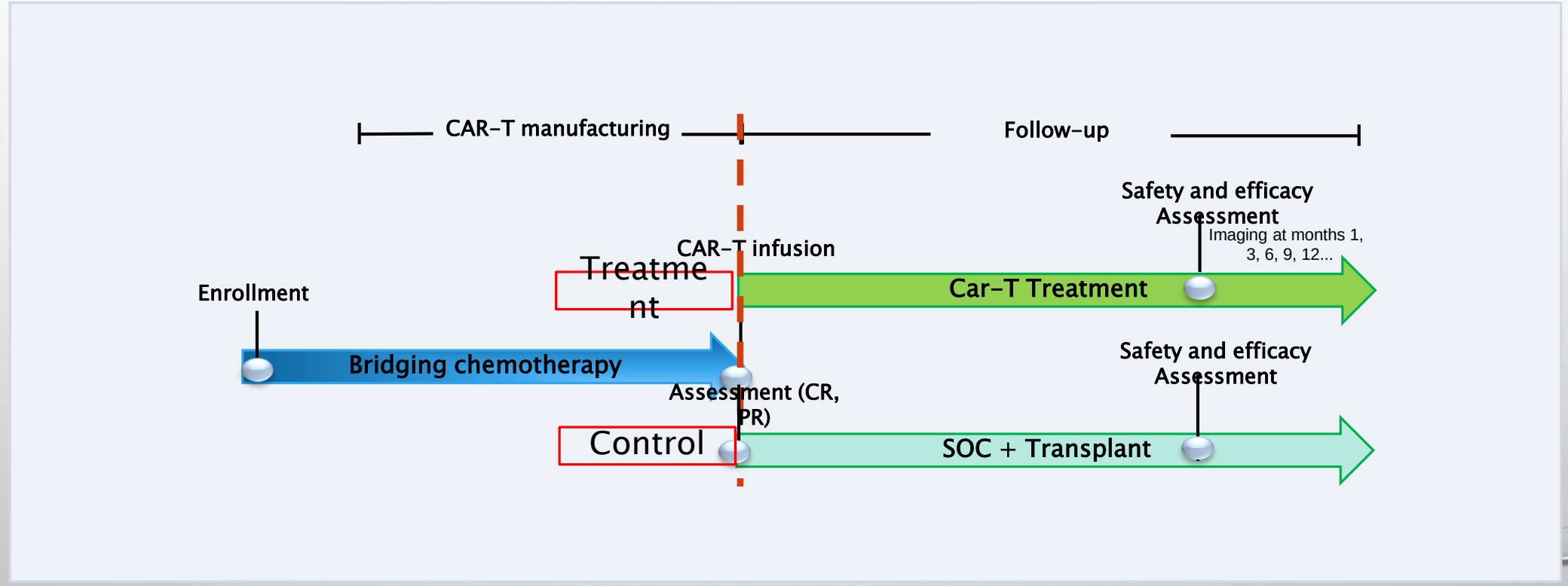
CHALLENGE #1.

MANUFACTURE FAILURE AND DURATION

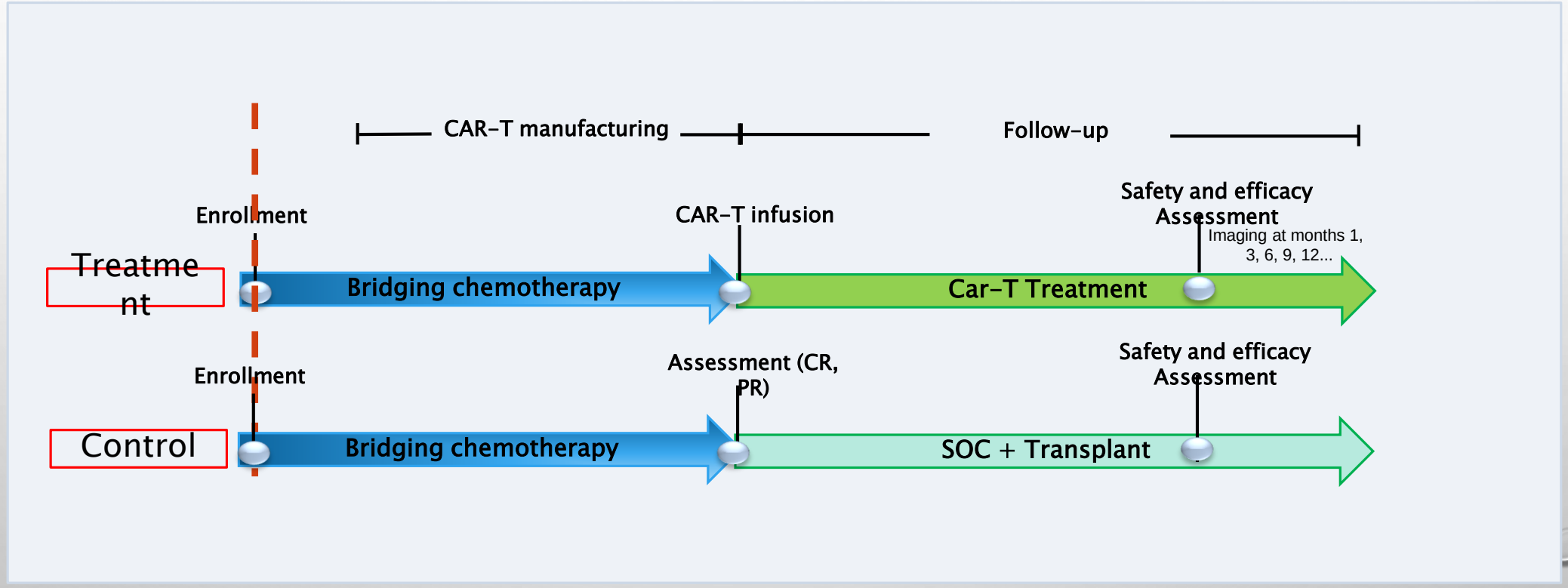
Randomization before manufacture



Randomization post manufacture assessment for transplant



Randomization before manufacture



Randomization before manufacture

Drawback 1. Under-estimation of treatment effect

- MANUFACTURE FAILURES OR INELIGIBILITY FOR TRANSPLANT:
  - NEGATIVELY AFFECT ASSESSMENT AND INTERPRETATION OF CAR-T EFFECT

Randomization before manufacture

Drawback 2. Measuring relative effect of treatment strategy

- CAR-T AND SOC ARMS RECEIVE A SEQUENCE OF TREATMENT REGIMENS:
  - TREATMENT VS SOC CONTRAST MEASURES RELATIVE EFFECT OF TREATMENT STRATEGY
  - WHAT IS TREATMENT EFFECT OF INTEREST?

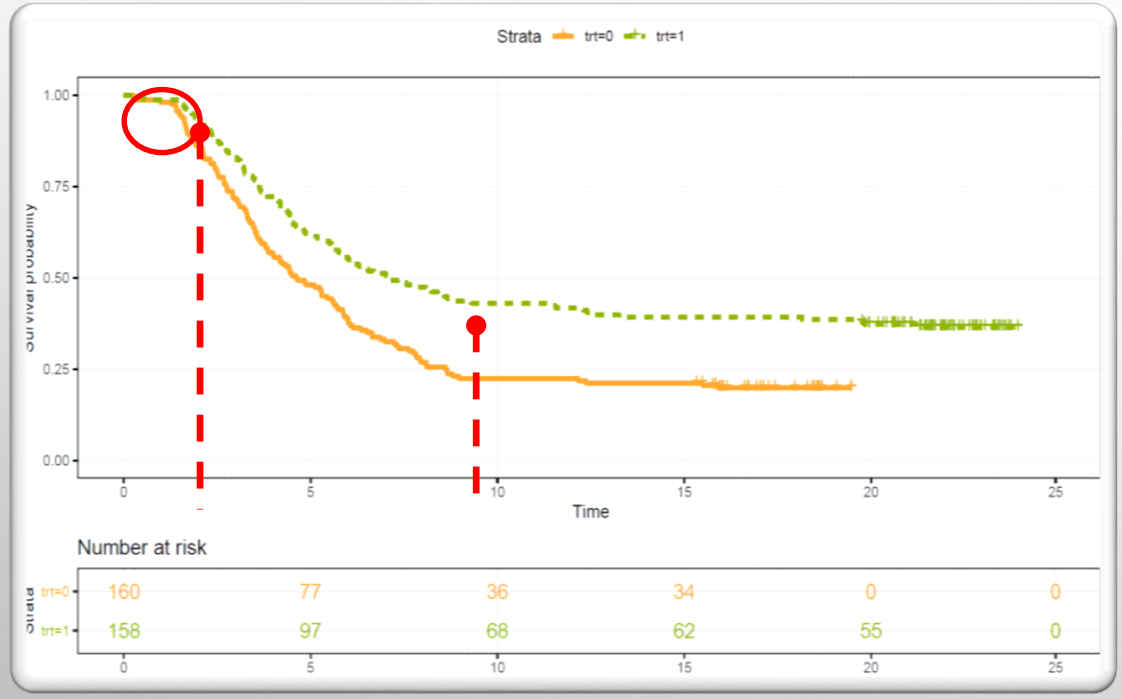
Randomization before manufacture

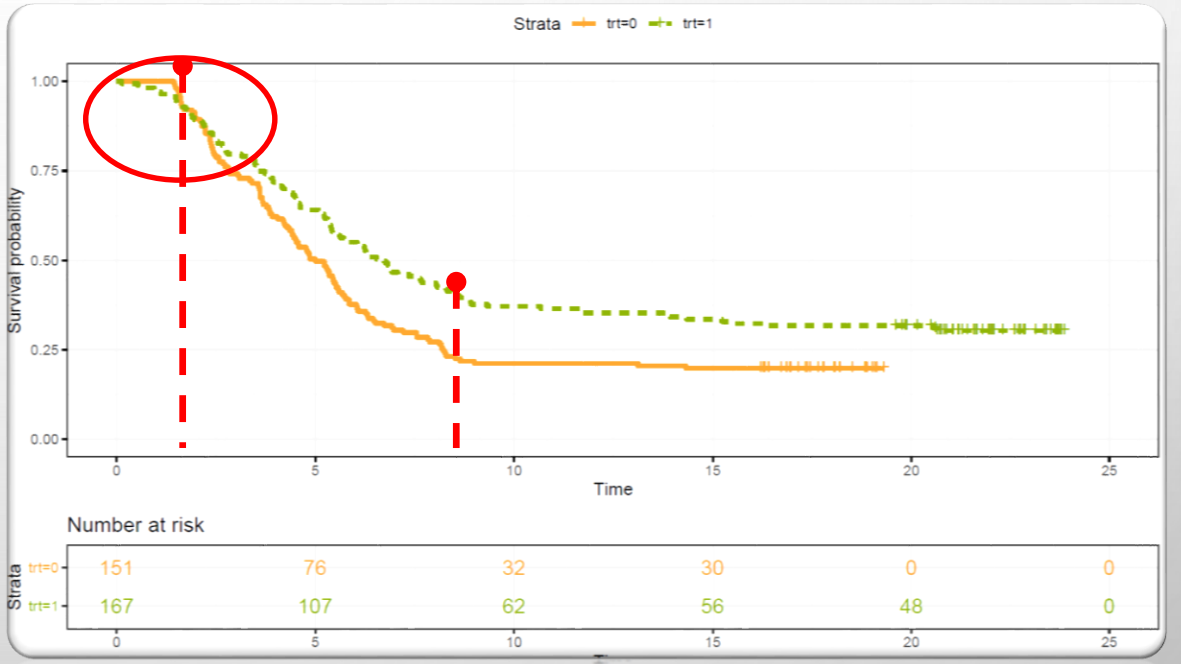
Drawback 3. Non-proportional hazards issues

- SOC ARM RECEIVES SIMILAR OR STRONGER BRIDGING THERAPY THAN CAR-T ARM
  - EFFECT NOT MANIFESTED DURING BRIDGING PERIOD
  - CAR-T APPEARS INFERIOR THAN SOC DURING BRIDGING PERIOD
- LONG-TERM SURVIVORS

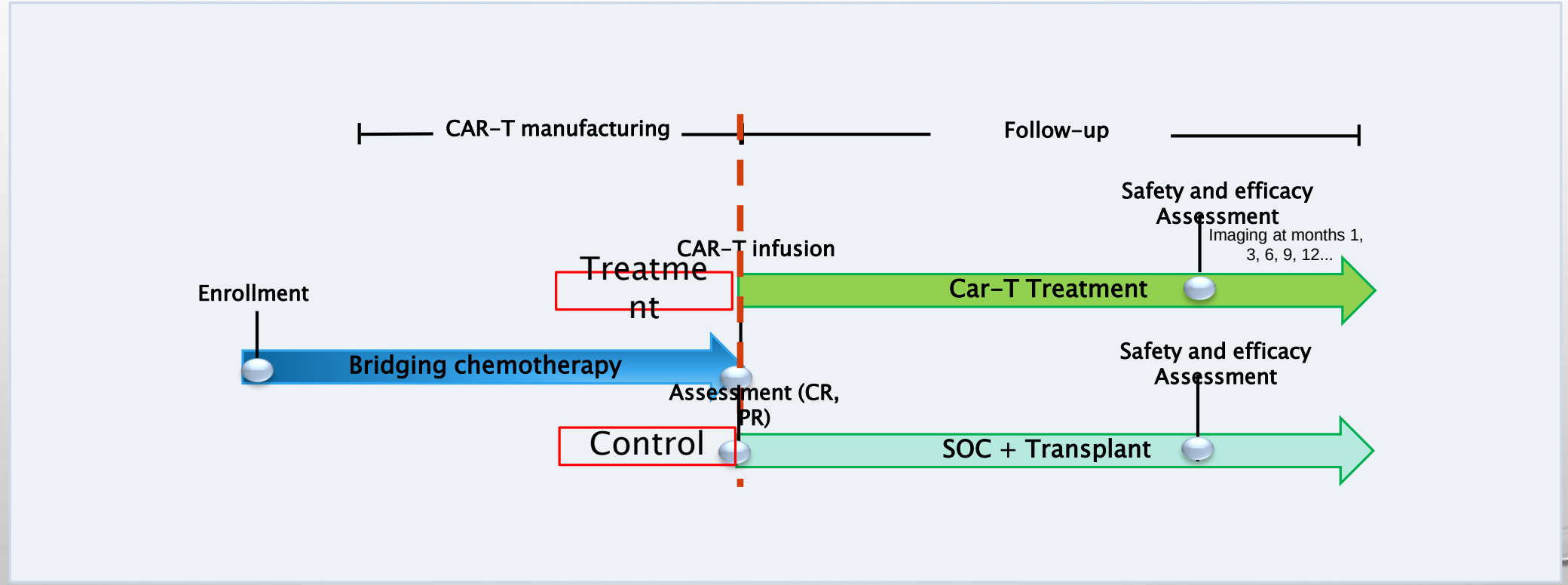
Randomization before manufacture

Drawback 3. Non-proportional hazards issues





Randomization post manufacture assessment for transplant

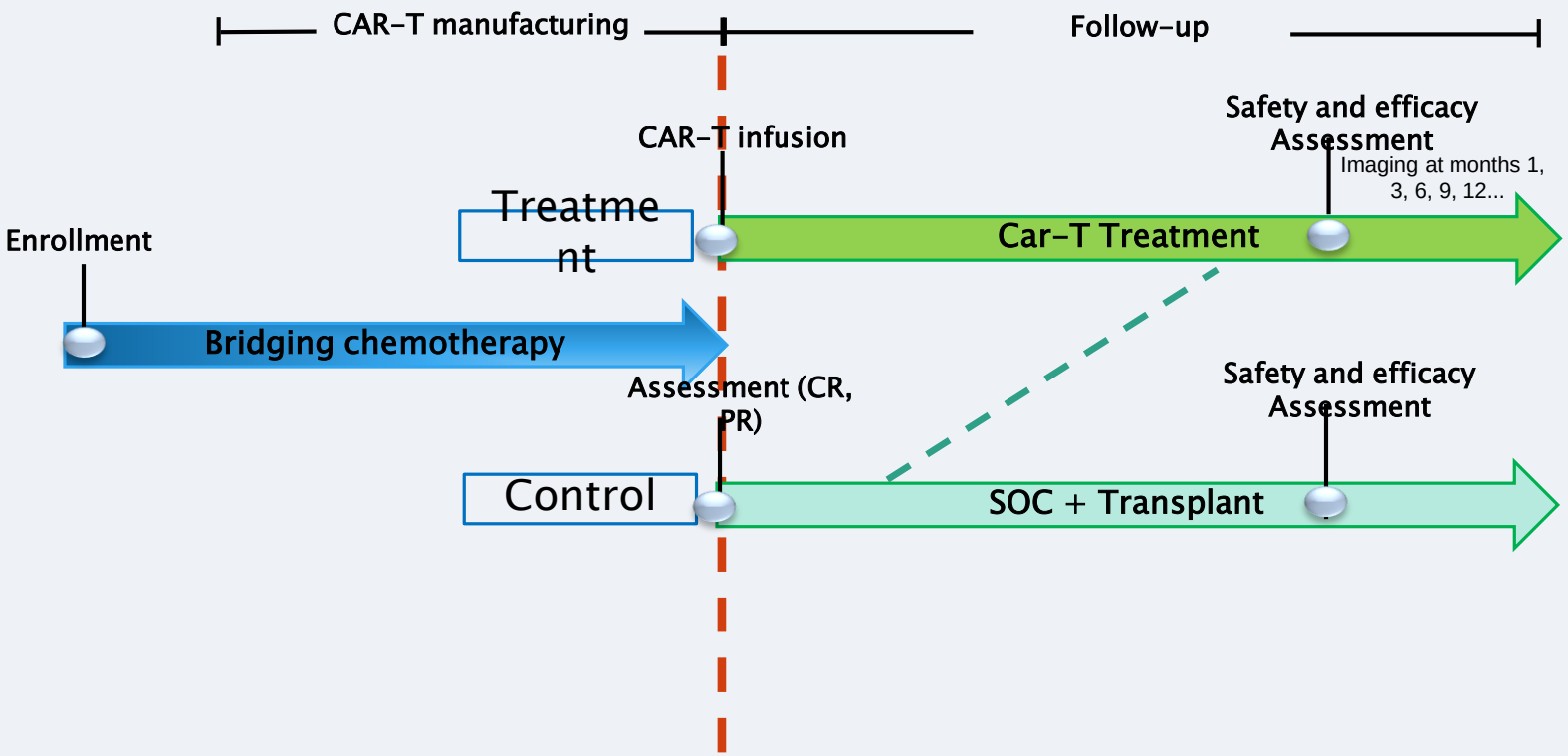


Randomization post manufacture assessment for transplant

- ADVANTAGES:
  - EFFECT OF CAR-T VS TRANSPLANT CAN BE PROPERLY MEASURED
  - NON-PROPORTIONAL HAZARDS ISSUE WOULD GO AWAY
- WASTE OF STUDY RESOURCES:

CHALLENGE #2.

CROSS OVER EFFECT


CAR-T manufacturing
Follow-up
CAR-T infusion
Safety and efficacy Assessment
Imaging at months 1, 3, 6, 9, 12...
Treatment
Enrollment
Car-T Treatment
Bridging chemotherapy
Assessment (CR, PR)
Safety and efficacy Assessment
Control
SOC + Transplant

REGULATORY RECOMMENDATIONS

ALIGN

Estimand

- objective:
- Design:
- Analysis:
- Interpretation:

ALIGN

Hypothetical Examples

- relative clinical benefit across the entire patient journey once Car-T or SOC treatment strategy is prescribed?
- Design:
- Analysis:
- Interpretation:

ALIGN

Hypothetical Examples

- relative clinical benefit across the entire patient journey once Car-T or SOC treatment strategy is prescribed?
- Randomization at enrollment
- Analysis:
- Interpretation:

ALIGN

Hypothetical Examples

- relative clinical benefit across the entire patient journey once Car-T or SOC treatment strategy is prescribed?
- Randomization at enrollment
- INTENT-TO-TREAT set; No need to consider NPH issue;
- Interpretation:

ALIGN

Hypothetical Examples

- relative clinical benefit across the entire patient journey once Car-T or SOC treatment strategy is prescribed?
- Randomization at enrollment
- INTENT-TO-TREAT set; No need to consider NPH issue;
- Intercurrent events should be ignored;

ALIGN

Hypothetical Examples

- relative clinical effect of CAR-T against transplant administration only?
- Design:
- Analysis:
- Interpretation:

ALIGN

Hypothetical Examples

- relative clinical effect of CAR-T against transplant administration only?
- Randomization after manufacture and patients reaching remission
- Analysis:
- Interpretation:

ALIGN

Hypothetical Examples

- relative clinical effect of CAR-T against transplant administration only?
- Randomization after manufacture and patients reaching remission
- INTENT-TO-TREAT set: Eligible subset
- Interpretation:

ALIGN

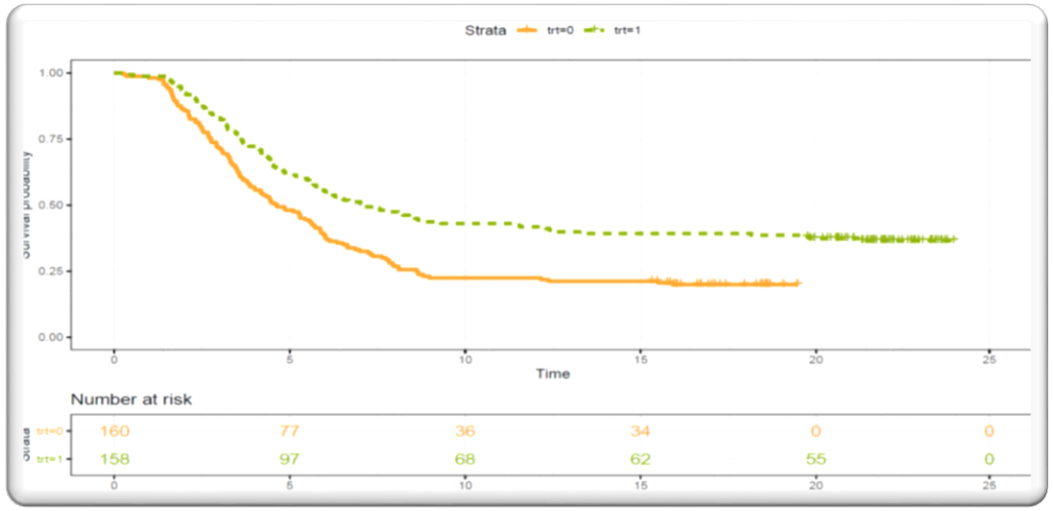
Hypothetical Examples

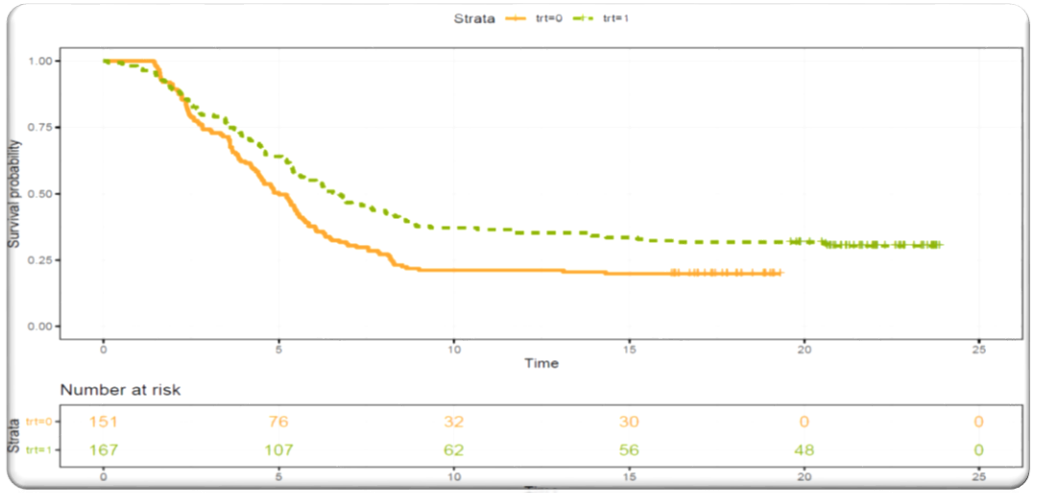
- relative clinical effect of CAR-T against transplant administration only?
- Randomization after manufacture and patients reaching remission
- INTENT-TO-TREAT set: Eligible subset
- Manufacture failures, transplant failures would not be included

ALIGN

- DEFINITION OF OBJECTIVE IS CRITICAL:
  - TREATMENT EFFECT OF INTEREST
  - POPULATION OF INTEREST
  - DESIGN AND ANALYSIS STRATEGY CAN BE TAILORED
  - HANDLING INTERCURRENT EVENTS CAN BE SPECIFIED
- ESTIMAND: *ICH E9 ADDENDUM 2019*

NPH


Strata trt=0 trt=1
1.00
0.75
0.50
0.25
0.00
Survival probability
0
5
10
15
20
25
Time
Number at risk
trt=0 160 77 36 34 0 0
trt=1 158 97 68 62 55 0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20
25
Time
Number at risk
trt=0 151 76 32 30 0 0
trt=1 167 107 62 56 48 0

NPH

- Regular logrank test
- Weighted log-rank test
- Restricted mean survival time (RMST) approach
- Max-combo test
- PRIME strategy targeting heterogeneous patient population

NPH

- REGULAR LOG-RANK TEST:
  - SIMULATING PLAUSIBLE NPH PATTERNS
  - ANALYZING USING REGULAR LOG-RANK TEST
  - LOSS OF STUDY EFFICIENCY
  - LIMITATION OF SIMULATION-BASED DESIGN

NPH

- MAX-COMBO TEST:
  - $G(\rho = 0, \gamma = 0), G(\rho = 0, \gamma = 1), G(\rho = 1, \gamma = 0), G(\rho = 1, \gamma = 1)$
    - $G(\rho = 0, \gamma = 0)$: EQUALLY WEIGHTING ALL EVENTS
    - $G(\rho = 0, \gamma = 1)$: EMPHASIZING LATE EVENTS
    - $G(\rho = 1, \gamma = 0)$: EMPHASIZING EARLY EVENTS
    - $G(\rho = 1, \gamma = 1)$: EMPHASIZING MID-EVENTS
  - ALLOW DATA TO PICK THE MOST SIGNIFICANT STATISTIC

NPH

- MAX-COMBO TEST: NOT RECOMMENDED FOR PRIMARY METH

- Across-trial inconsistency:
  - 1ST TRIAL: $G(\rho = 0, \gamma = 1)$: emphasizing late events
  - 2ND TRIAL: $G(\rho = 1, \gamma = 0)$: emphasizing early events
- Justification from clinical and biological perspectives

NPH

- PROPER PRE-SPECIFICATION OF DESIGN PARAMETERS
- SUFFICIENT JUSTIFICATION
- ADEQUATE EVALUATION OF MIS-SPECIFICATION RISK

THANK YOU AND QUESTIONS?