Comments on Delayed-Start Design, Doubly Randomized Delayed-Start & Matched-Control Design

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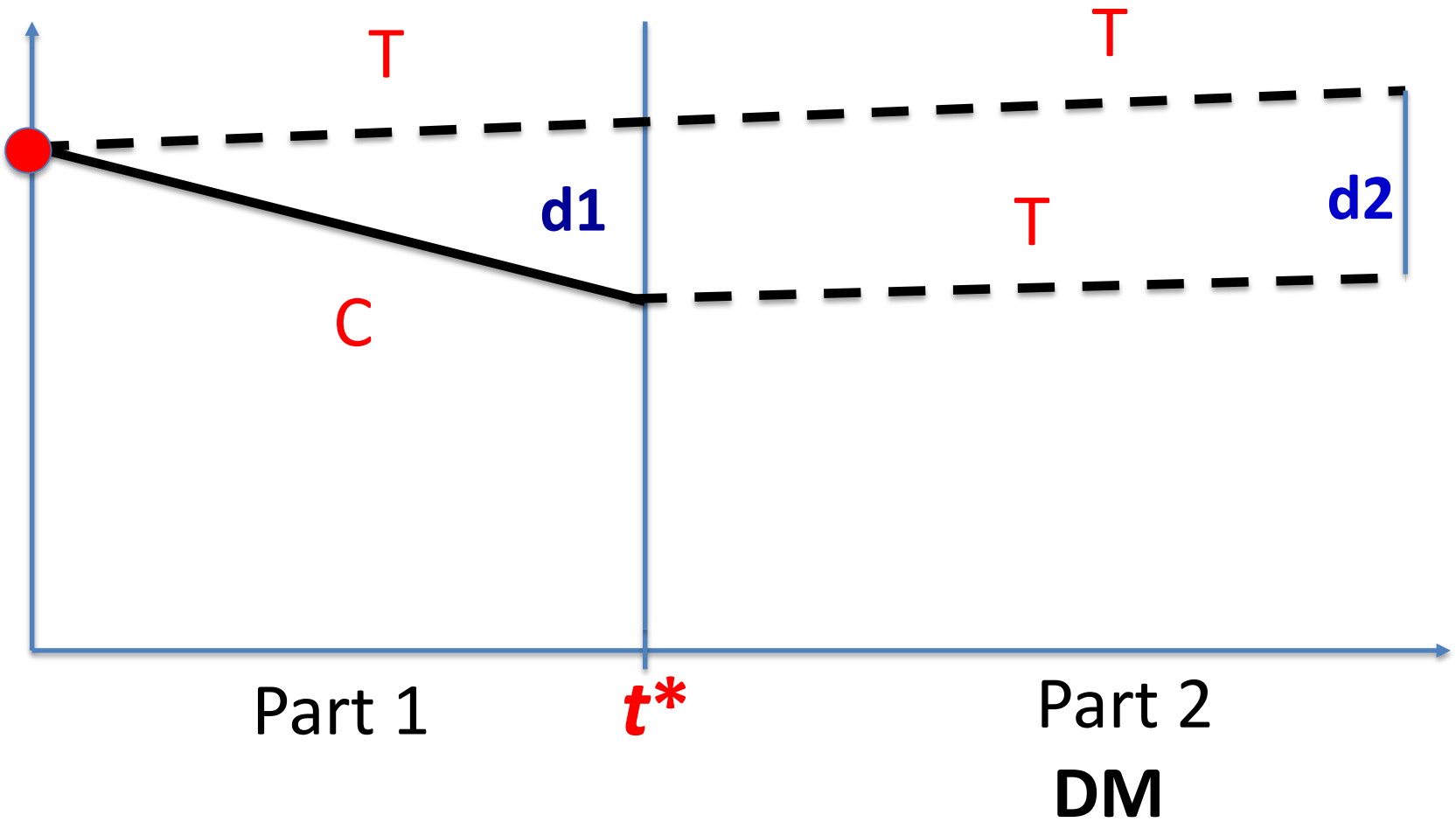
Delayed Start Design



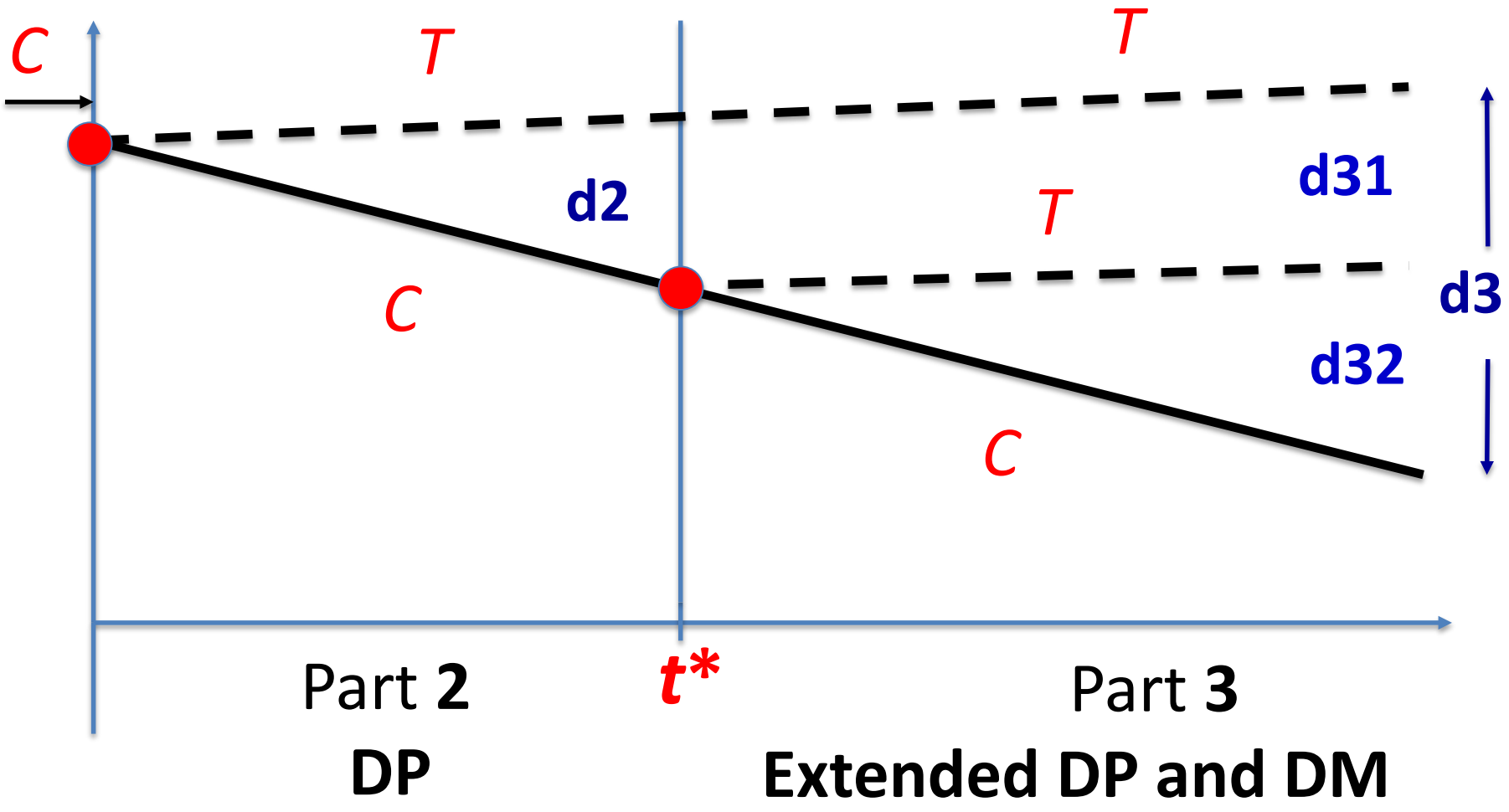
Leber (1997)

Delayed Start Design

- Differential/early dropouts
  - trt arms comparable at baseline of P2?
  - handling missing data
- Non-inferiority margin
  - population or patient level?
  - response linear over time?
  - slope? final time point?
  - lack of knowledge of rate of change

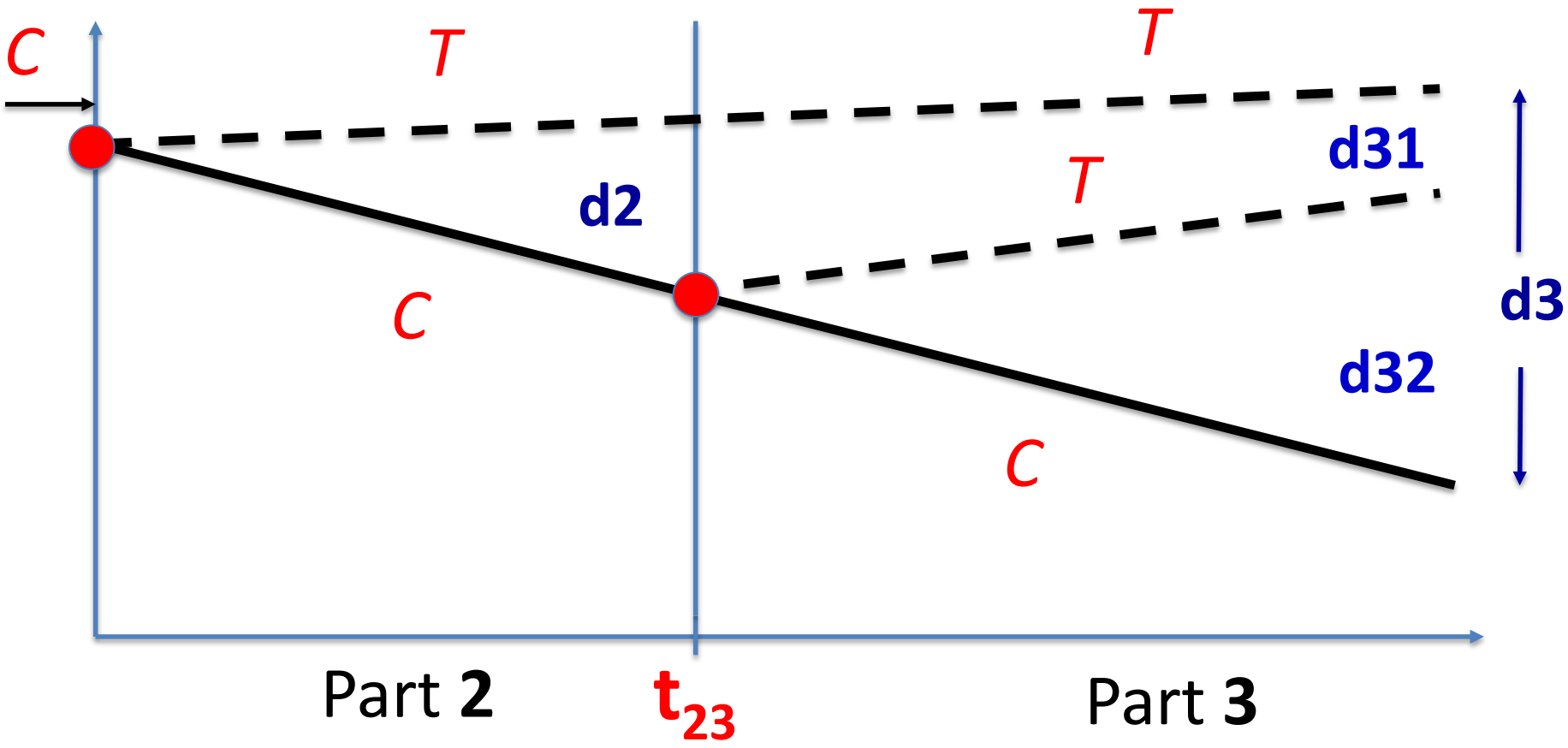
…….. etc; see summary by Dr. Turkoz

DRDS-MC: *T* effect on DP w/ DM



Turkoz et al (2018)

DRDS-MC: *T* effect on DP w/o DM



Turkoz et al (2018)

D-R Delayed-Start with M-C

- Control lead-in screens out some dropouts
- NI margin - conditional on the size of treatment effect in Part II (DP) & others
  - probably more sensible than a fixed margin on treatment effect in Part III
  - if the size of treatment effect in Part II is not large, why care?

Statistical Challenges to DSDs

- Estimand (ICH E9 R1)
- Differential/early dropouts
  - trt arms comparable at baseline of P3?
  - handling missing data
- NI margin
  - population or patient level?
  - response linear over time?
  - slope? final time point?
  - lack of knowledge of rate of change

Statistical Challenges to DSDs

- NI margin for ratio d31/d2
  d31: TT – CT at end of extended DP / DM
  d2: T – C at end of "DP"
  - min ratio to test needs to be prespecified at the initial design stage? (not at the interim analysis after seeing the estimated d2)
  - once passing the min ratio, can test any larger ratio with no alpha adjustment

Statistical Challenges to DSDs

- Missing data
  - dropouts may need to be assigned "treatment failure"
  - d31 (Part 3 difference: TT – CT) and d2 (Part 2 difference: T – C) are estimated by two different sets of patients

Statistical Challenges

- Rerandomization
  - C entering part III may be a different group than those randomized to C in part II
    - Design Asymmetry between T and C in part III
      - Estimation of d32 at expense of precision of d31 and both could be biased if differential or significant control dropouts in Part II
- What happened to the original concept of parallelism?
  - The difference at the last time point may miss a trend towards convergence

Statistical Challenges

- Any comparative evidence Bayesian approach is better for delayed start designs?
  - model averaging seems to require a major paradigm shift
  - Use of Splines places minimum number of visits constraint on the design
  - Justification of priors could be an issue

- Presented Simulation Results for Scenario 2D
  - Model Averaging Credible Intervals have zero length which seems Incredible
    - What about bias-variance tradeoff?

Statistical Challenges

- Managed withdrawal with re-entry (slide 18)?
  - this created a complicated analysis issue for ADAGIO trial in Parkinson's disease
    - Could be hard to distinguish symptomatic effects of managed withdrawal from DM effects of experimental therapy in short term on a symptomatic efficacy measure