Using target trials to study effectiveness of TB Preventive Therapy in people living with HIV

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Background

- TPT has been shown to reduce TB incidence and mortality in PLHIV
- In 2018, PEPFAR committed at the UNHLM to provide TPT to all PLHIV under its support
- TPT has since been widely scaled up in PLHIV (right).
- The impact of large-scale TPT implementation in program settings on TB incidence and mortality is not known

PR TECT study

- **Pr**eventing **O**ccurrence of **T**B by **E**xpanding **C**overage of **T**PT among **PLHIV**
- Multi-country evaluation of effectiveness of TPT programs on reducing TB incidence and all-cause mortality
- Uses data from electronic medical records (EMR)
- PEPFAR programs in Haiti, Kenya, Nigeria, Uganda, Ukraine, Zimbabwe

EMORY UNIVERSITY
CDC Centers for Disease Control and Prevention
CDC Foundation Together our impact is greater
Bill & Melinda Gates foundation
cmmb Healthier Lives Worldwide
GGHN
Monitoring and Evaluation Technical Support (METS) Program
Zim-TTECH Zimbabwe Technical Assistance, Training & Education Center for Health

PROTECT country snapshots

Country	People with HIV (2021, all ages)	TB incidence (per 100,000)	TB patients who are HIV positive	TPT regimens to be evaluated
Haiti 	150,000	159 (119–204)	14%	6H, 36H
Kenya 	1.4 million	251 (152–373)	24%	6H
Nigeria 	1.9 million	219 (143–311)	5.9%	6H
Uganda 	1.4 million	199 (119–298)	32%	6H, 3HP
Ukraine 	240,000	71 (47–100)	20%	6H
Zimbabwe 	1.3 million	190 (135–253)	50%	6H, 3HP

UNAIDS Data 2022
WHO Global TB Report 2022

PR TECT study

- Project implementation commenced in Dec 2021

- Biweekly calls with almost all countries to develop protocol, review data quality, plan for data entry and monitoring, review preliminary analysis

- My role has been developing a harmonized statistical analysis plan for answering primary objectives of PROTECT study

PROTECT workshop 2023

Statistical Analysis Plan

Primary Analysis

- Goal: Quantify *an* effectiveness measure of *a TPT program* at preventing TB and all-cause mortality.

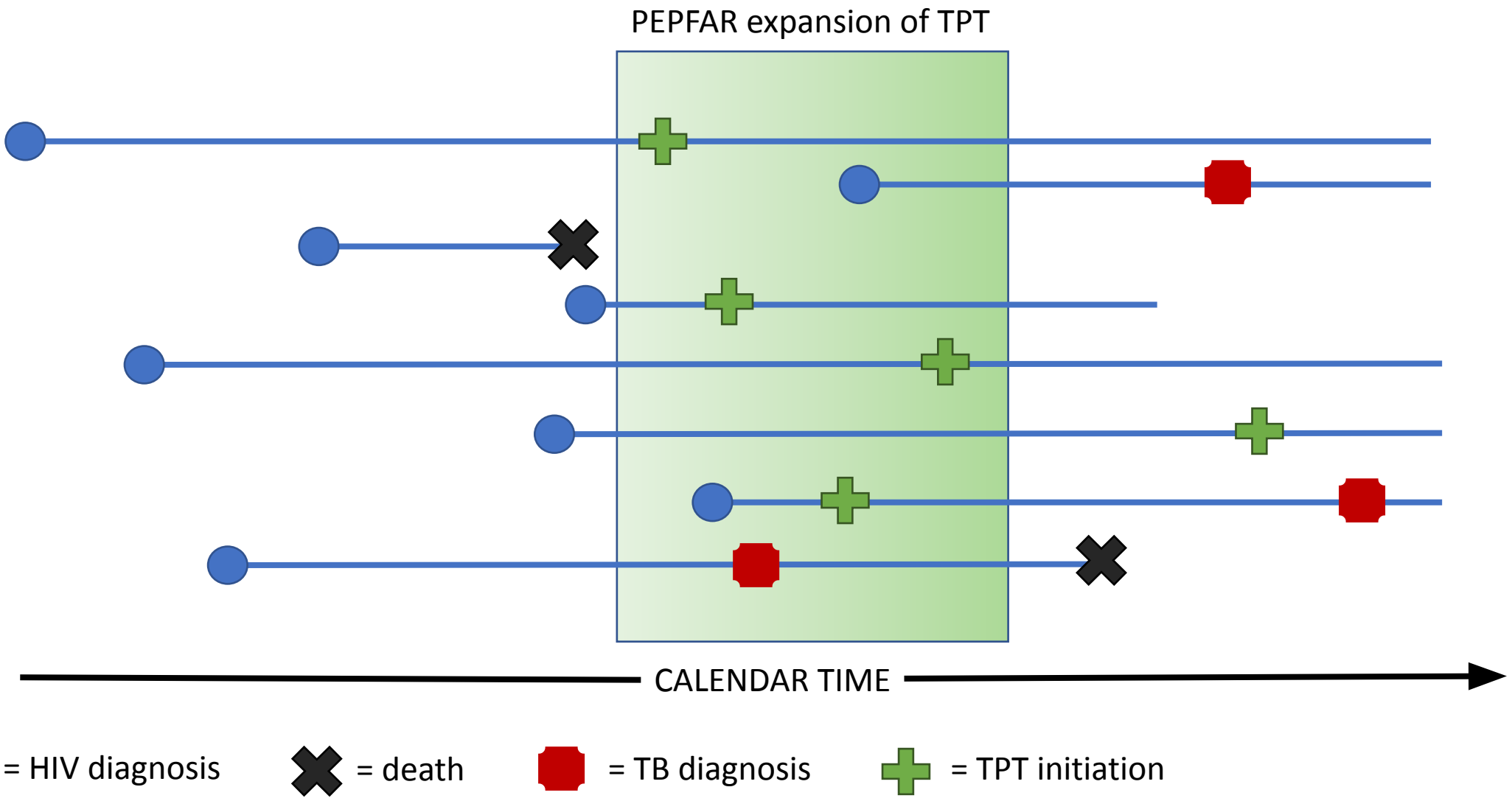
What this question is…

- A *programmatic evaluation* of TPT as a program that provides treatment to individuals recently diagnosed with HIV.
- Public health-centered.
- Something that can be answered in a (mostly) standardized way using each of the PROTECT cohorts.

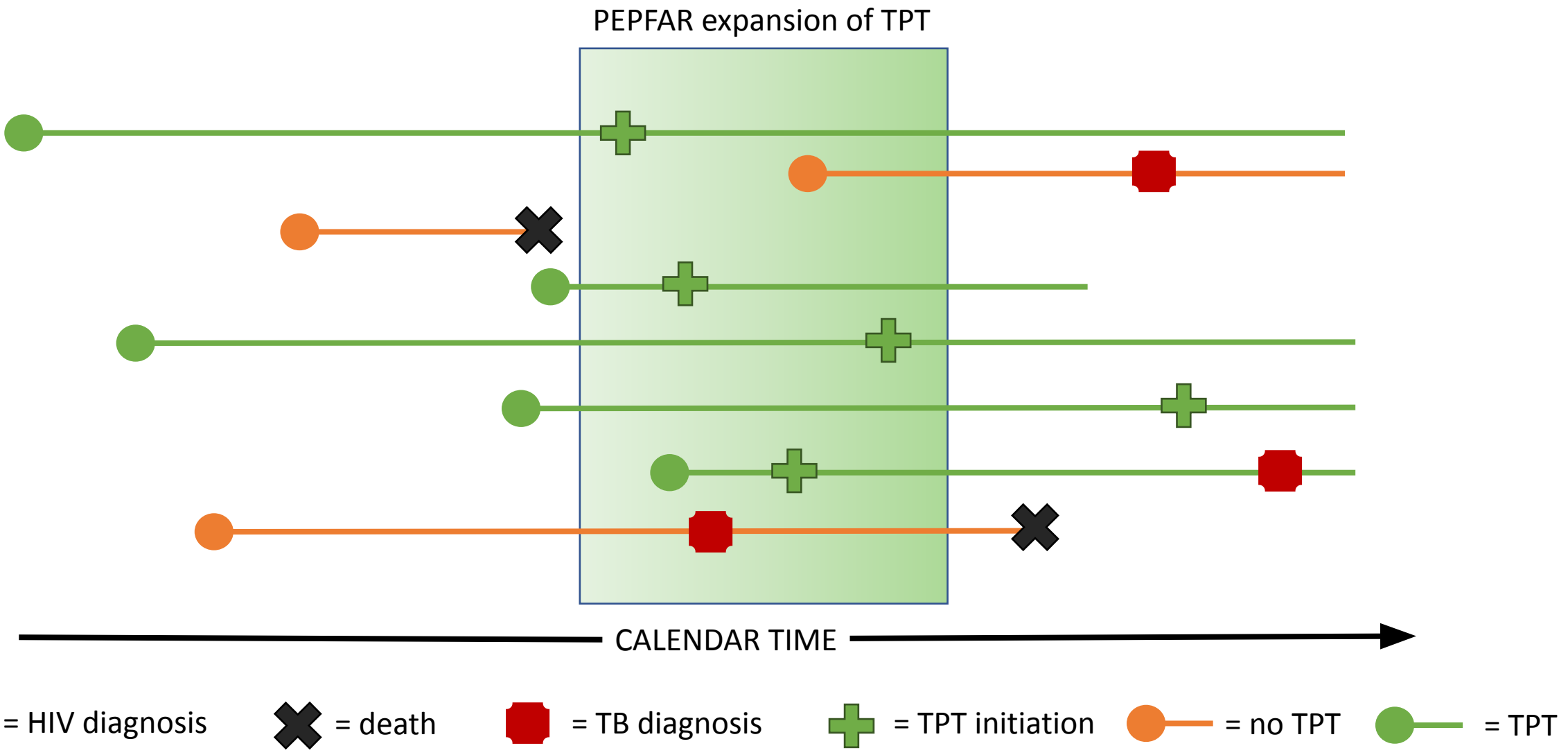
What this question is not…

- The only question that can be asked using PROTECT data.
- An evaluation of the PEPFAR TPT scale up program itself.
- The same question a pharmaceutical company is interested in.

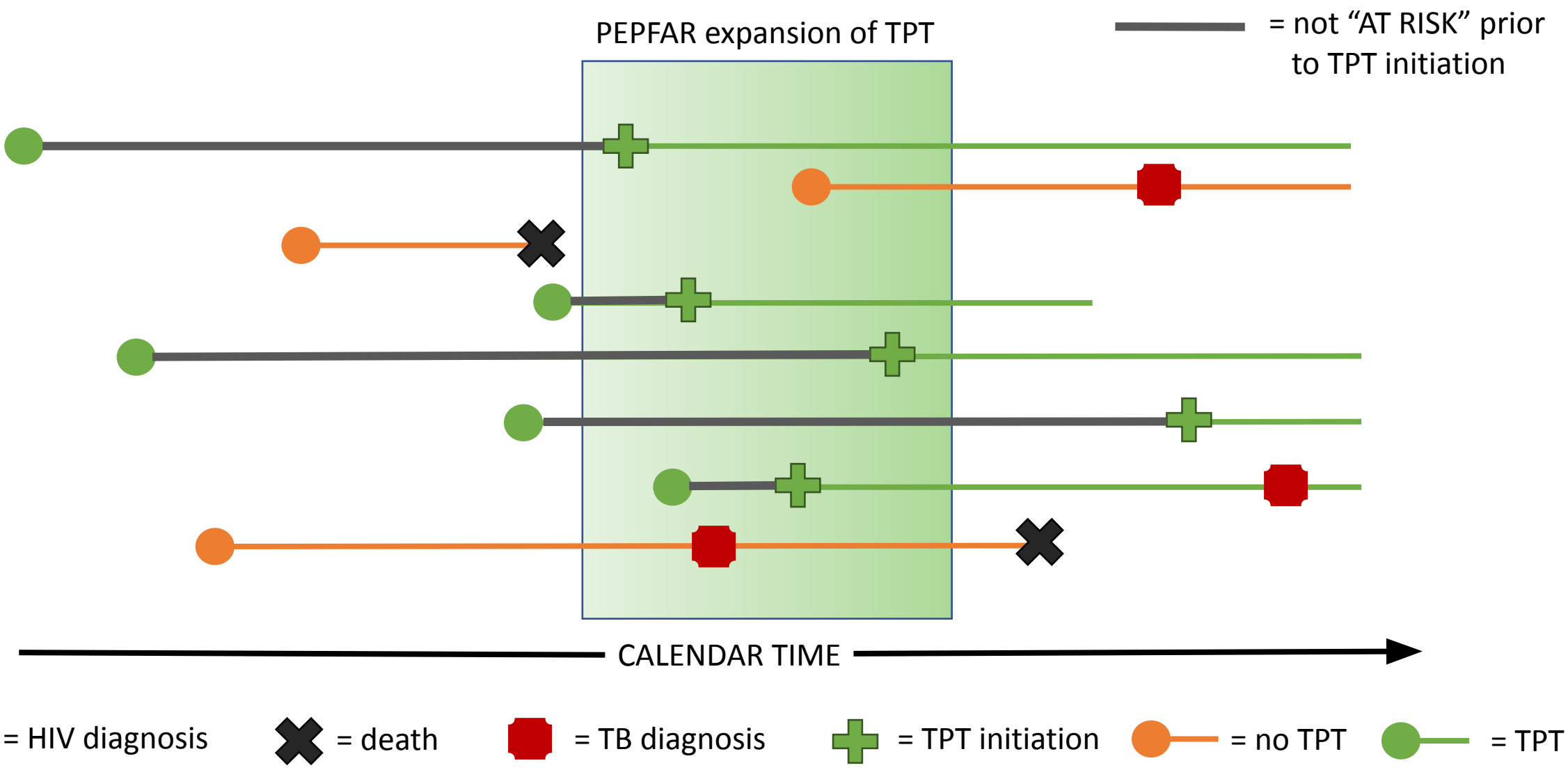
Challenges of observational data



Defining TPT “treated” and “untreated”



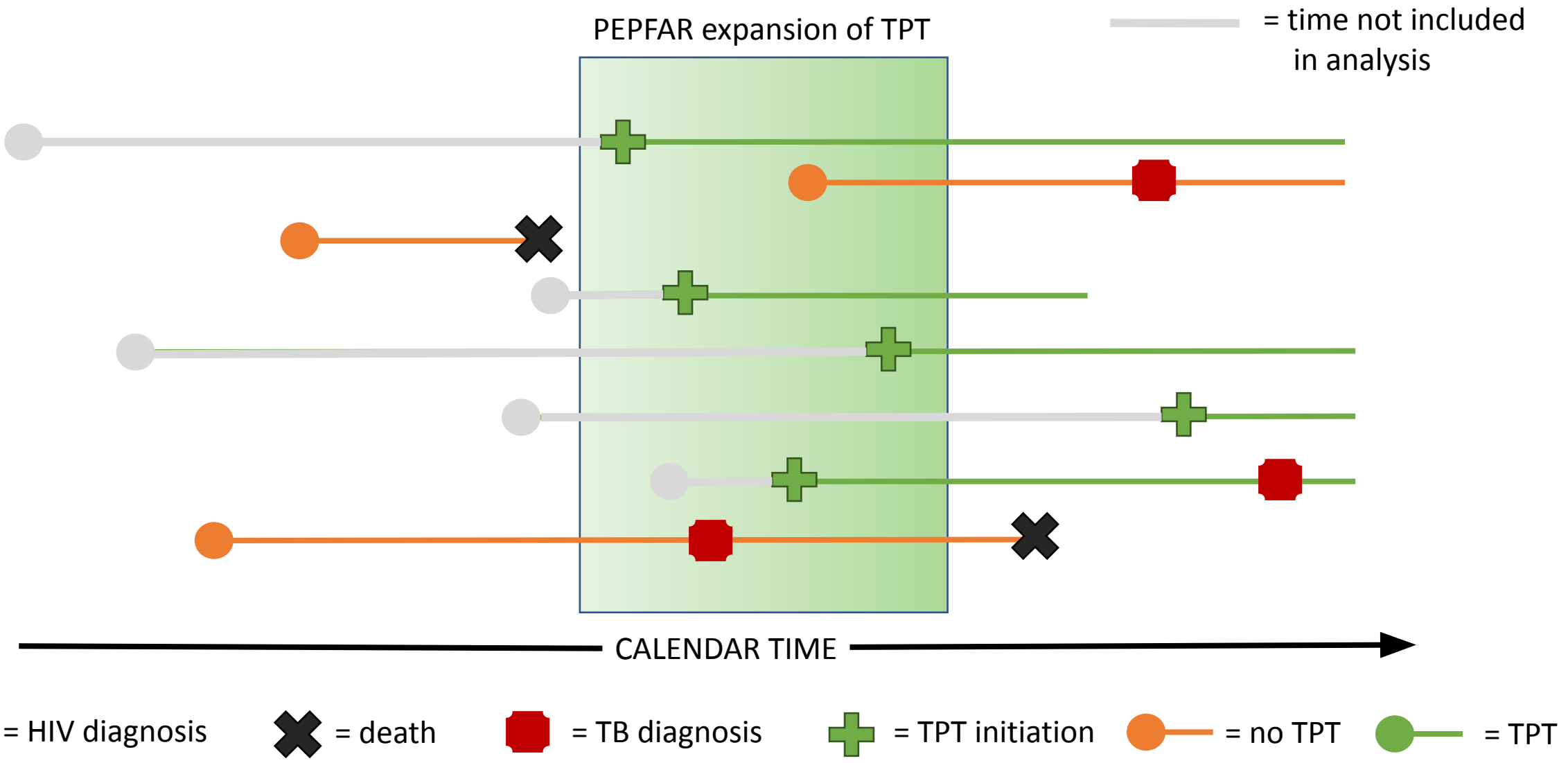
Immortal time bias



Immortal time bias

- Individuals in the TPT “treated” group must survive without TB long enough to initiate TPT.
- Adds “immortal time” where they are not “at risk” of primary endpoints.
- Biases treatment effectiveness measures away from null.

Start follow up time at TPT initiation?



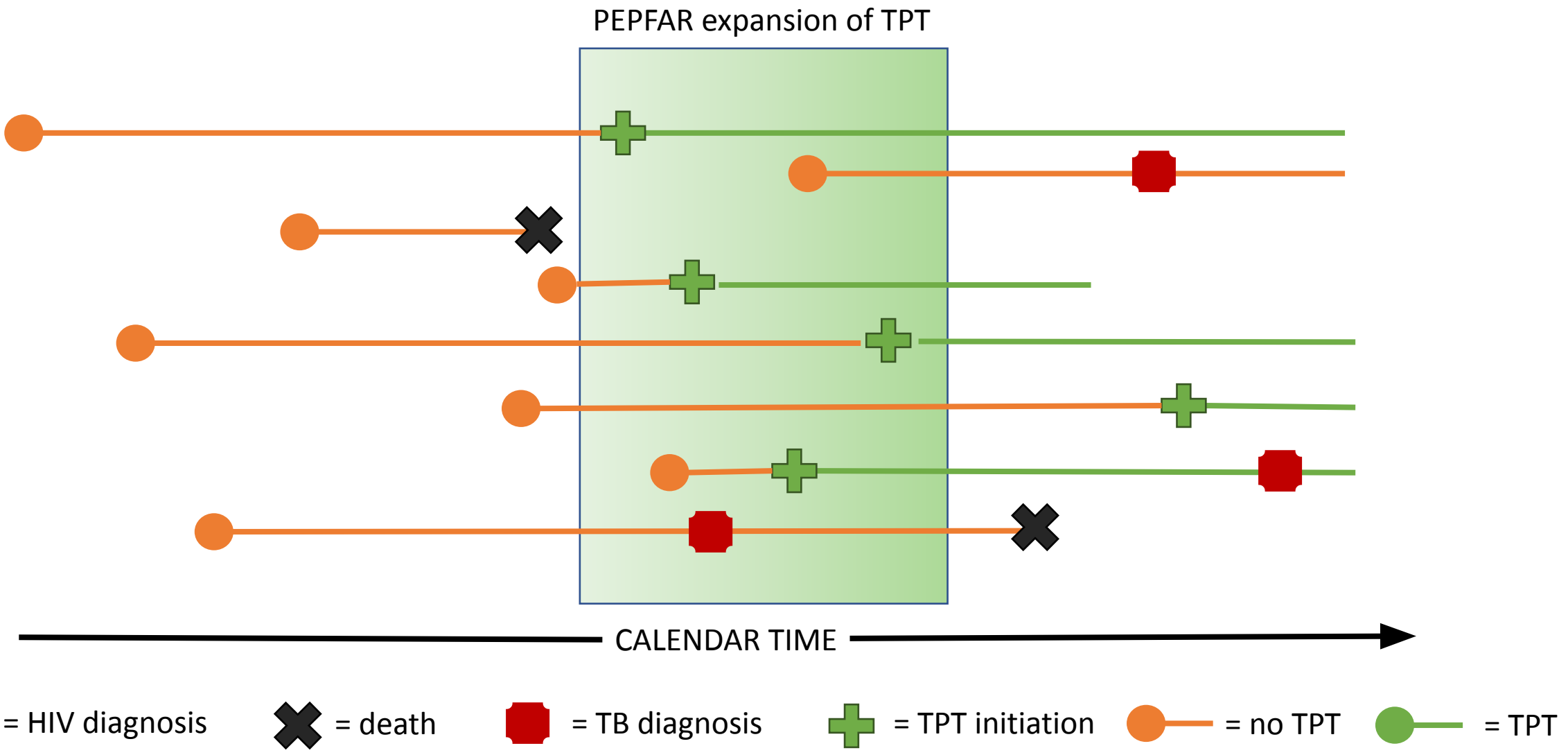
Start follow up time at TPT initiation?

- How to define start of follow up for those who never initiate TPT?

- ART initiation?
  - TPT users will have longer duration on ART than non-TPT users.
  - Adjustment may be possible, but time since ART initiation likely strongly correlated with TPT, complicating interpretation.

- Matching?
  - Matching non-TPT initiators with TPT initiators fundamentally changes underlying population of interest.

Time-varying treatment?



Time-varying treatment?

- TPT treated individuals may tend to have longer times since HIV diagnosis (ART initiation).

- If time since HIV diagnosis (ART initiation) modifies effectiveness of TPT then potential for bias.
  - Bias could be toward or away from null.
  - If TPT initiation proximal to HIV diagnosis (ART initiation) is harmful, then a harmful treatment may appear protective.

- Possible to adjust for time since diagnosis (ART initiation), but interpretation becomes more complicated.

Target trials

- Hypothetical randomized controlled trial that the observational study is trying to mimic.

- Explicitly consider all aspects of planning a randomized trial:
  - Eligibility criteria
  - Treatment definition (intent-to-treat vs. per-protocol, immediate vs. delayed TPT initiation)
  - Monitoring schema (active vs. passive follow-up)
  - Outcome definition (including origin time)
  - Study termination window

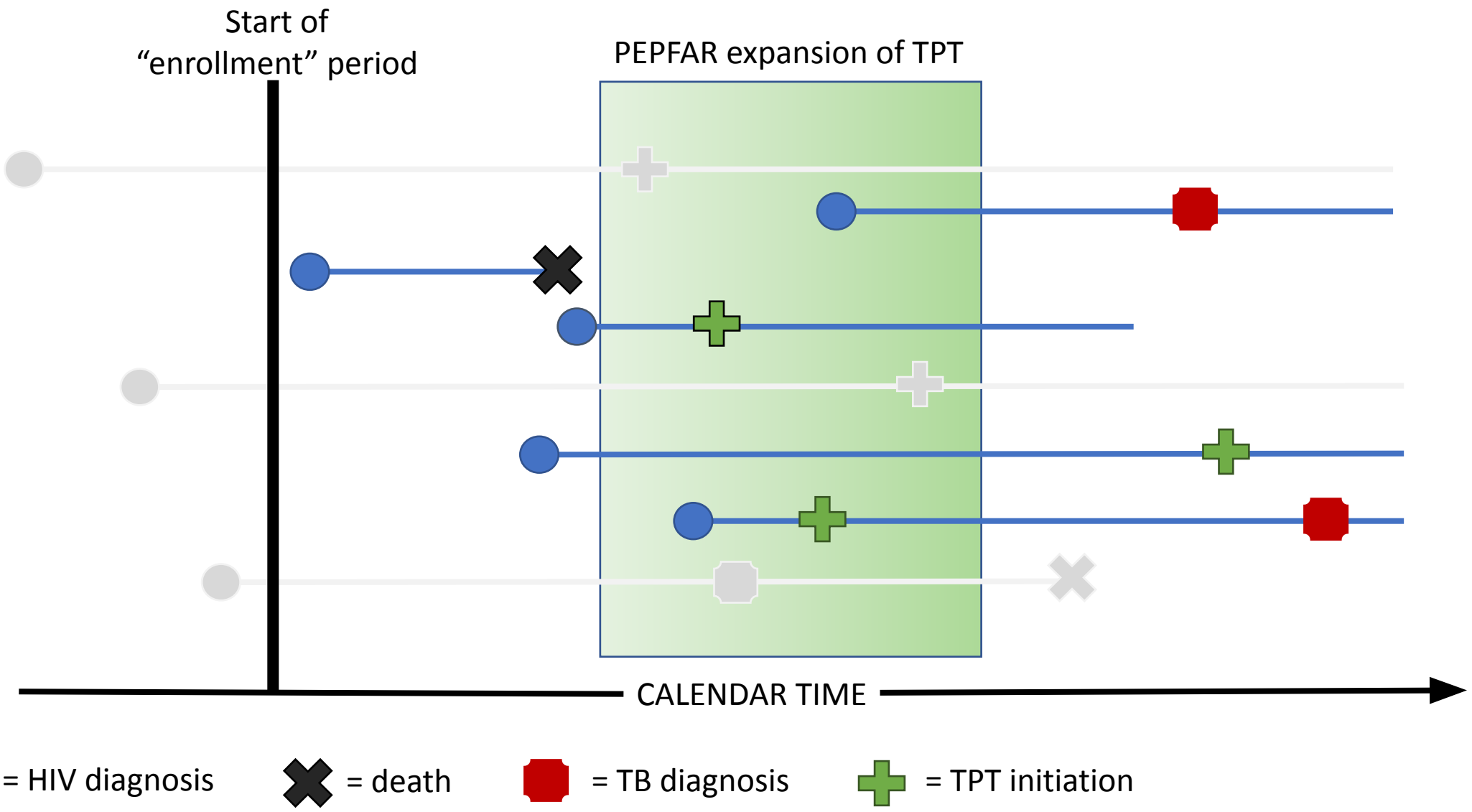
Target trial: Population

- Who would we enroll in our clinical trial? Who will TPT be targeted towards in the future?

- Primary analysis focuses on individuals with initiating HIV care.
  - How impactful will TPT programs be if integrated into routine HIV care for individuals newly engaged with HIV care?

- Secondary analyses to address questions of impact on individuals with longer term HIV infections.
  - How impactful would it be to actively seek out individuals with chronic HIV infection to give TPT?

Target trial: Population



Target trial: treatment definition

- Participants randomized to either TPT program or no TPT program at first “study visit.”

- Participants given a grace period to initiate therapy.
  - Needed to reflect programmatic reality that some individuals will not start TPT immediately after enrollment into HIV care.

Target trial: treatment definition

- David's hot take: primary analysis should be intent-to-treat.

- In other words, in the primary analysis, there should not be consideration of adherence to TPT or completion of therapy
  - Not what a pharmaceutical company would be interested in!
  - We are evaluating a real world policy.
  - In the real world, people discontinue TPT for many reasons. This should "count against" the TPT intervention.
  - More policy-relevant, less biologically relevant analysis.

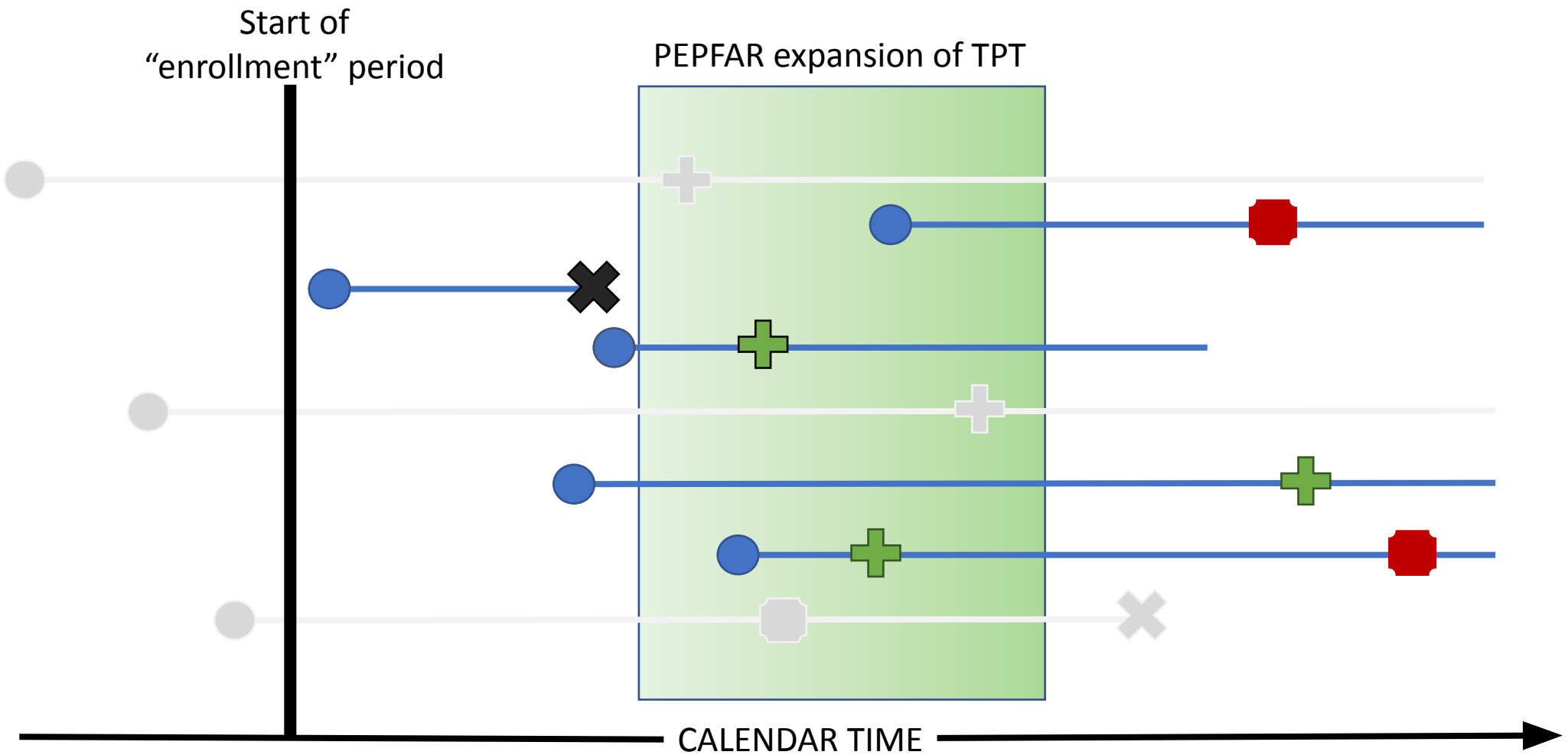
Target trial: time origin and outcome

- Follow-up time begins when individuals' eligibility is confirmed after initial enrollment into HIV care.
  - I.e., when active TB is ruled out, if such information is available in the EMR.

- Patients contribute time at-risk until occurrence of TB or mortality.
  - For TB outcome, death is considered a competing event (but not vice versa).

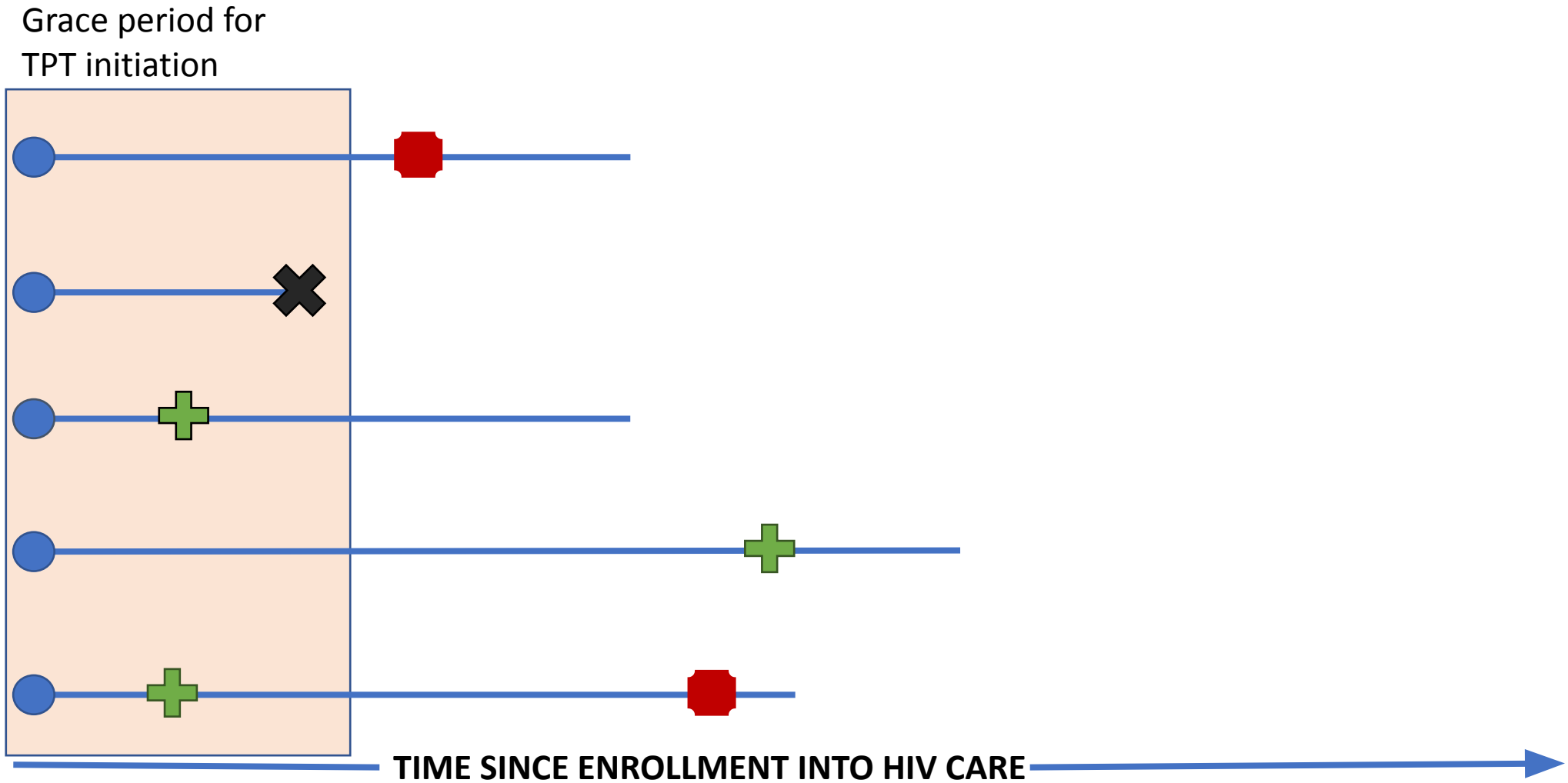
- Follow-up is completed and participants are administratively censored after some period.
  - End of period in which it is plausible to have biological effectiveness of TPT.

Target trial: time origin + treatment definition



= HIV diagnosis = death = TB diagnosis = TPT initiation

Target trial: time origin + treatment definition

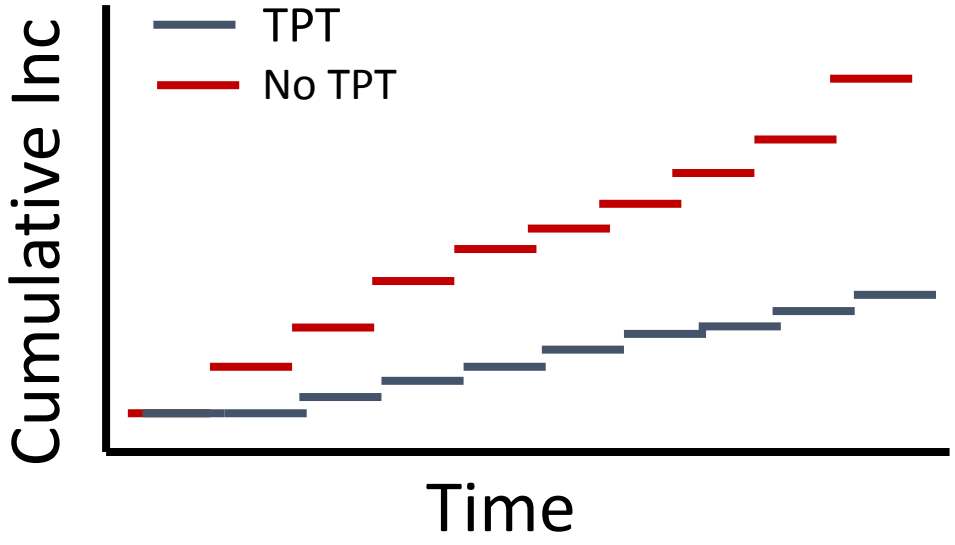


Target trial: estimand

- Two counterfactuals for any individual:
  (1) time to endpoint if TPT initiated during grace period;
  (2) time to endpoint if TPT never initiated during follow up.

- If we somehow observed both counterfactuals, we could use ordinary survival analysis methods.

ptid	TPT	Time to TB (days)	TB indicator
1	0	62	1
1	1	730+	0
2	0	16	1
2	1	730+	0
…	…	…	…



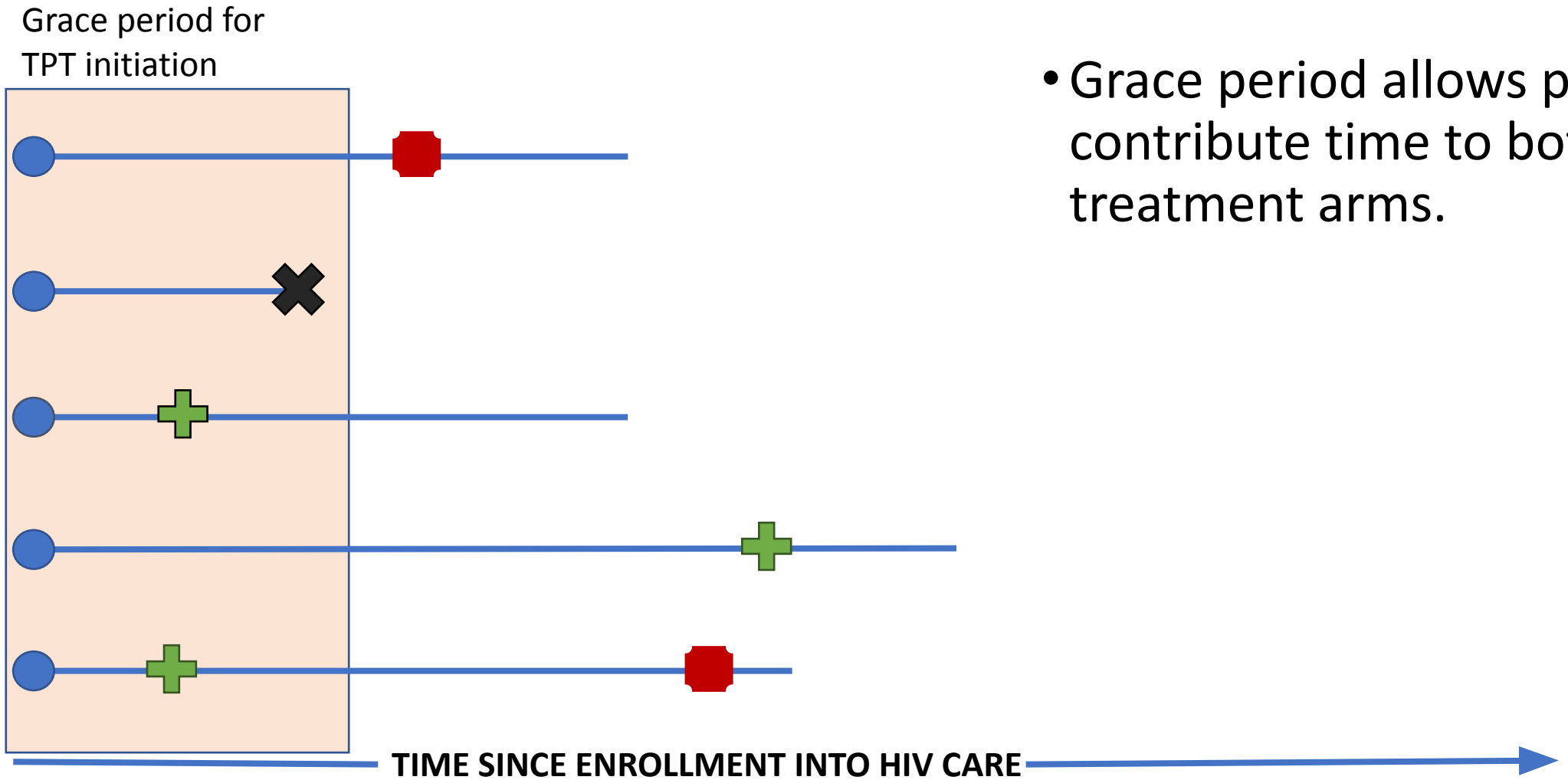
Target trial: estimation

- Inverse probability weighting is used to adjust for:
  - differences in individual who do vs. do not initiate TPT during grace period; and
  - differences in individuals who initiate outside of the grace period or are otherwise right censored.

- Propensity models required for:
  - TPT initiation over time as function of measured covariates; and
  - right censoring over time as function of TPT and measured covariates.

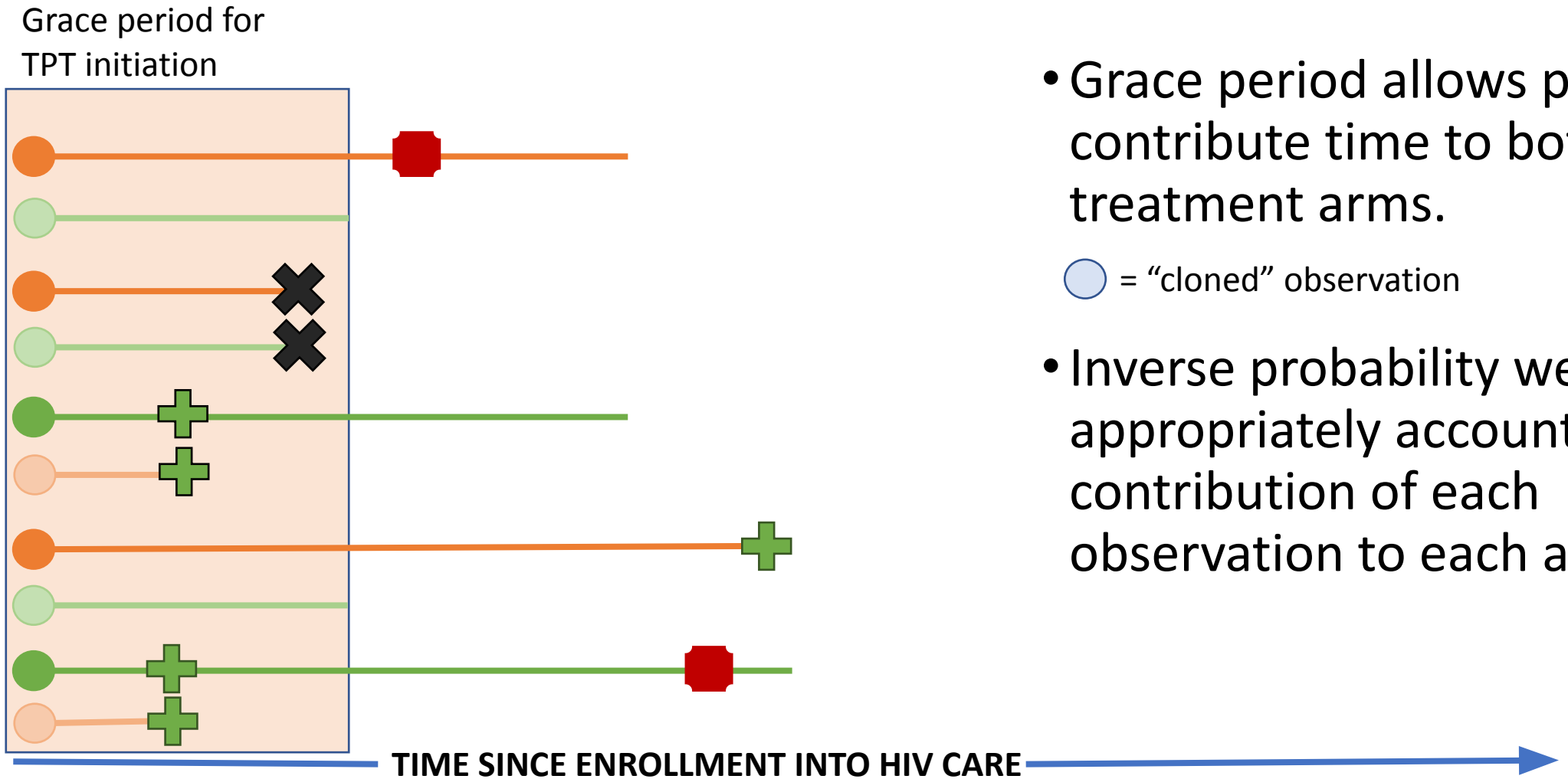
- Covariates should include all variables that may be prognostic of TB and/or all-cause mortality.
  - Prioritize covariates that also predict TPT initiation and/or right censoring.

Target trial: estimation*



- Grace period allows people to contribute time to both treatment arms.

Target trial: estimation*



- Grace period allows people to contribute time to both treatment arms.

  = "cloned" observation

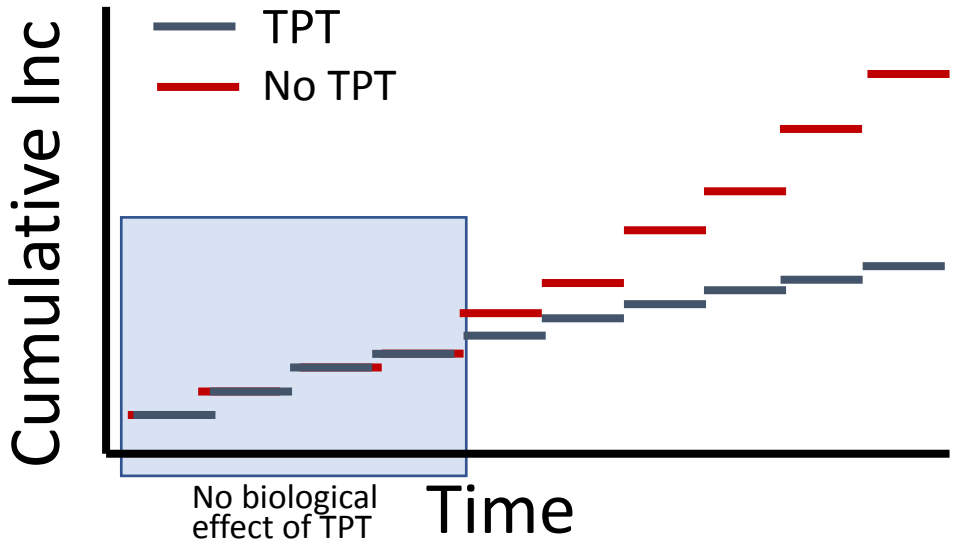
- Inverse probability weighting appropriately accounts for contribution of each observation to each arm.

Target trial: challenge*

- Early cases of TB – real or not?

- Published randomized trials would not have excluded early cases of TB from primary analysis.
  - However, enrollment screening likely more robust in clinical trial setting.

- Symptom data at “enrollment visit” could be helpful to understand confounding induced by screening failure.



Conclusions

Conclusions

- Target trials can be a useful device for elucidating fundamental concepts in causal inference.

- Science > statistics

- On-the-ground problems > statistical problems