Follow-up for time to event endpoints in randomized trials: Learnings for RWE studies

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Background

Overall goal

to get a sense of the adequacy of RWE data for good estimates.

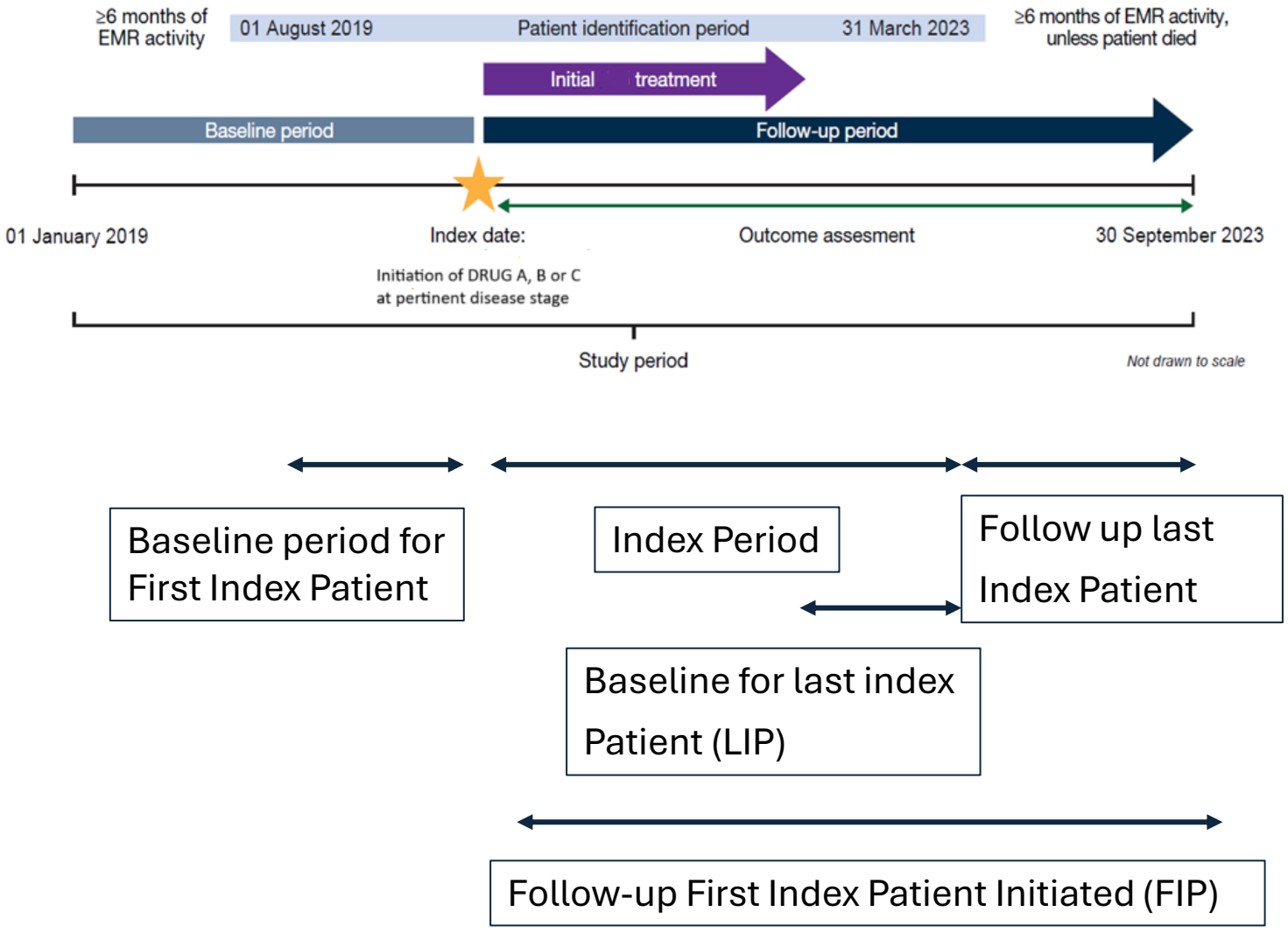
More rigorous approaches could be done on an as needed basis.

Caveats: Inherent biases, Missing data issues and Replicability of results from retrospective data.

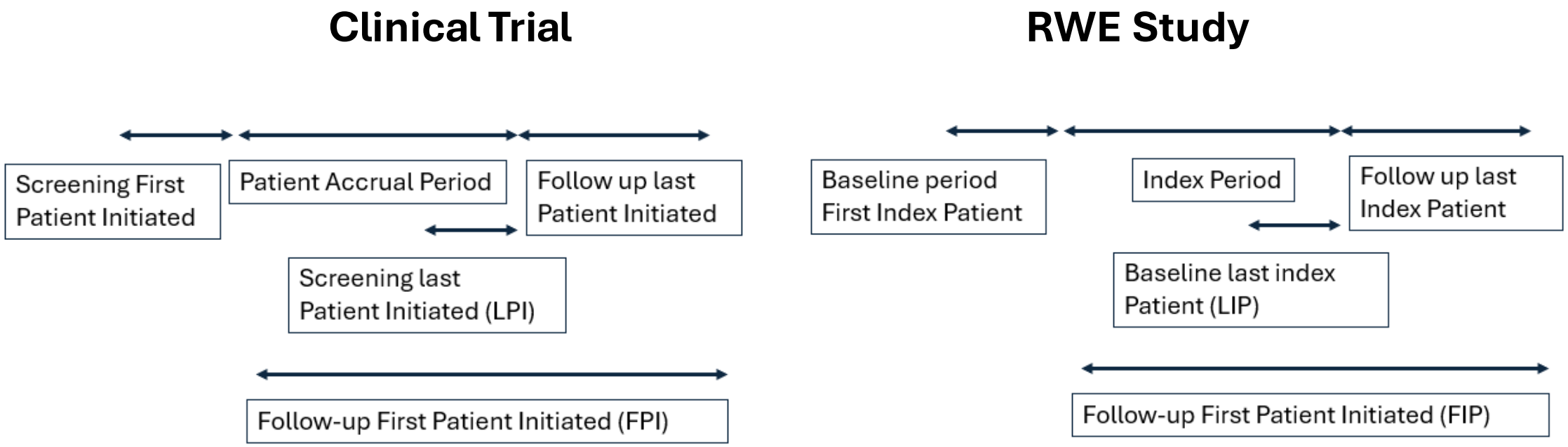
Outline

- Schema and terminology for follow-up for Clinical Trials and RWE
- Use of Time after Initiation or Index in analyses
- Follow-up to obtain appropriate exposure
- Carving appropriate Index periods
- Other Topics: Discussion

Schema and terminology: RWE Study



Schema and terminology: Trial vs RWE



Both contexts involve variable follow-up as patients are followed to end of study period irrespective of where they start.

Calendar time vs Time after initiation

Calendar time

This is a study feature

This is how we look at the planning and operations of a trial/RWE

Start at first patient initiated (FPI) in a clinical trial

Starts at first index patient (FIP) for RWE data

Ends at end of follow-up for LPI or LIP.

Time after initiation

This is a patient wise feature

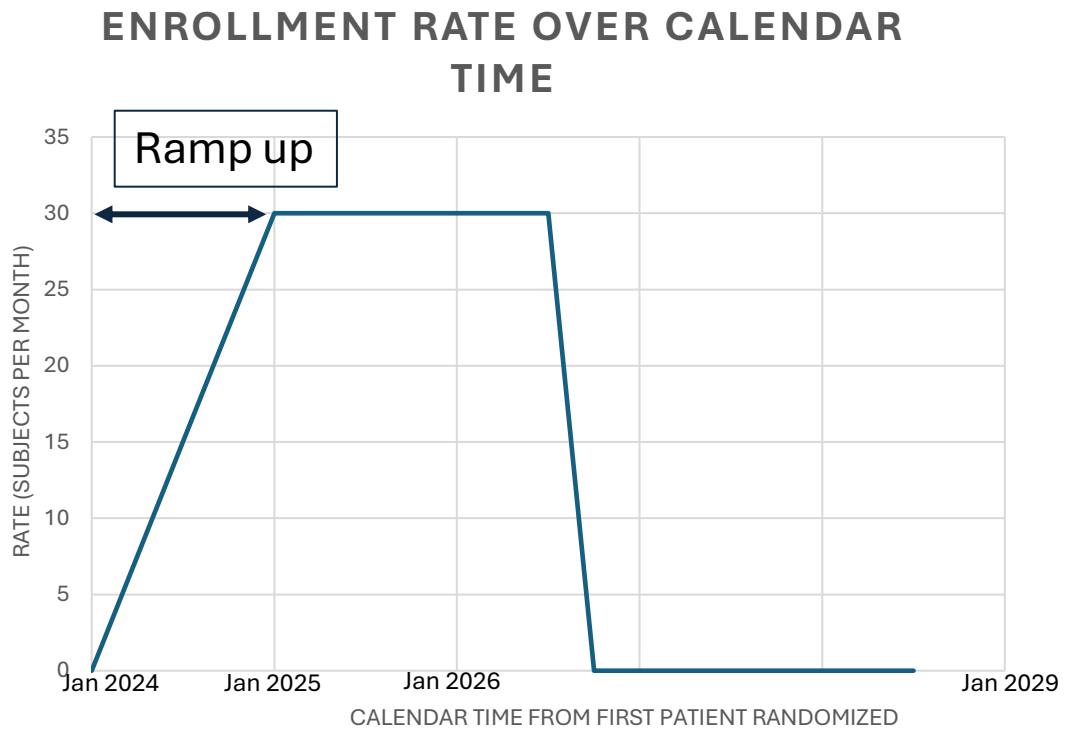
This is what we look at during analysis using durations from patient specific starts.

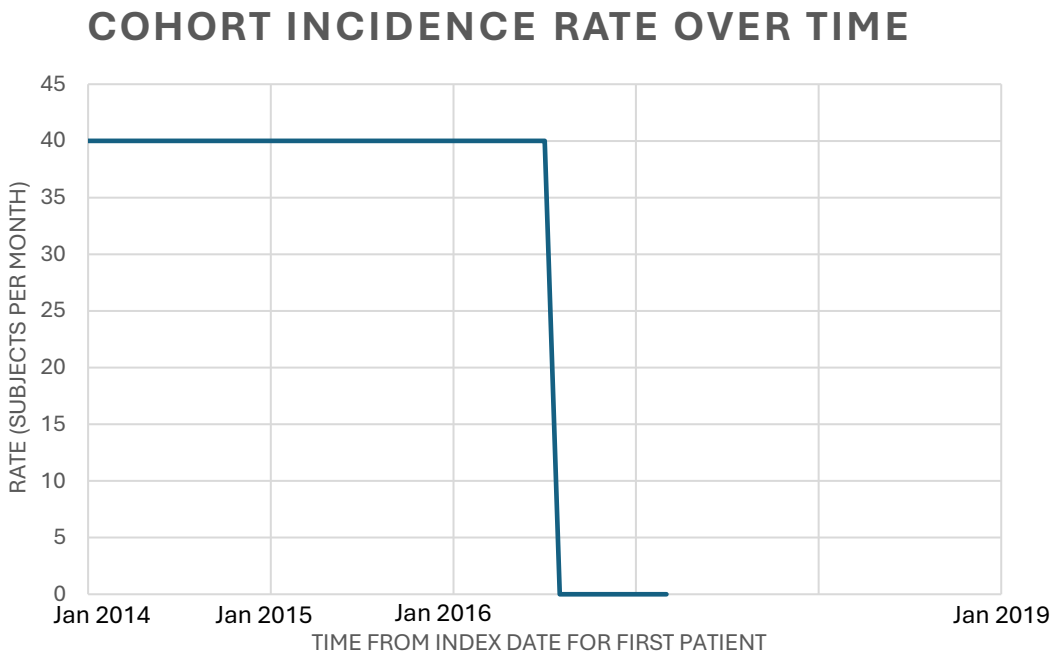
Is the time from initiation of treatment in a clinical trial

Is the time post index in the RWE context

Longest duration is usually one of early initiated or early index as FPI or FIP may not make it to end

Calendar Time: For study planning
Enrolment rate (Trial left) vs Cohort* Incidence (RWE Right)





Patient Accrual Period

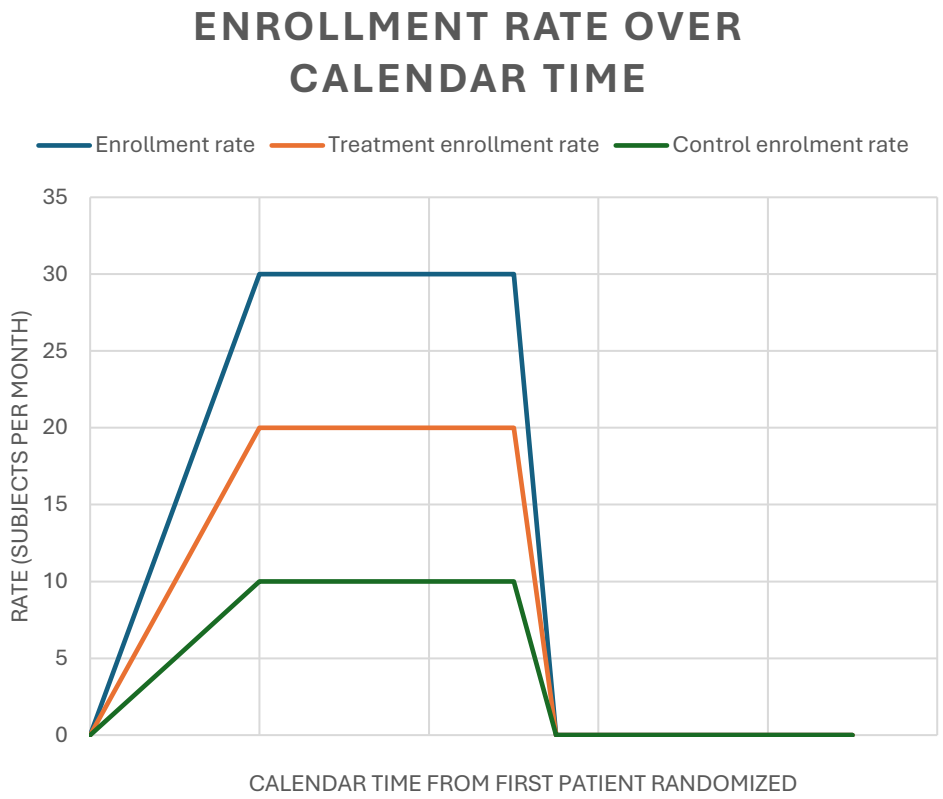
Follow up LPI

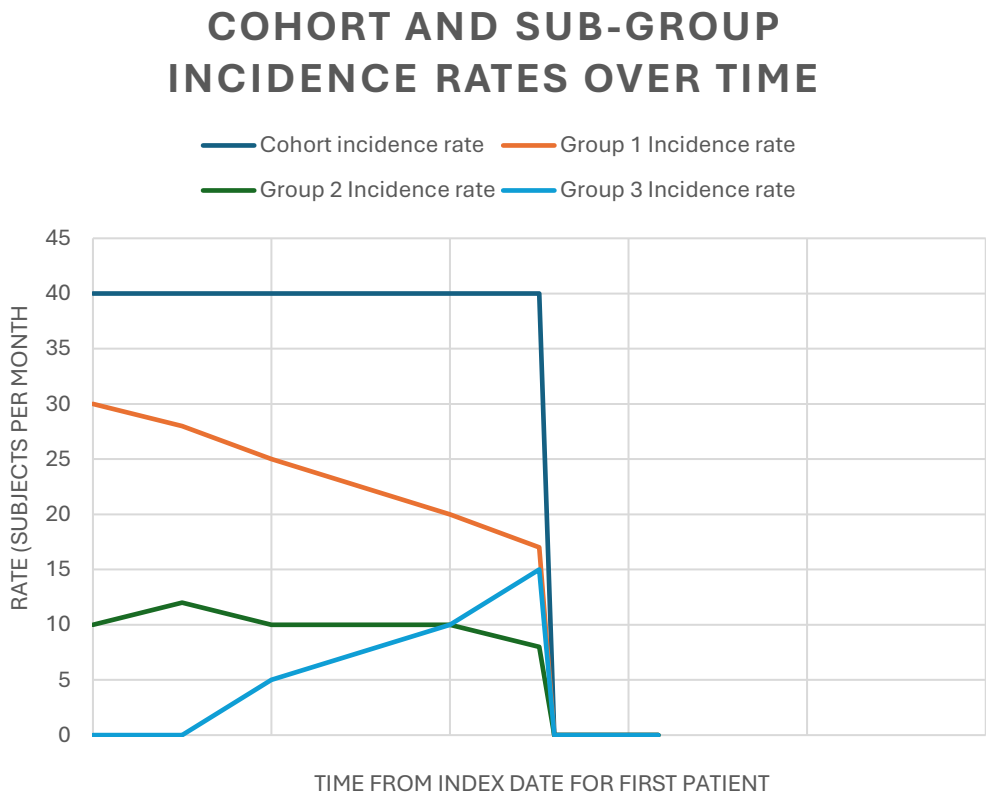
Index Period

Follow-up
Last Index Patient

*Cohort incidence given criteria for inclusion of patients will differ from population incidences

Multiple Groups:
Enrolment rate (2:1 Trial left) vs Cohort Incidence* (RWE Right)

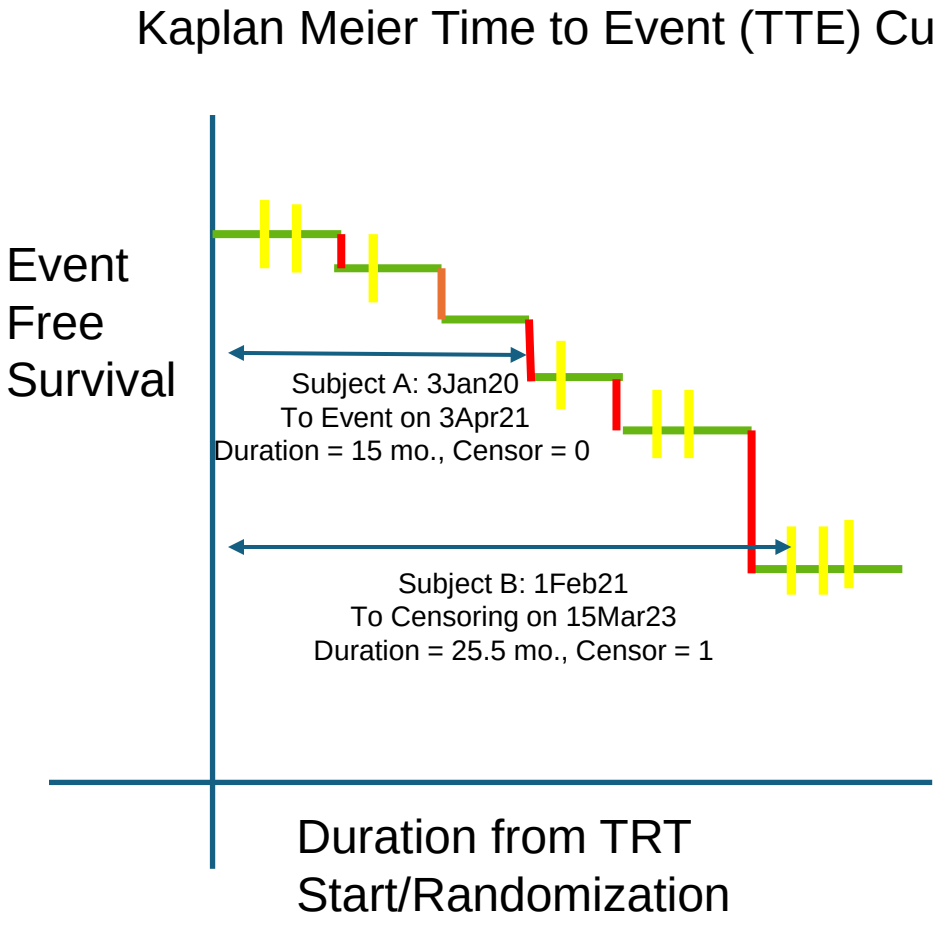




*Cohort incidence of scripts depend on product approval. Incidence of Procedures could be flatter.

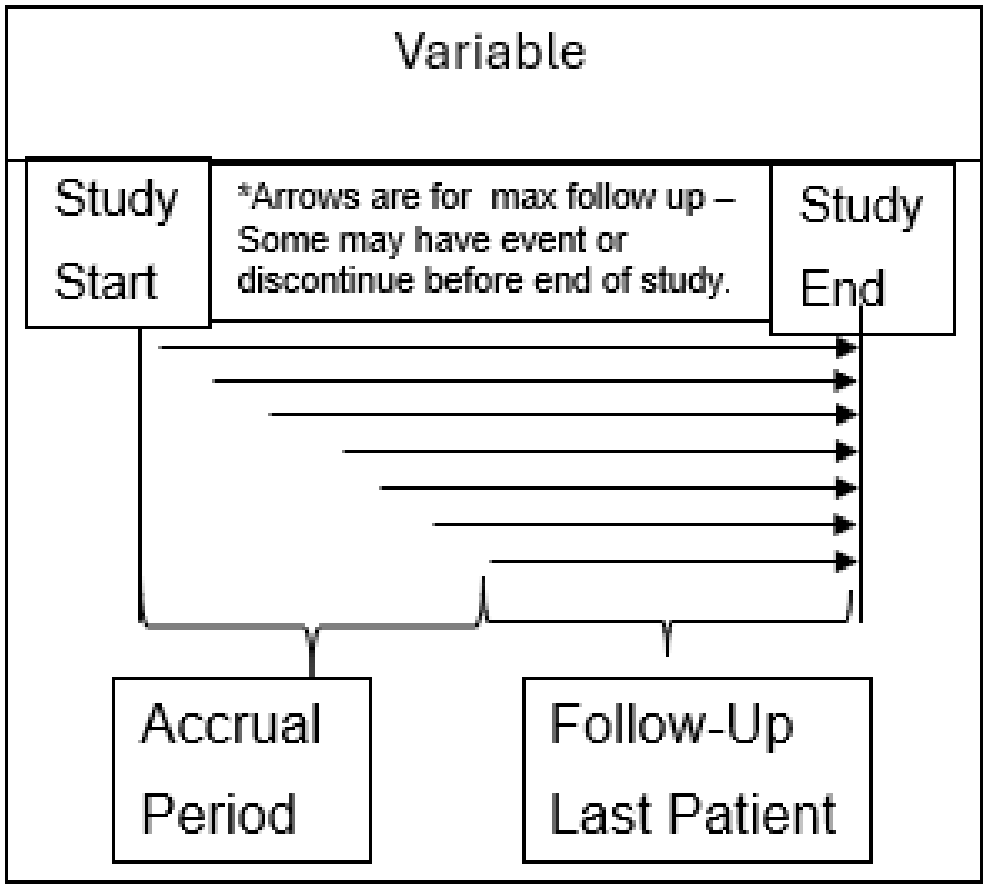
Time after Initiation or Index: For Analysis

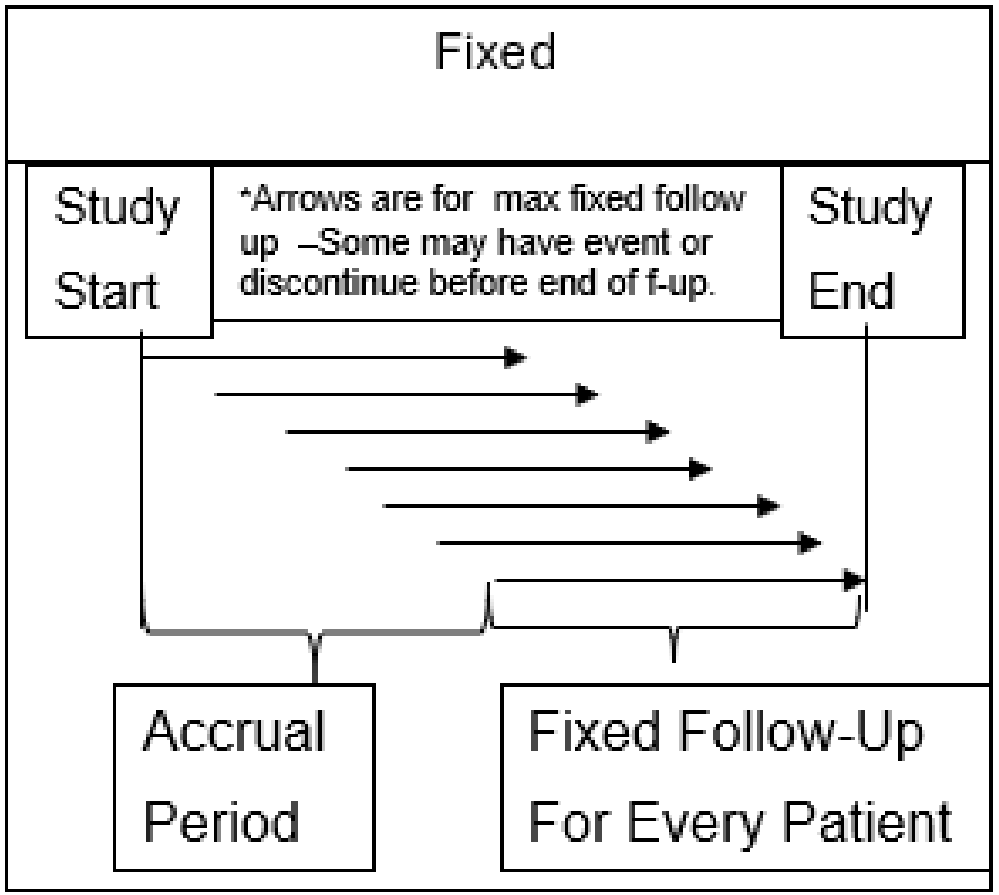
Time after Initiation or Index: For Analysis



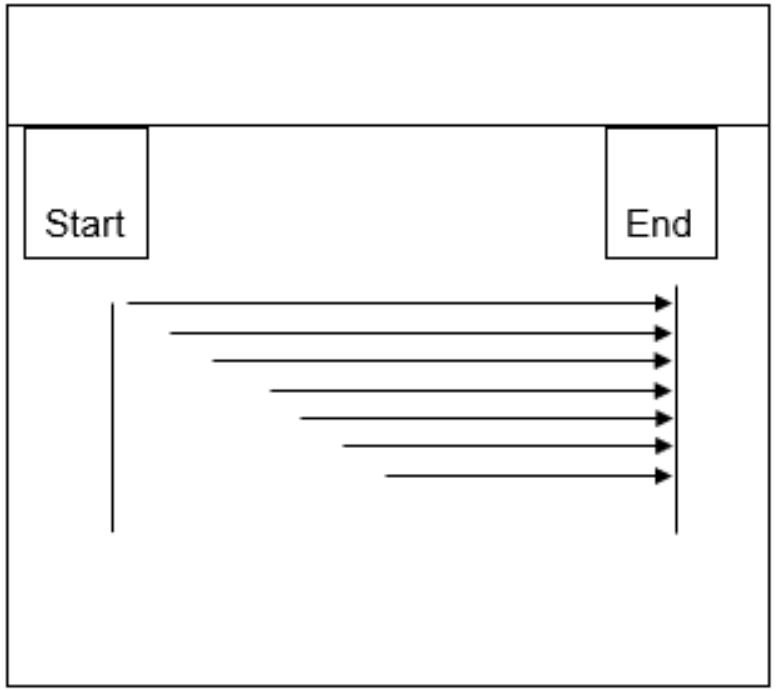
- Time to Event Data is a tuple consisting of
  - the duration of time from randomization till the end of observation for the event and
  - whether that end of follow-up is due to a loss to follow-up (censor = 1) or due to the occurrence of that event (censor = 0).
- In the figure,
  - the yellows ticks are the censoring denoting the 'neutral' loss to follow-up.
  - The green straights across are durations during which no event occurs.
  - The red drops are at durations where progression or other events occurs. The drop is proportional to the ratio of the # events at that duration by the # at risk.
  - The right tail tend to more erratic due to fewer # at risk

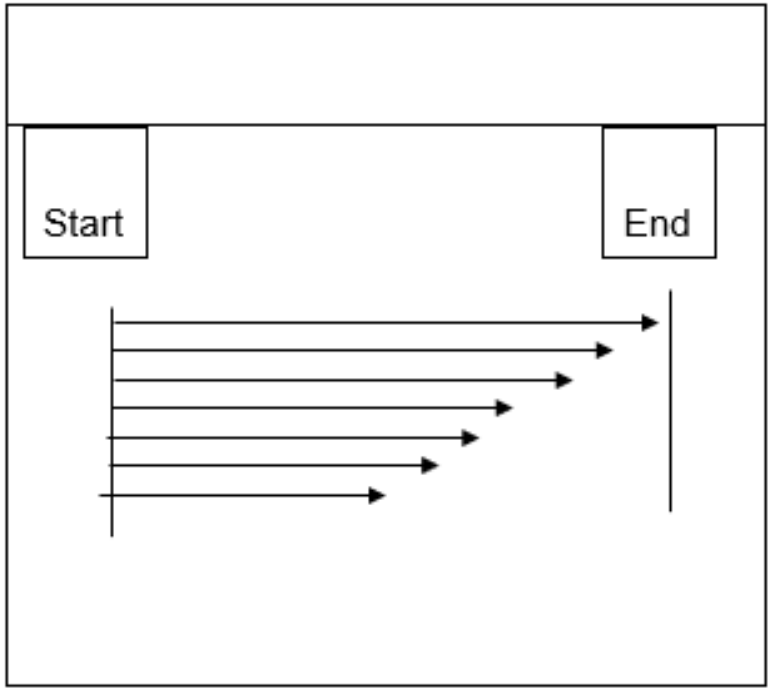
Calendar Time: Variable and Fixed Follow-up





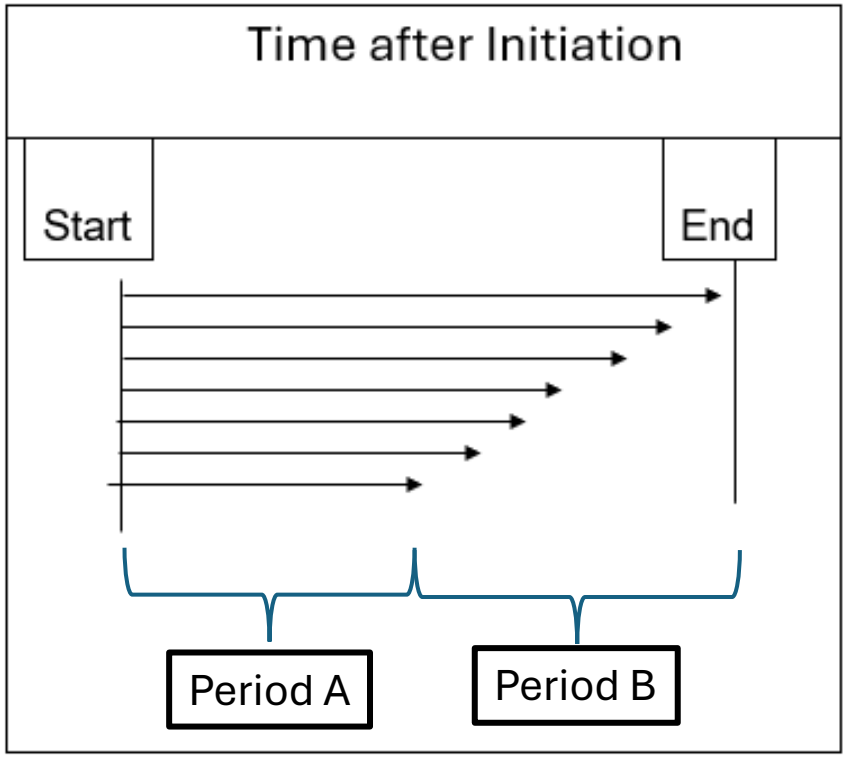
Variable follow-up: Calendar time versus Time after Initiation/Index

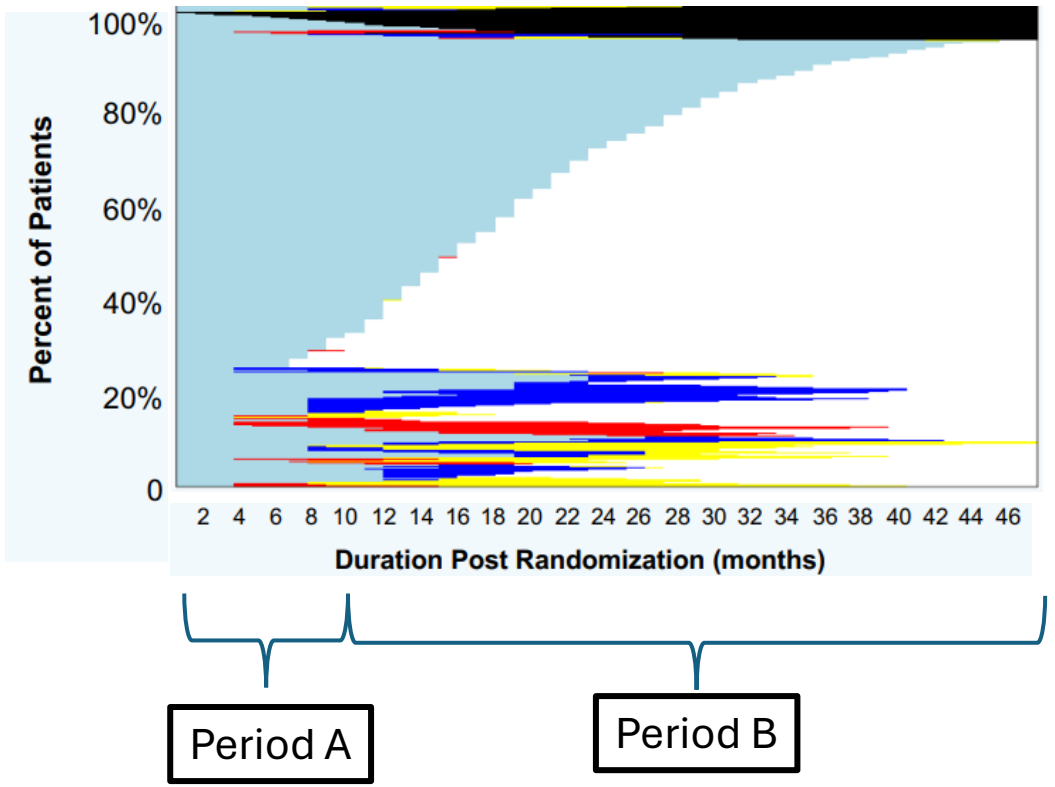




Puzzler: Which one is Calendar time, and which one is Time from Index

Time after initiation schema vs Actual for a trial treatment arm





Puzzler: Classify Period A and Period B as Accrual/Enrollment Period or Follow-up for LPI

Obtaining appropriate exposure

Brief look at the statistical design of TTE trials

The statistical design of time to event trials is a two-step process

First, we find the number of events to detect effect given a significance level (two sided 0.05 for registrational trials)

Depends additionally just on the power, the randomization ratio and the hazard ratio to be detected.

Second, we design operational characteristics to obtain the number of events.

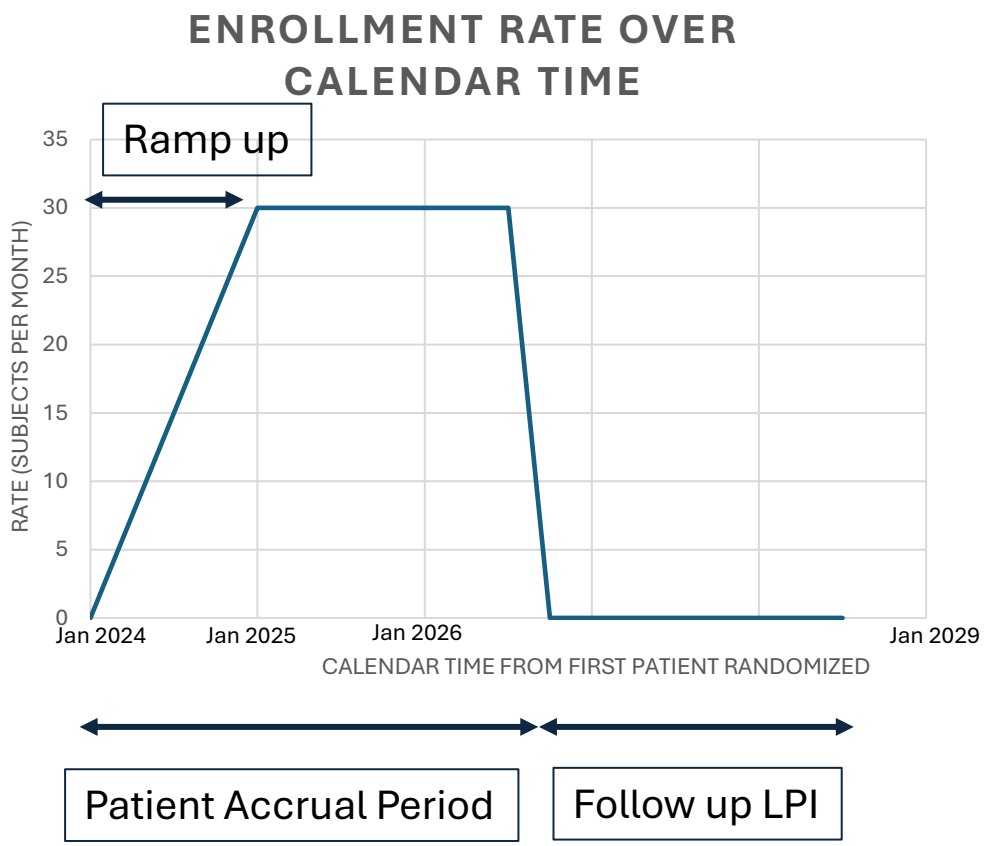
# of Events are proportional to the net patient months of exposure and hazards for an event in each group

Use permuted block randomization - like the near simultaneous release of horses from a starting gate in small sets (usually 4)

Example, a block of size 4 based on # of years of training (<2 vs >2) and two diets (treatments):

=> 4 at each training level released with randomly ordered diets occurring twice each.

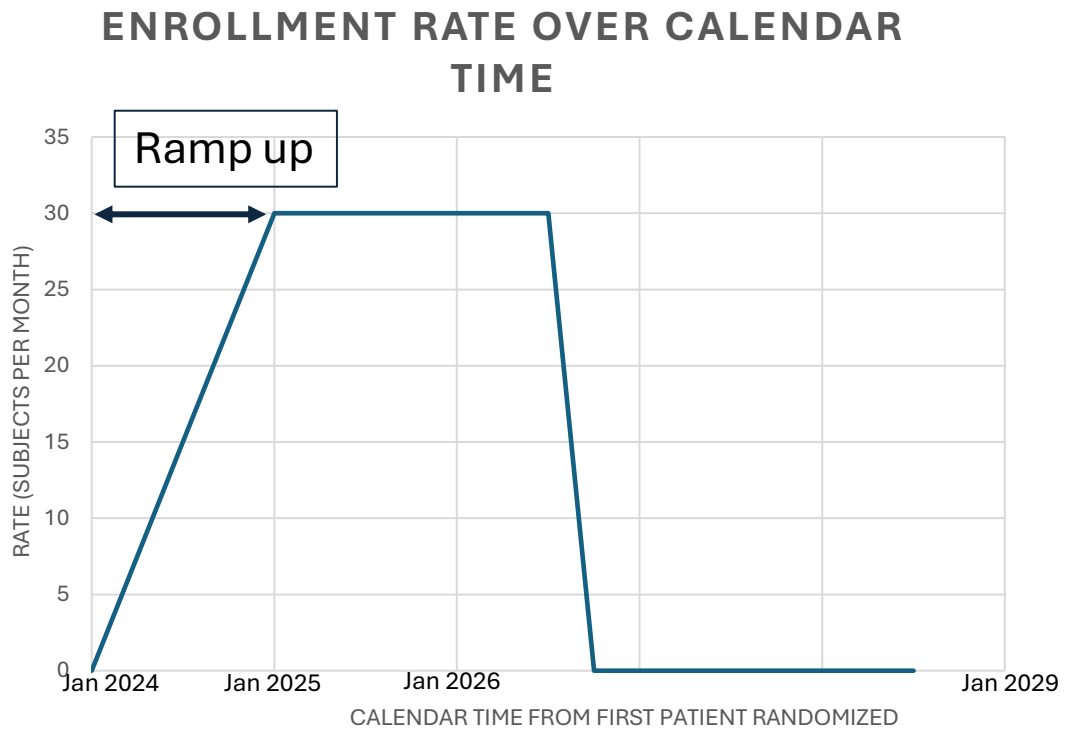
Going from enrollment over calendar time to patient months exposure

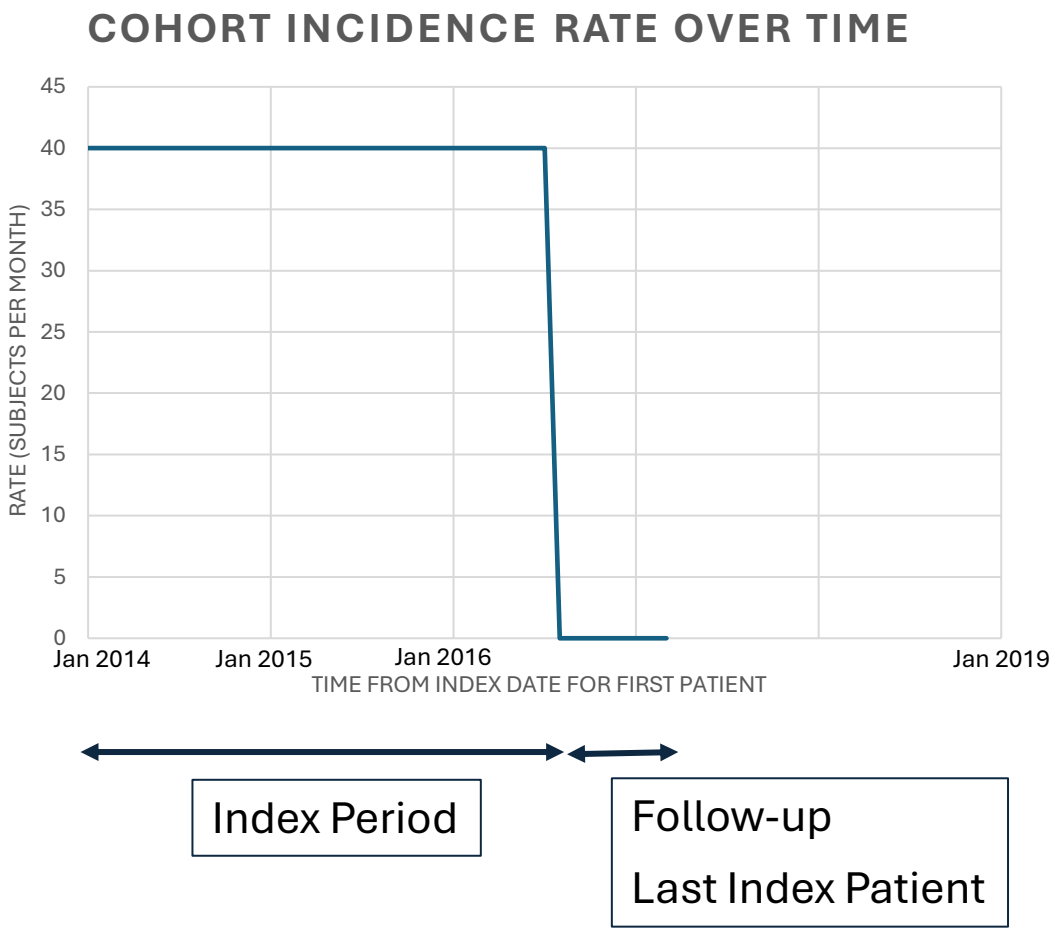


Time From First Patient Randomized (Months)	0	6	12	30	33	42	54
Calendar time	Jan-24	Jul-24	Dec-24	Jul-26	Oct-26	Jul-27	Jul-28
Enrollment rate (per month)	0	15	30	30	0	0	0
#Subjects enrolled	0	45	XXX	720	765	765	765
Patient Months of Exposure	0	135	810	8910	11138	18023	27203

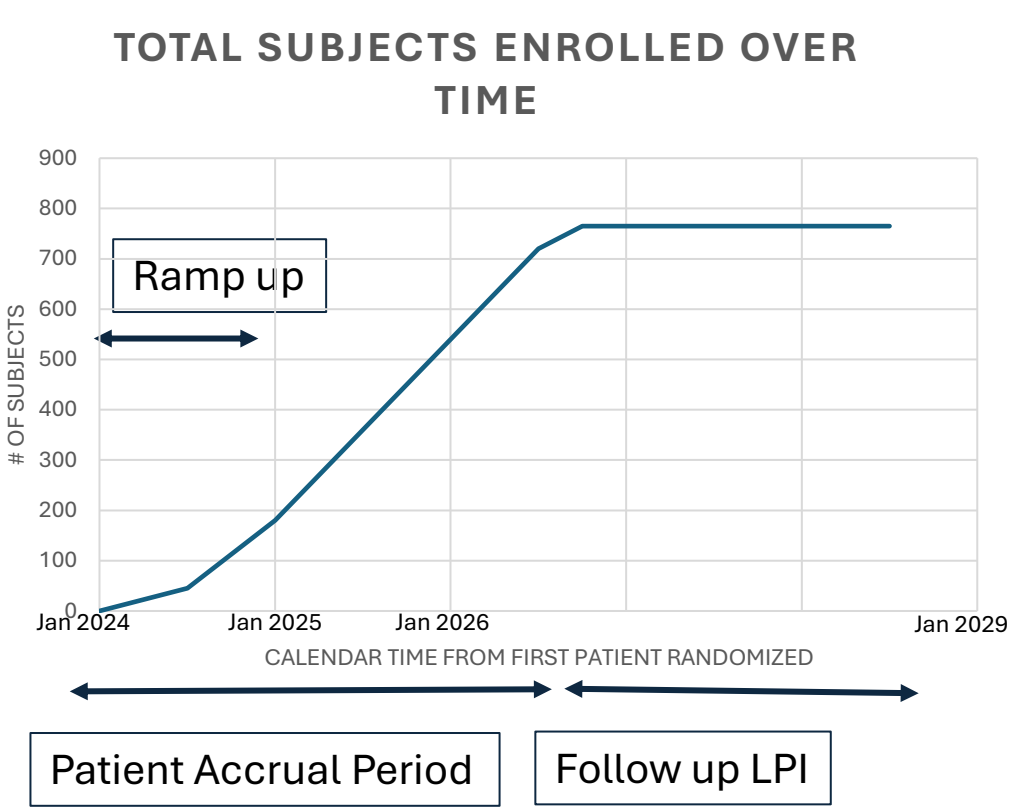
The number of subjects at month 6 computes as
(Average enrollment rate 0- 6 months)*6
= 0.5*(0+15)*6 = 45
The patient months of exposure computes as
(Average # of patients in period)*(period length)
+ (Exposure at previous period end)
Puzzler: Try figuring XXX at Month 12 from FPI

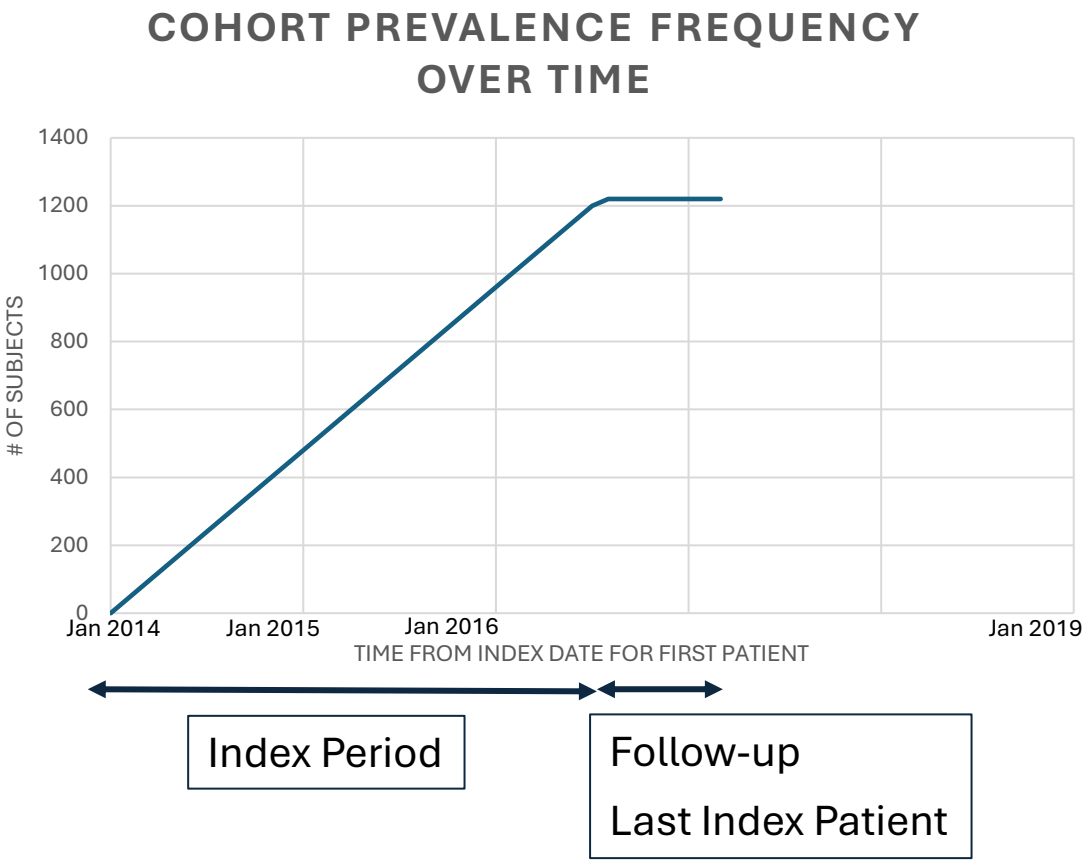
Recall: Enrolment rate (Trial left) vs Cohort Incidence (RWE Right)



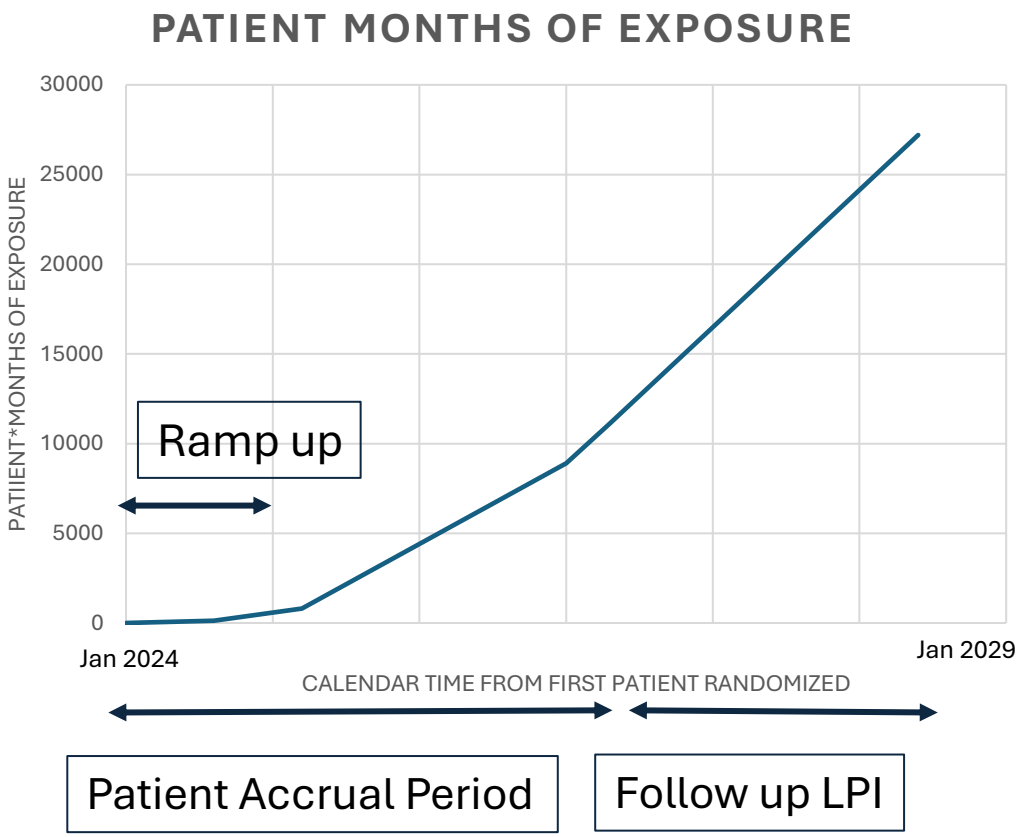


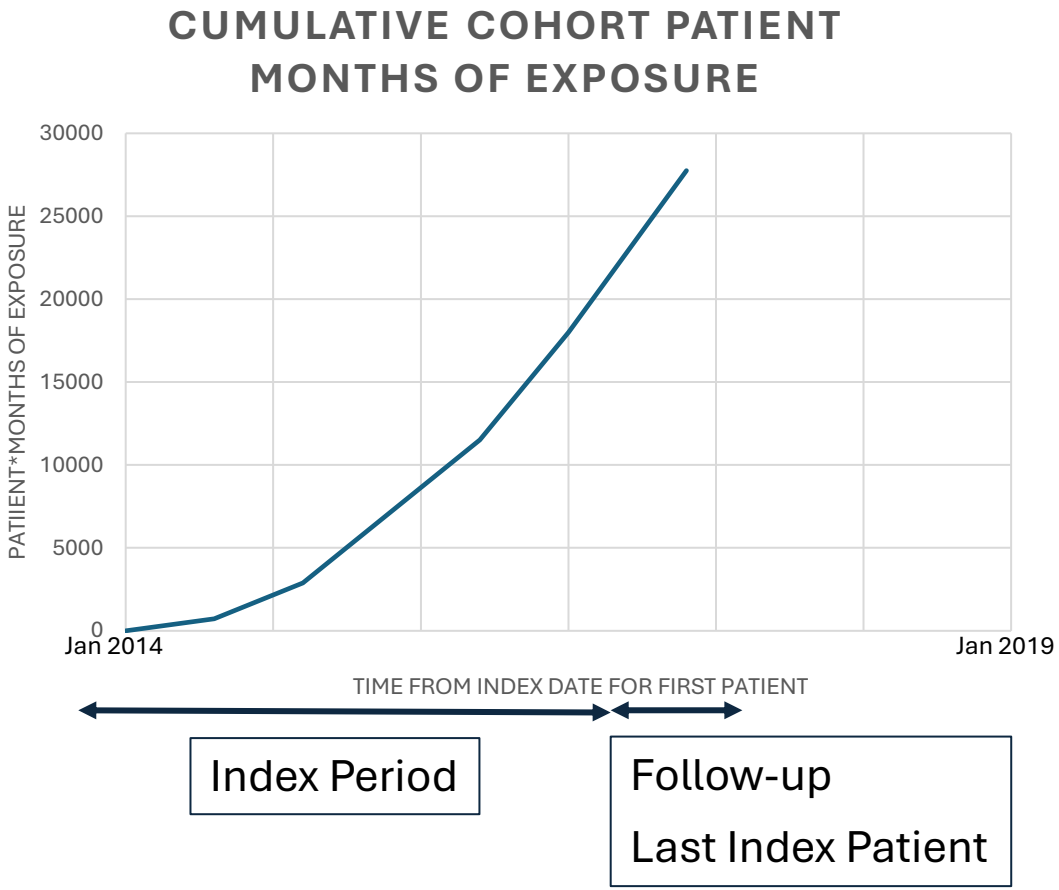
Resulting Subjects Enrolled (Trial left) vs Cohort Prevalence (RWE Right)





Resulting patient months of exposure (Trial left) vs Cumulative cohort exposure (RWE Right)

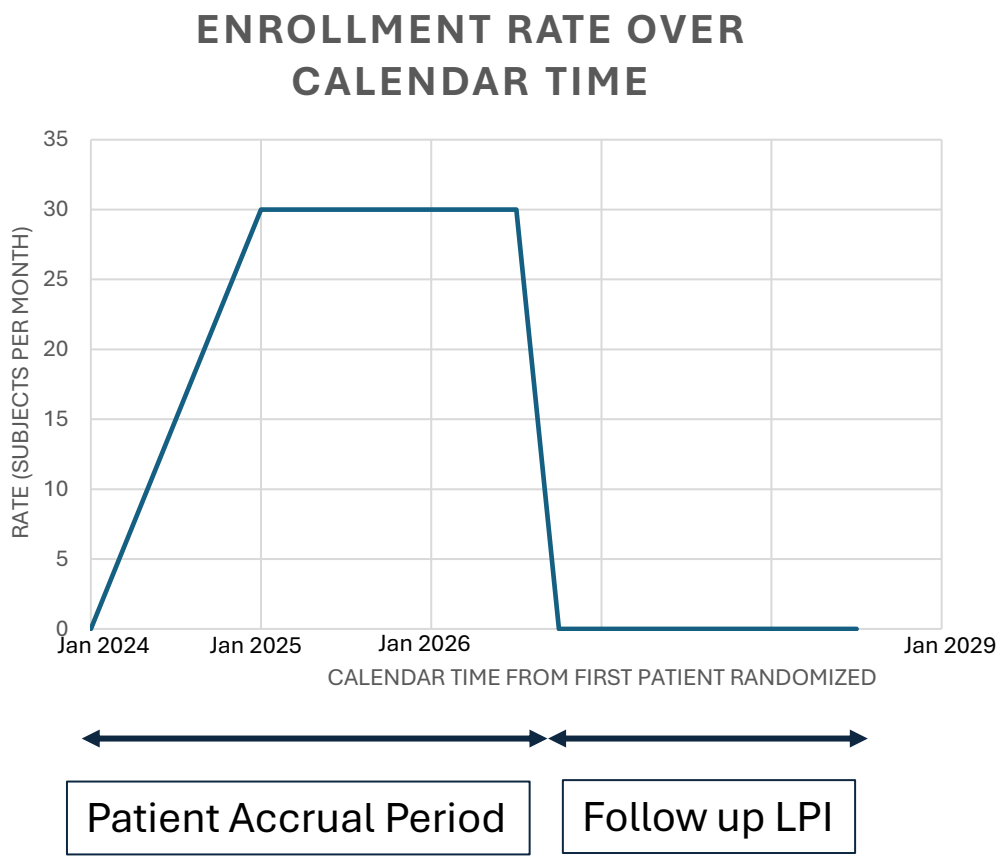


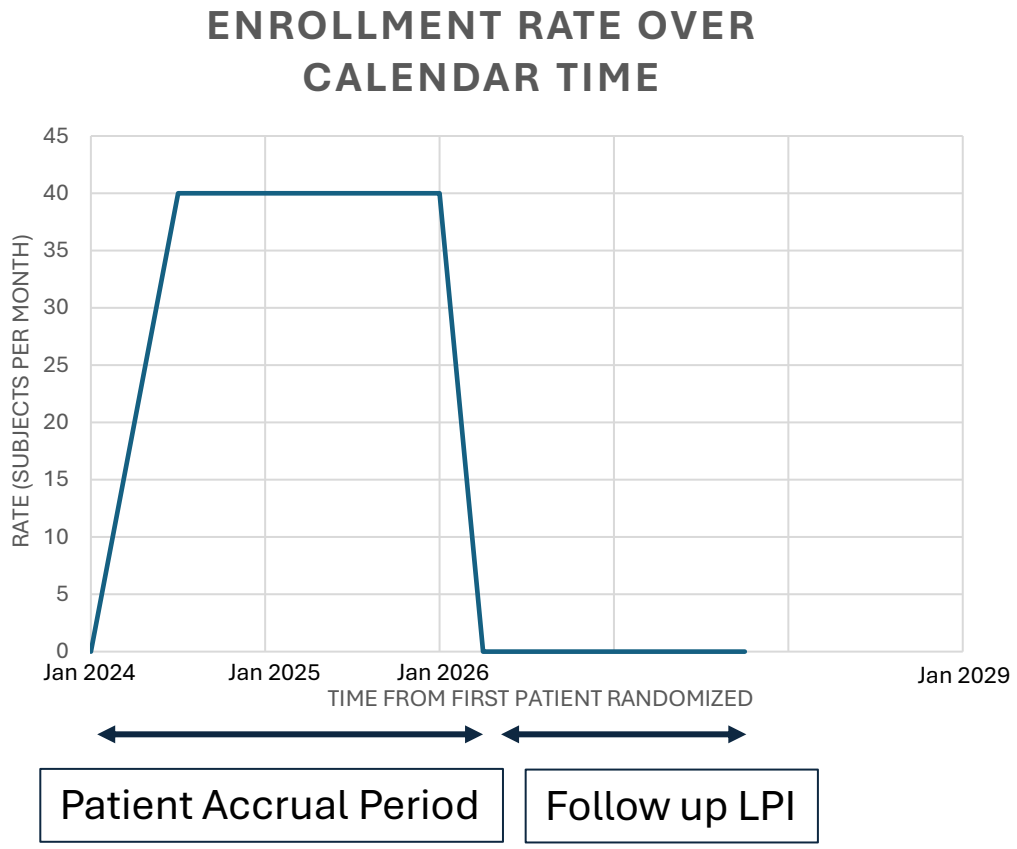


Exposure and the Pressure, Volume and Temperature Analogy

Constant $\frac{(Pressure * Volume)}{Temperature}$	Randomized Clinical Trial	Real World Data
You **can increase one and decrease the other** to maintain equilibrium: $(Pressure * Volume)$	You **can increase one and decrease the other** to maintain a constant N and a constant exposure: $(Enrollment\ rate * Accrual\ Time) \cong N$	You **can increase one and decrease the other** to maintain a constant N and a constant exposure: $(Incidence\ rate * Index\ period\ duration) \cong N$
This can be **increased** with increases in the numerator to maintain equilibrium: $Temperature$	This can be **decreased** when the above product increases to obtain the same exposure: $Follow - up\ LPI$	This can be **decreased** when the above product increases to obtain the same exposure: $Follow - up\ LIP$
This can be **decreased** with decreases in the numerator to maintain equilibrium: $Temperature$	This can be **increased** when the above product decreases to obtain the same exposure: $Follow - up\ LPI$	This can be **increased** when the above product decreases to obtain the same exposure: $Follow - up\ LIP$

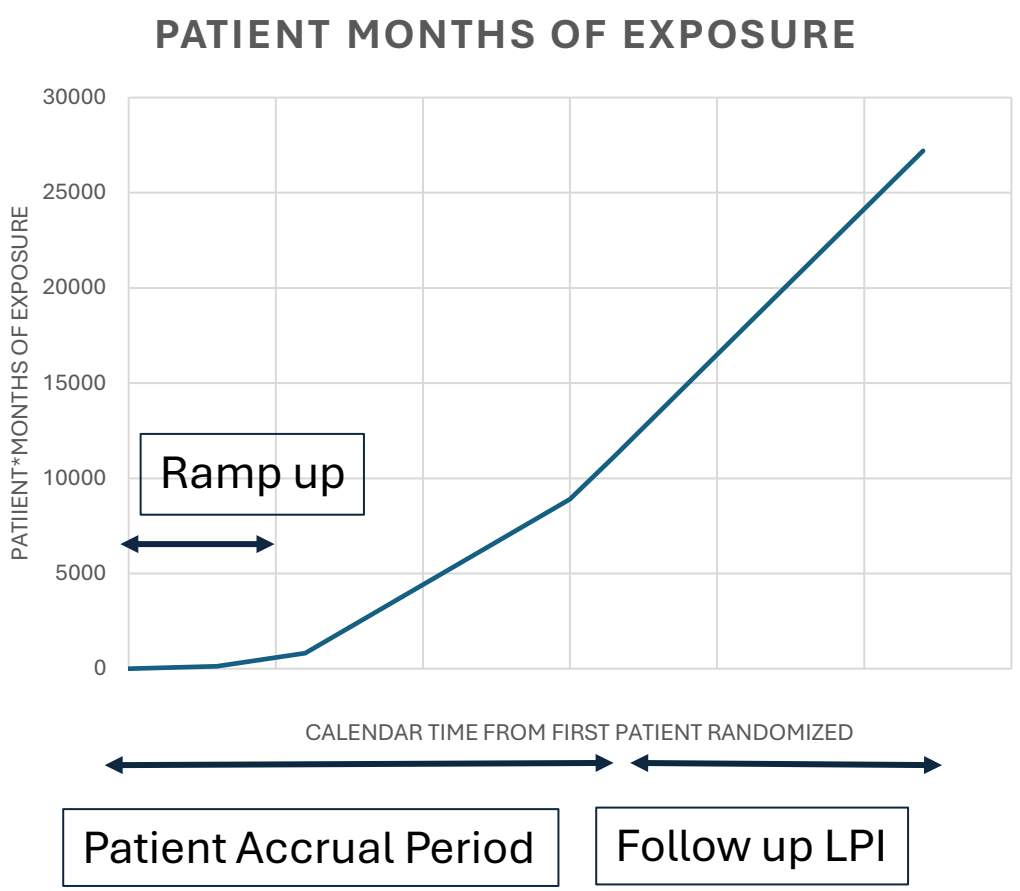
Enrolment rate over time for two trials

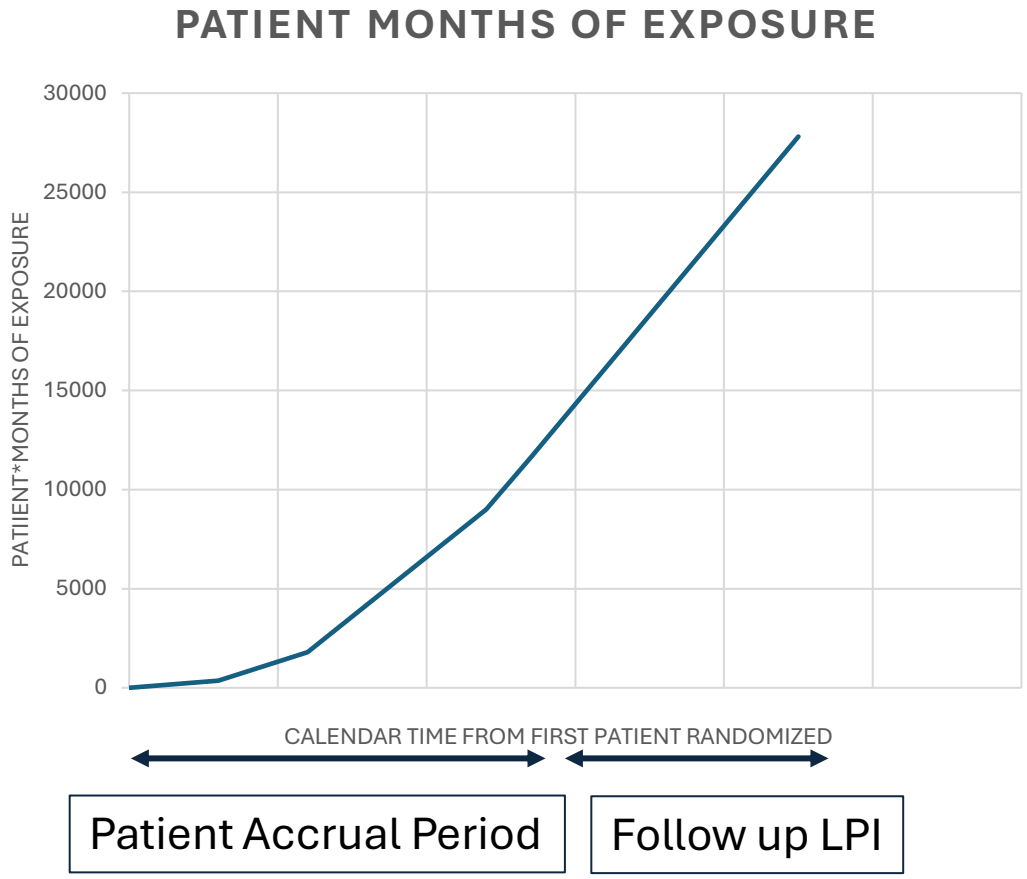




Puzzler: Which enrollment scenario is more likely that for a pivotal phase III study? – Left or Right

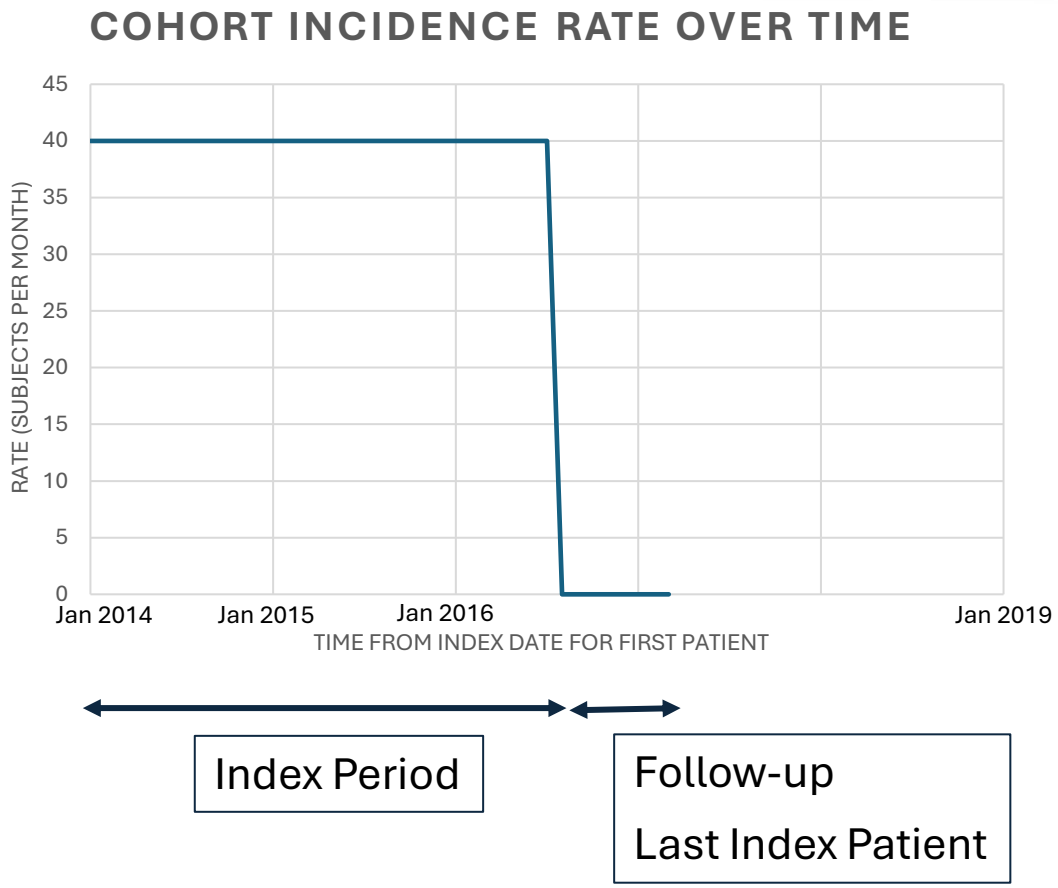
Resulting patient months of exposure (Trial left) vs Cumulative cohort exposure (RWE Right)





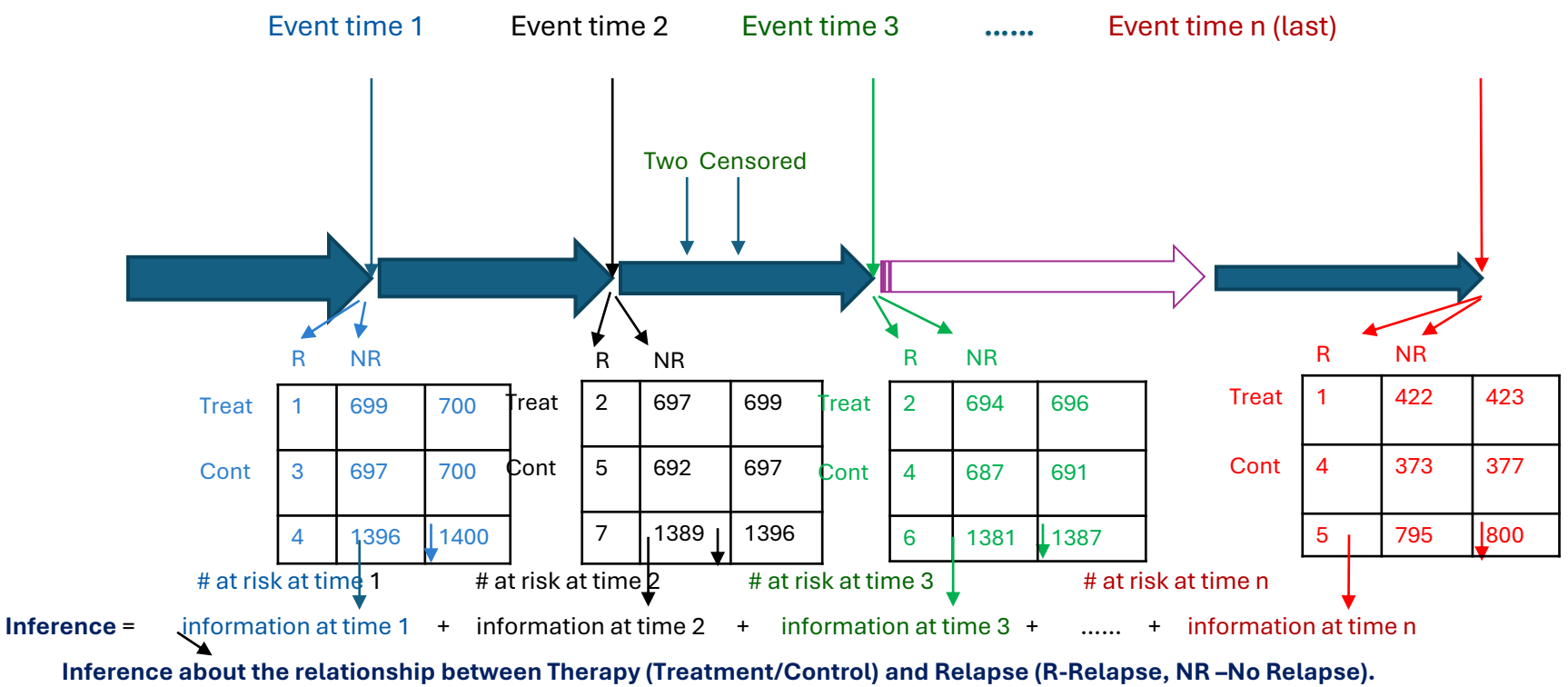
Carving appropriate Index periods

For well estimated time to event statistics



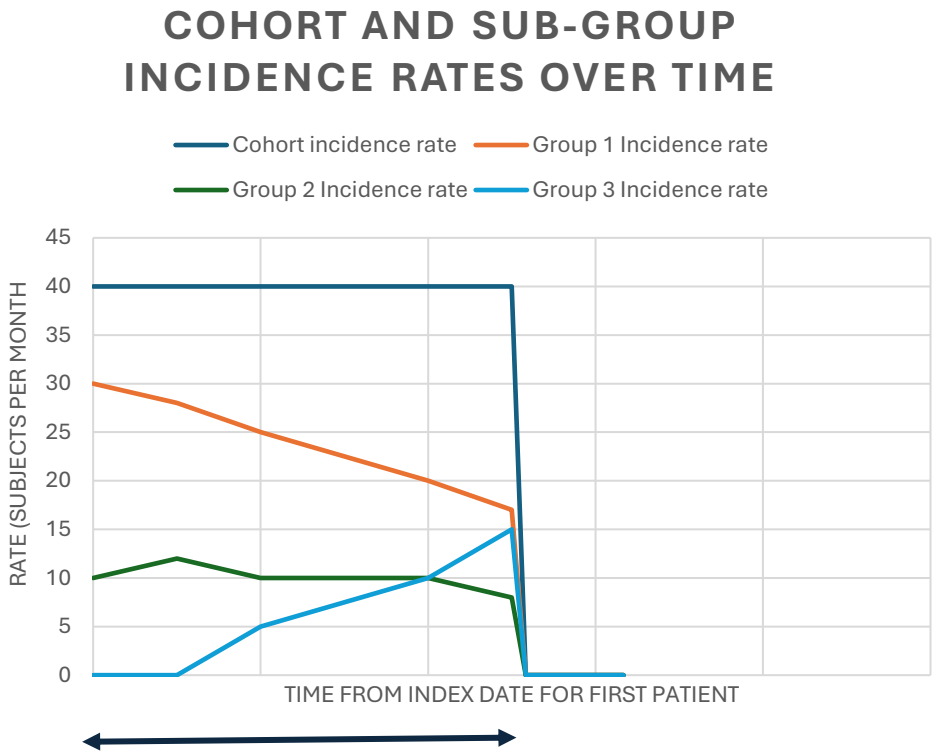
- Need a large data source to get a large Incidence rate
- Long Index period would also help
- Usually, shorter Follow-up for Last Index Patient (LIP)
  - A prospective extension to retrospective could extend F-up LIP

Brief look at Analyses:
The agglomerative survival statistic



Groups with no incidence in periods

- The KM graphic would stop earlier for group 3 while others would extend for the entire follow-up.
- Comparisons to Group 3 would not use any information across groups in the no incidence period.

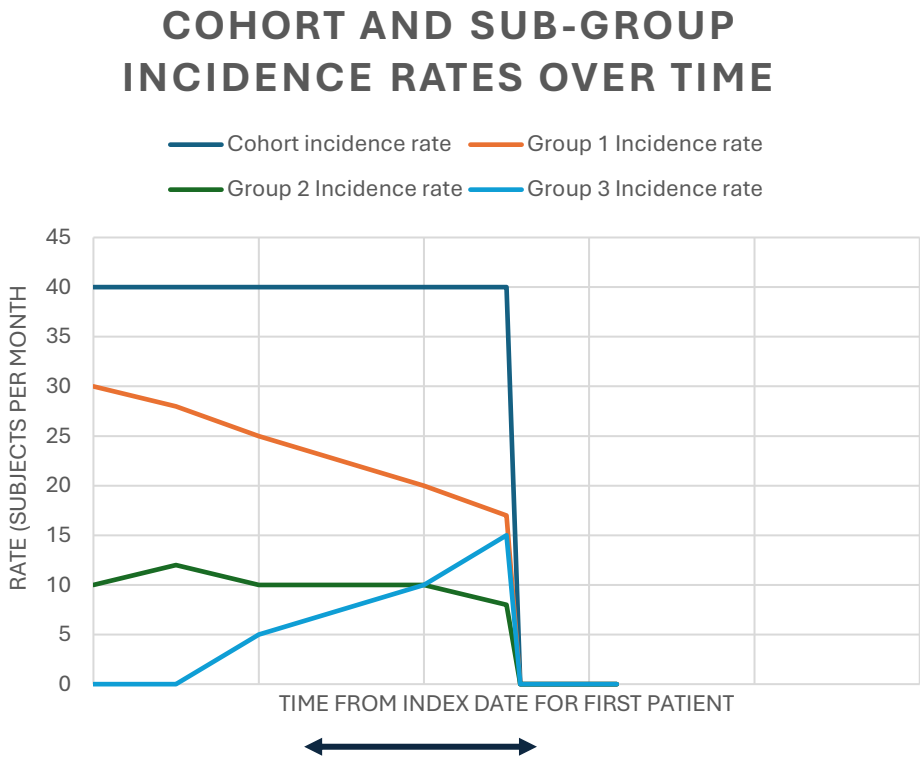


Un-curtailed Index Period includes a no incidence period for Group 3

Groups with changing incidence over time

Hazard by follow-up post index	Control	Treated	Hazard Ratio
Duration Interval			
Hazard Interval 1	0.02	0.01	0.5
N Period 1	30	120	
Hazard Interval 2	0.04	0.02	0.5
N Period 2	130	40	
Net hazard	0.0363	0.0125	0.345

- OK under constant hazards
- May bias estimates under proportional but differing hazards



Index Period Curtailed to reasonably stable period

Need for Intentionality for RWE TTE data

- Planned, deliberate and transparent analyses without data driven last-minute changes generate confidence and reduce stress at final data presentation
- On the fly decisions, sometimes needed for a new data and analytical context, can be limited in the RWE context, as in a trial context, **by**:

  Using a small feasibility subsample
  - To determine the fraction of the sample that remains on applying inclusion criteria and assessing availability of core fields
  - To make decisions on baseline periods, index periods and follow-up periods for last index patient and the first index patient
  - To tally, in such fractions and data carve-outs, the overall event rates and group composition
  - Test methods to address bias, missing data and other real world data issues.
- **Querying** any independent data provider on the above items
  - to obtain an assessment of the fraction of data that would be fit for purpose
  - to add rigor to RWE analyses by obtaining blinded data such as overall event rates

Discussion and other topics

Trial planning ideas on enrollment rates, follow-up for LPI and accrual time

could help in assessing adequacy of TTE analyses in RWE studies by evaluating cohort incidences, index periods, and F-up after LIP.

Learning **FROM RWE in trial settings** is just as useful as learnings **FOR** RWE from clinical settings.

Immortal time issues

Evaluating post baseline factors converts trial data to observational data with bias

Missing data

References: Collett D (2003) Modelling survival data in Medical research. Chapman and Hall.
Selvin S (2004) Statistical analysis of epidemiological data. Oxford University Press.