Lessons Learned from use of Real-World Data as External Controls

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Introduction

Use of real-world data/evidence[1,2]

- Describe natural history of disease
- Identify risk factors
- Post-marketing surveillance
- **Use external controls as comparator with treated patients**
  - When unmet need
  - Difficult to perform RCTs
  - Rare disease, paediatric population, long follow-up required

Examples treated patients without control arm

- Phase 2 study in rare paediatric disease
  - extended long term follow-up
  - all treated
- Phase 3 study of rare disease in adults
  - extended long term follow-up
  - all treated
  - placebo roll over after end phase 3
- External Control comparisons needed to understand if treatment improves event free survival

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1. Corrigan-Curay J, et al. *JAMA* 2018; **320**:867–868
2. www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence (Accessed 30 June, 2021)

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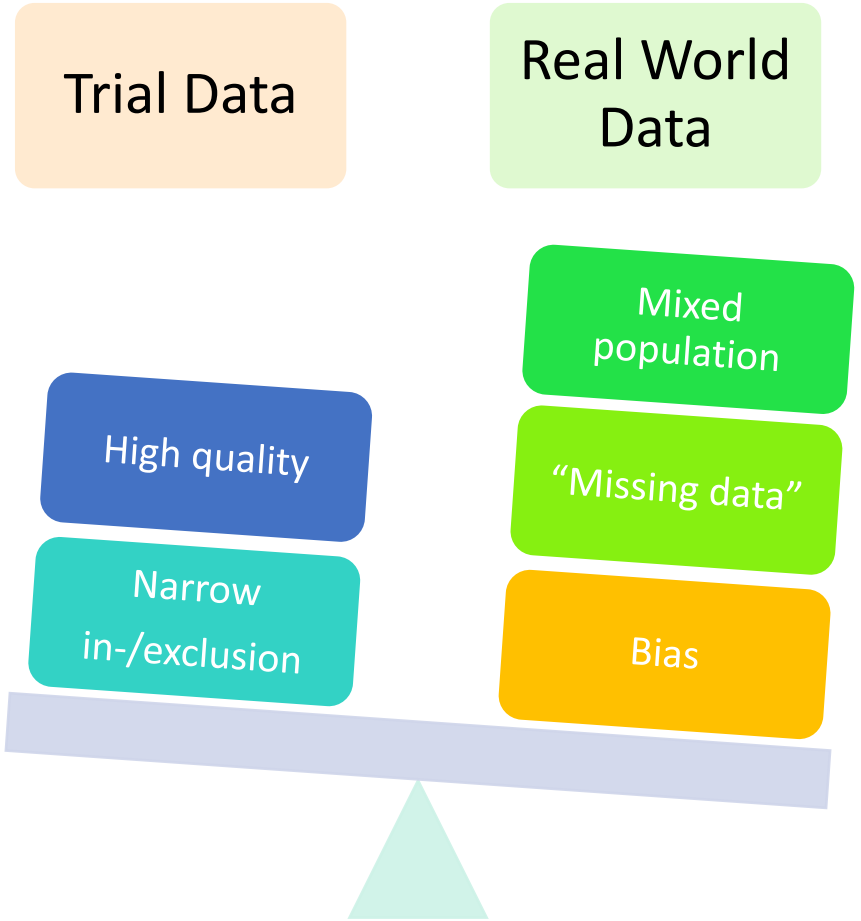
Is it feasible to use RWD as External Controls?



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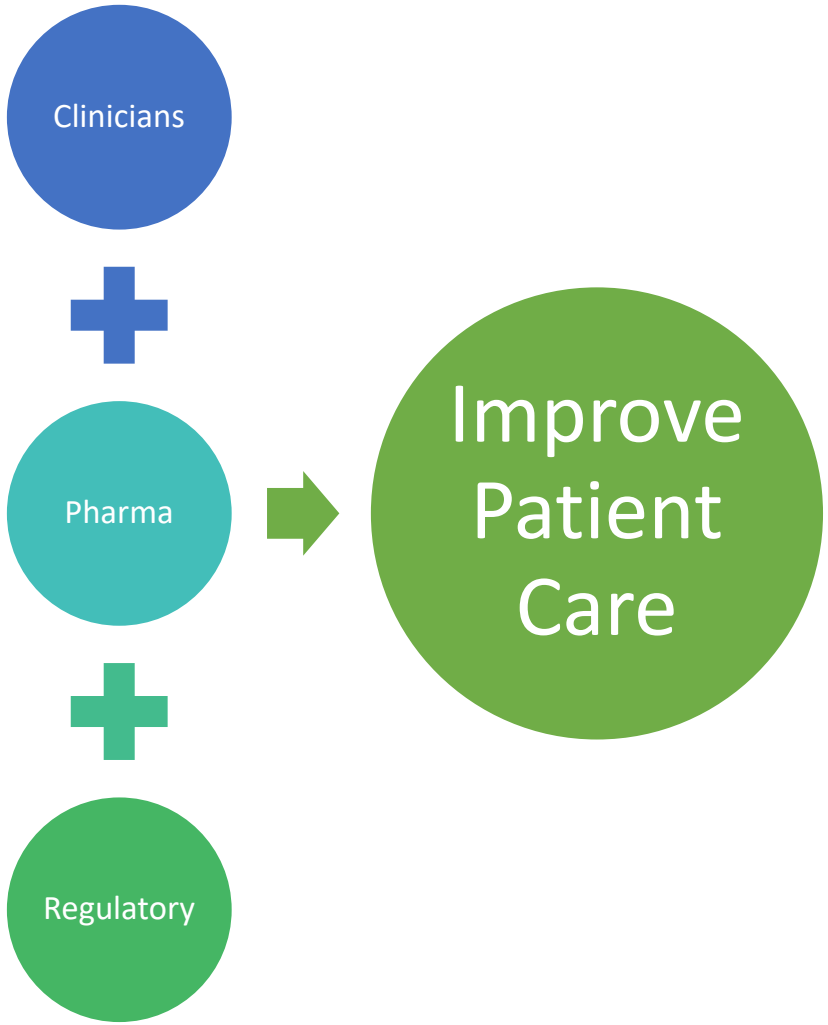

Stakeholders

- Pharma: trial data
- Independent researchers / scientists: RWD
- Regulatory: guarding the integrity

Collaboration: willingness, transparency and trust

- Data sharing
- Protocol
- Statistical Analysis Plan

- Analysis conducted independent from pharma
  Consider bringing in an independent partner (stats team)

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RWD

Real World Data

High bar of standardization and quality

- Prospective/ Hybrid/ Retrospective
- REB, Data Sharing, e-CRF
- Completeness, accuracy, and consistency
- Standardized outcome assessment
- Adjudication criteria
- Quality control
- Audits

Examples Real World Data

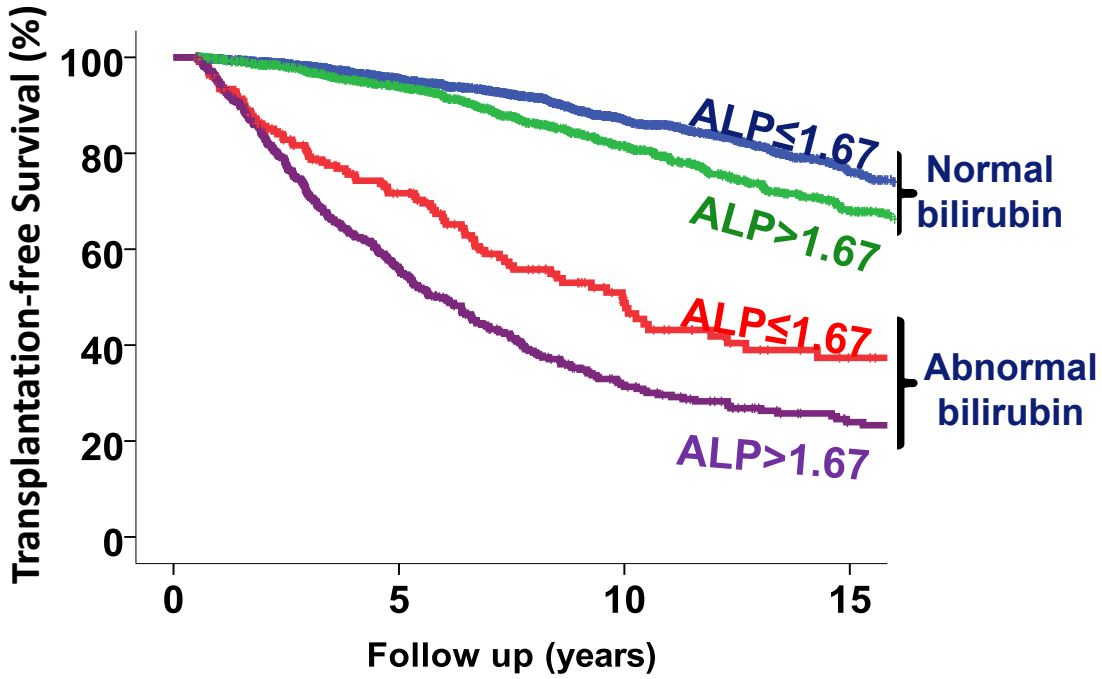
- The GLOBAL PBC Study Group: studies on primary biliary cholangitis (PBC)
  - PBC a rare chronic autoimmune liver disease, slowly progressive
- GALA: the global Alagille Alliance Study
  - Alagille syndrome (ALGS): a rare, autosomal dominant disorder, characterized by high-γ-glutamyltransferase (GGT) cholestasis in children

Examples Real World Data

Launched in 2012

Retrospective, >6000 patients, 40.000 visits,

40 sites from 18 countries [1,2]

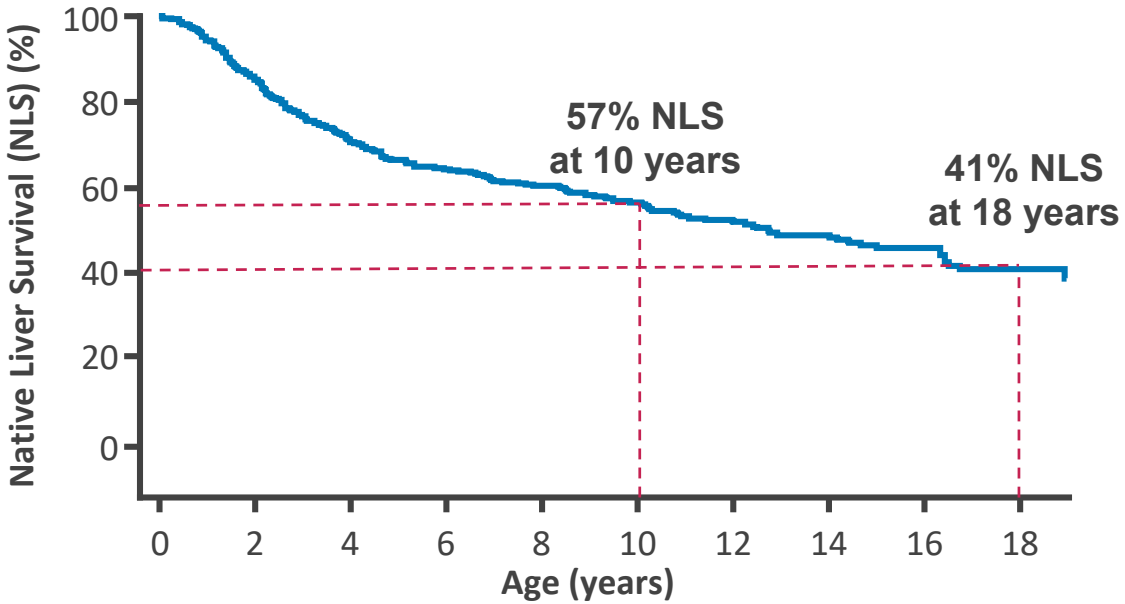


1. Lammers W, et al. AASLD 2014 (oral presentation); 2. Lammers et al., *Gastroenterlogy* 2014

Launched in 2018

Retrospective, >1400 patients, 12.000 visits,

56 sites from all regions of the world [3,4]



3. Vandriel SM, et al. EASL 2020 (oral presentation); 4. Kamath BM, et al. *Hepatol Comms* 2020; **4**:387–398.

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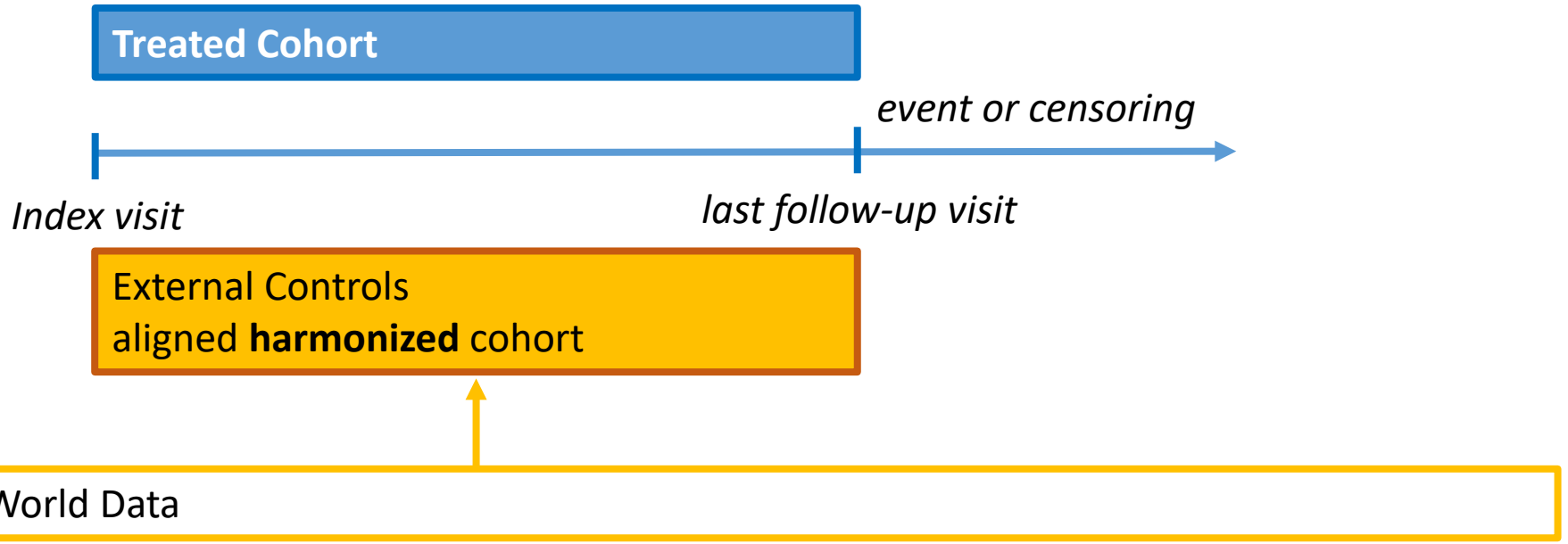
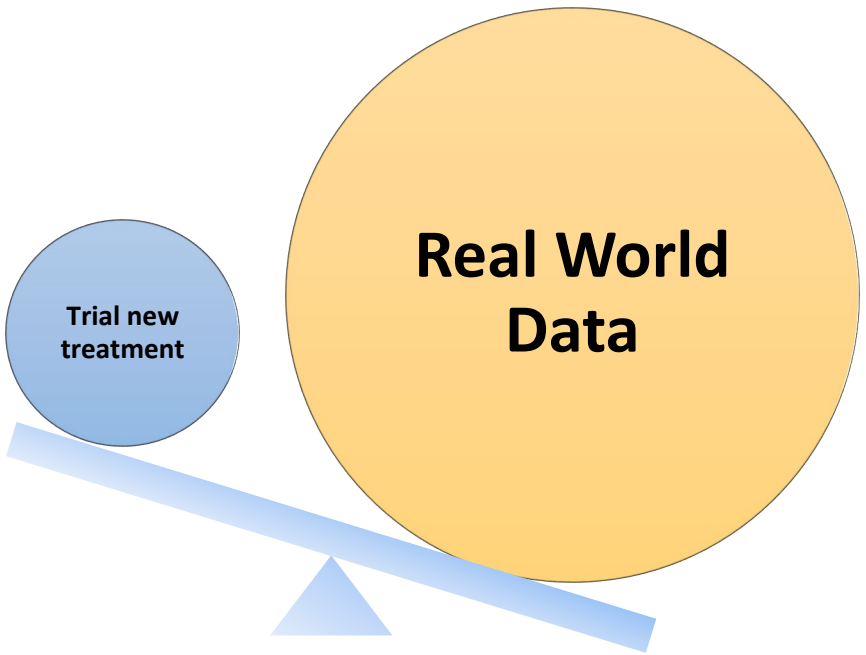
Primary aim

To compare time to clinical event in treated patients with external controls

Examples PBC and Alagille: Event defined as liver transplantation or death



Harmonize Design

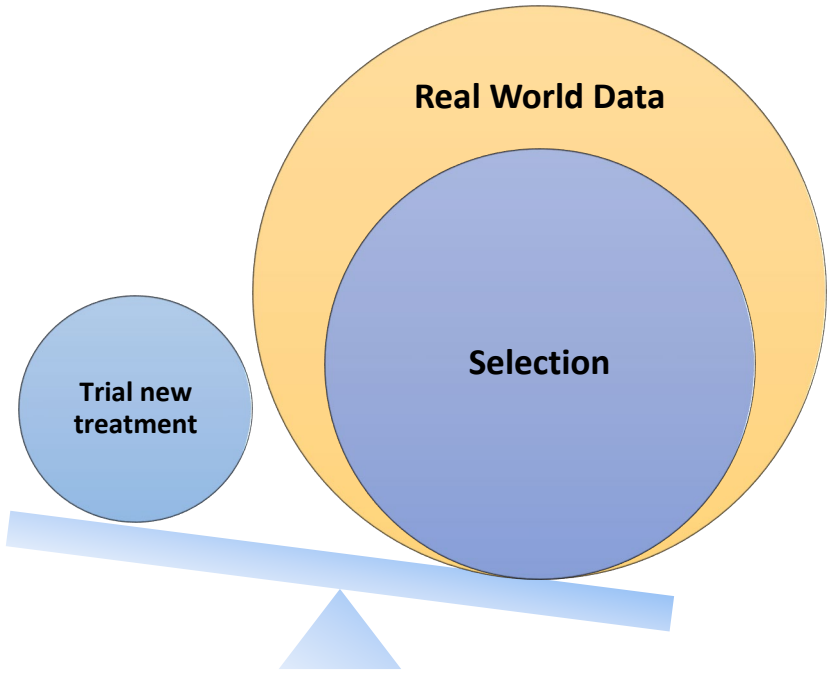


Feasibility assessment

- Quality of data
- Outcome(s) – use same definition
- Lab-values – different labs, ULN, unit
- Patient factors
- Investigate completness
- Identification of confounders

- Power analysis: pre-specified effect size or min. clinical relevant effect size

Identification of Patients & Visits



Selection process

- Apply aligned inclusion/exclusion criteria
- Overlay sites / regions
- Overlay calendar time / SOC treatment

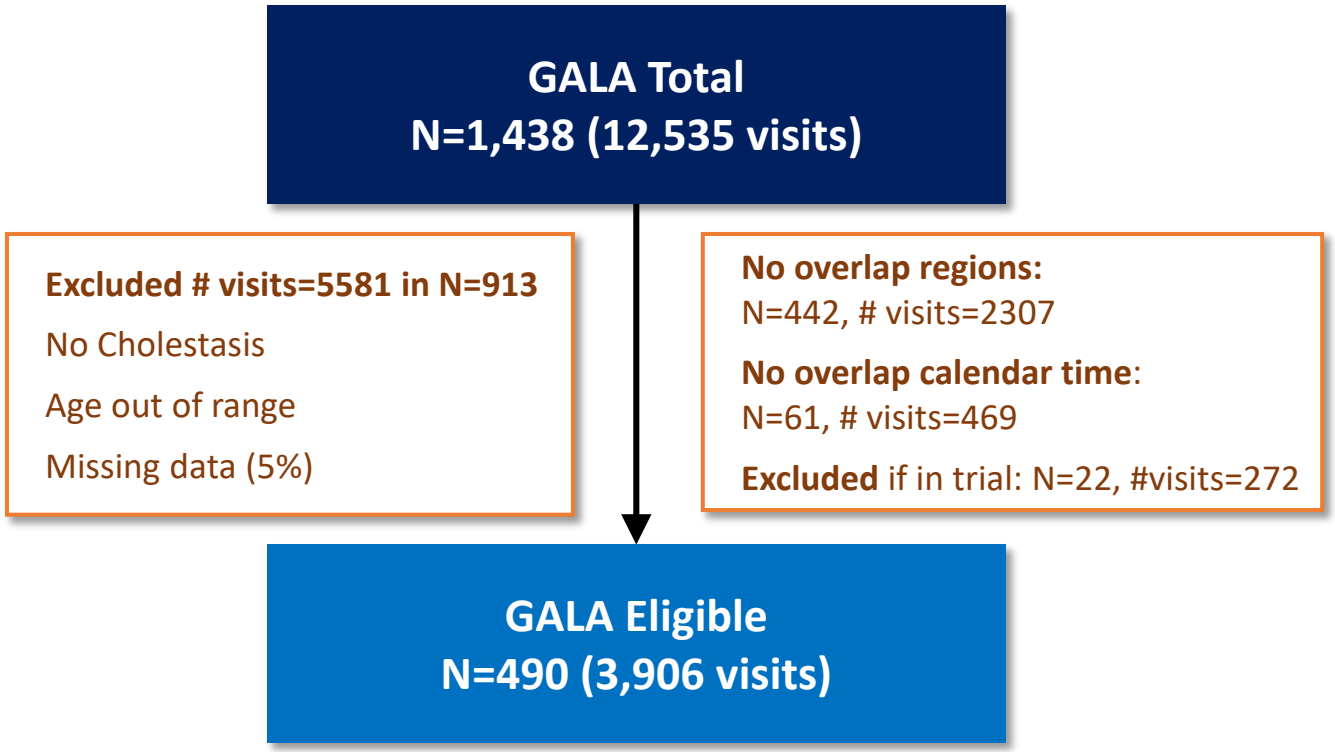
Example external controls selection Alagille

Alagille phase 2 trial: inclusion severe cholestasis, age 1-18yr

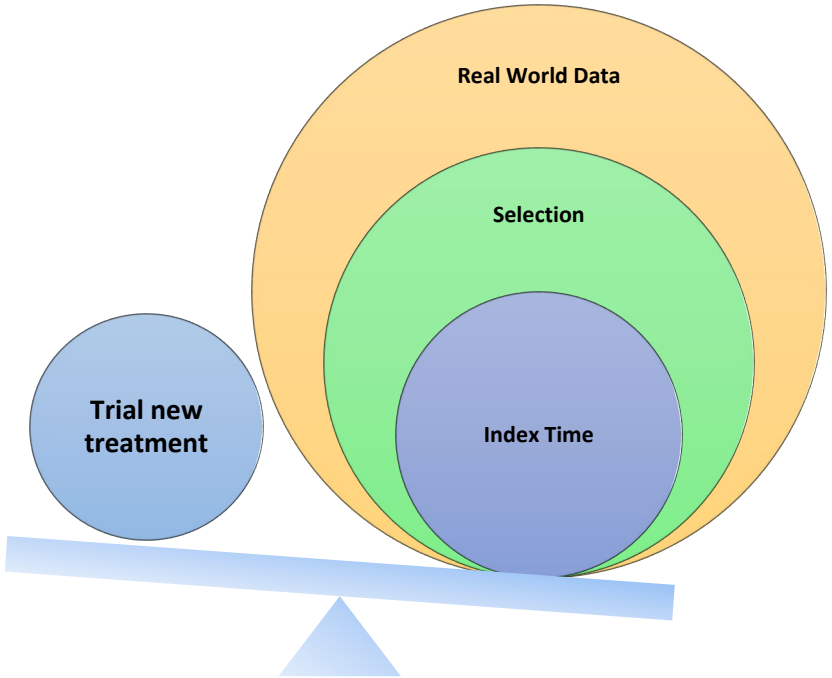
RWD = External controls from GALA

Identification of patients and visits:

- A patient may be eligible with multiple visits



Index visit



Choice of Index Time = start of follow-up

- First visit
- Confirmatory visit
- Random visit(s)
- Last visit
- Other methods: multiple visits, ML-method

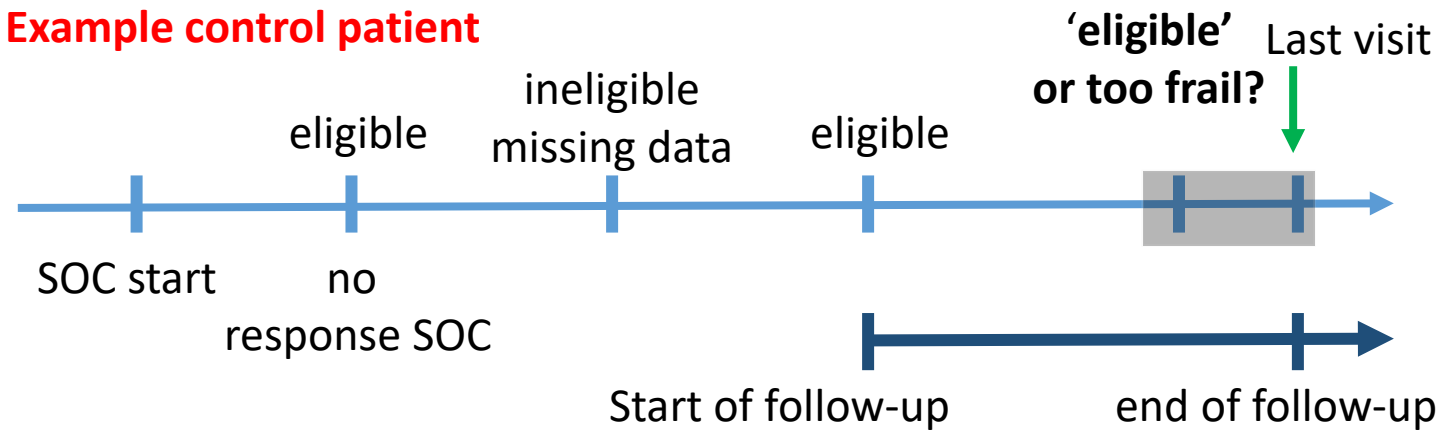
Example external controls selection PBC

PBC – phase 3 trial: inclusion non-response to SOC treatment

External controls from GLOBAL PBC

Step-wise selection procedure of patients/visits:

- **Identification of patients and visits:** 1391 patients identified with a mean of 4.8 eligible visits pp
- **Selection of index time = start of follow-up – avoid immortal time bias**



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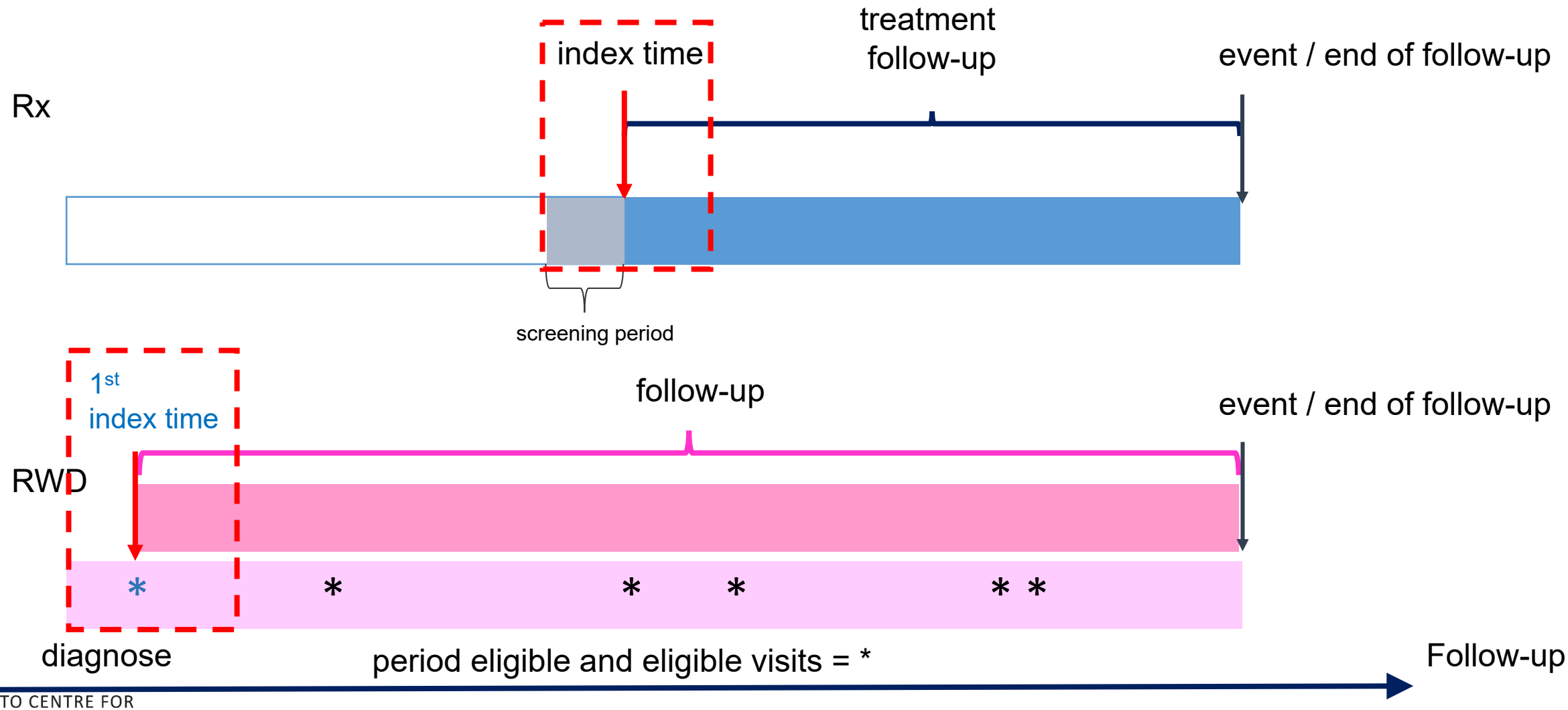
Selection of index time



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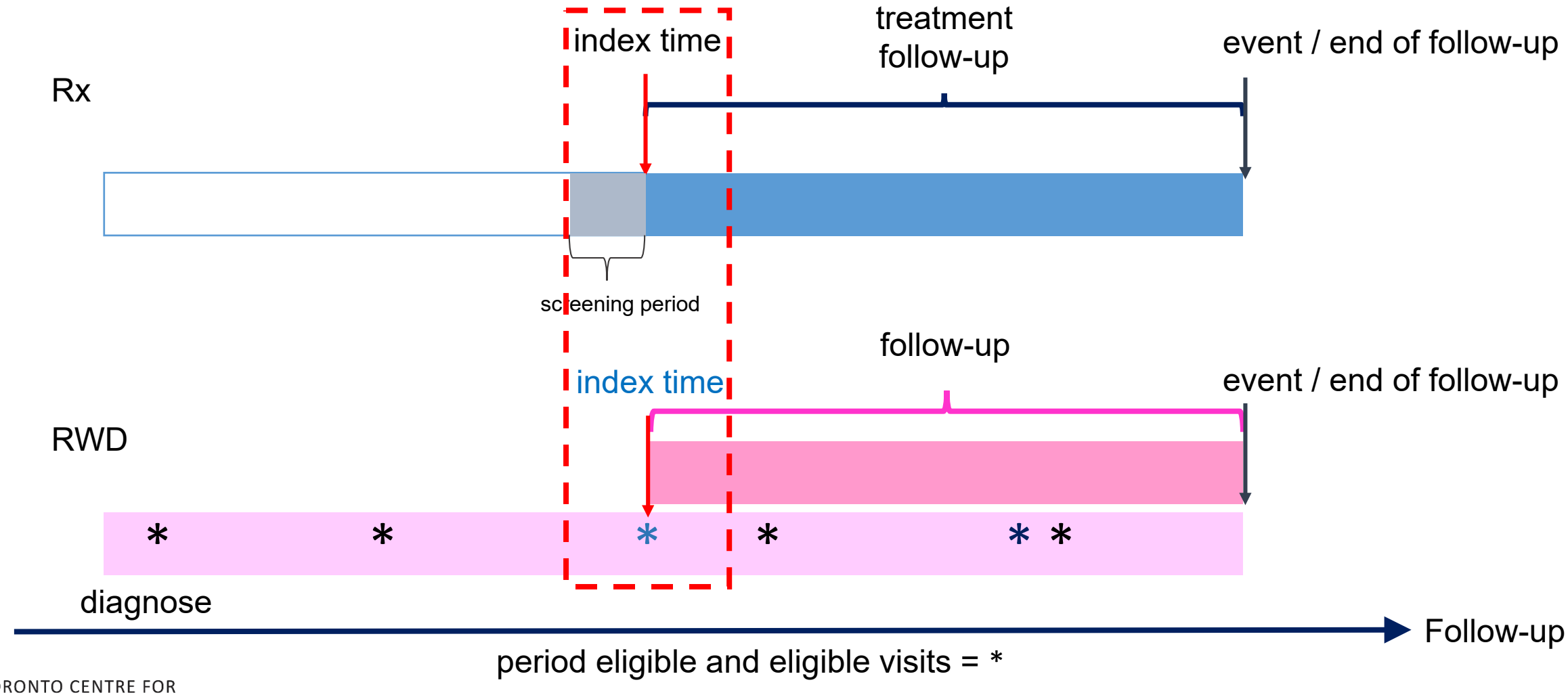
Selection of index time



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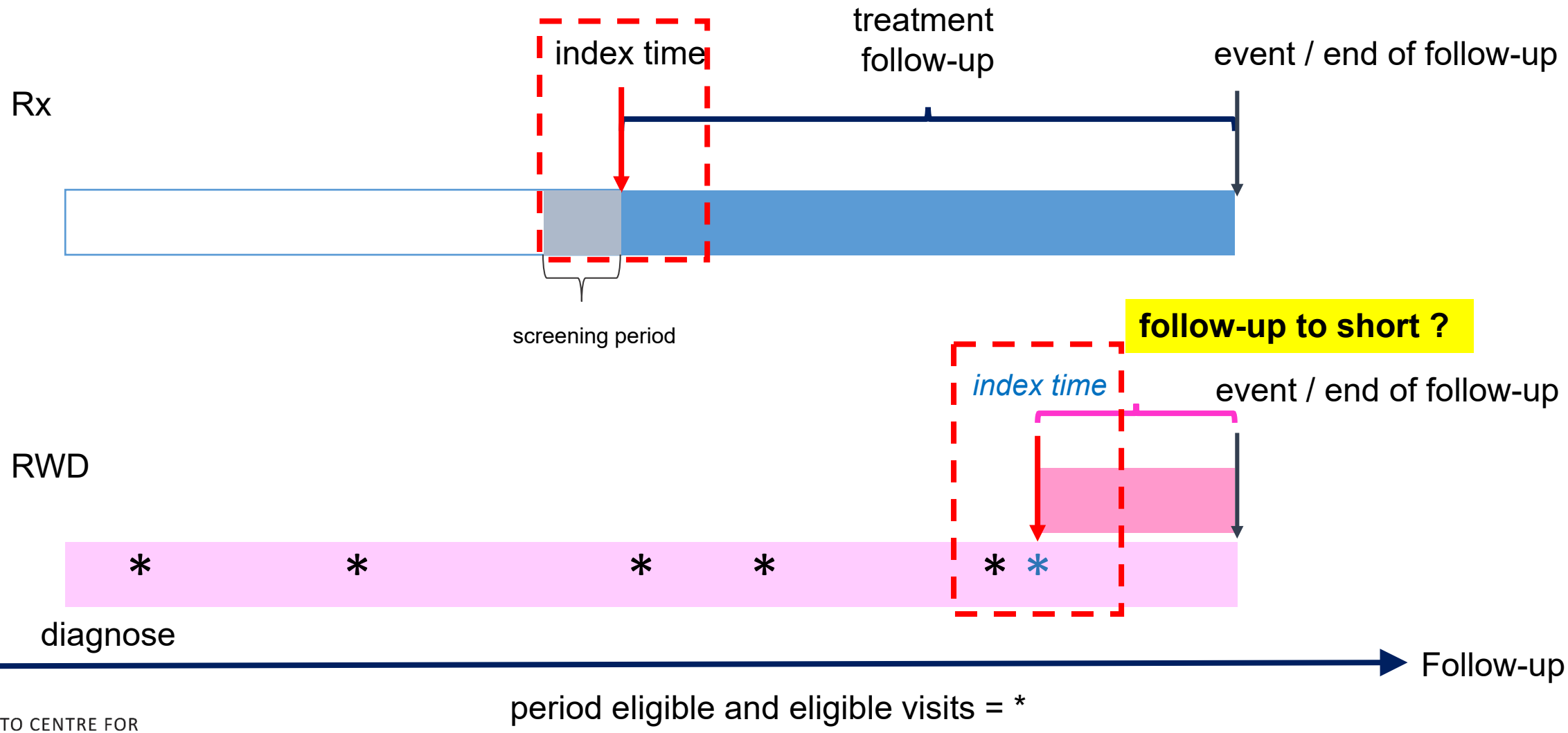
Immortal time bias – too frail for inclusion?



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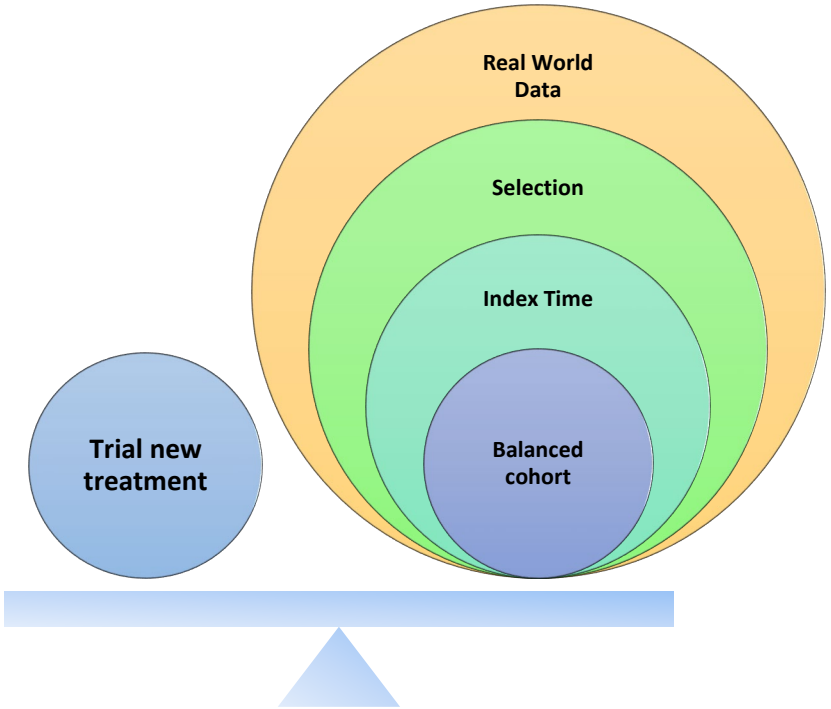
Balanced design using weights



Assessment of balance

- pre-specified check and tests
- Estimate weights
  - Propensity scores
  - IPTW
  - ATT weights

Harmonize Design

Firewall: blinded for outcome

Feasibility assessment

- Define outcome, confounders
- Quality of Lab-values, patient and disease factors, missingness
- Power analysis

Selection

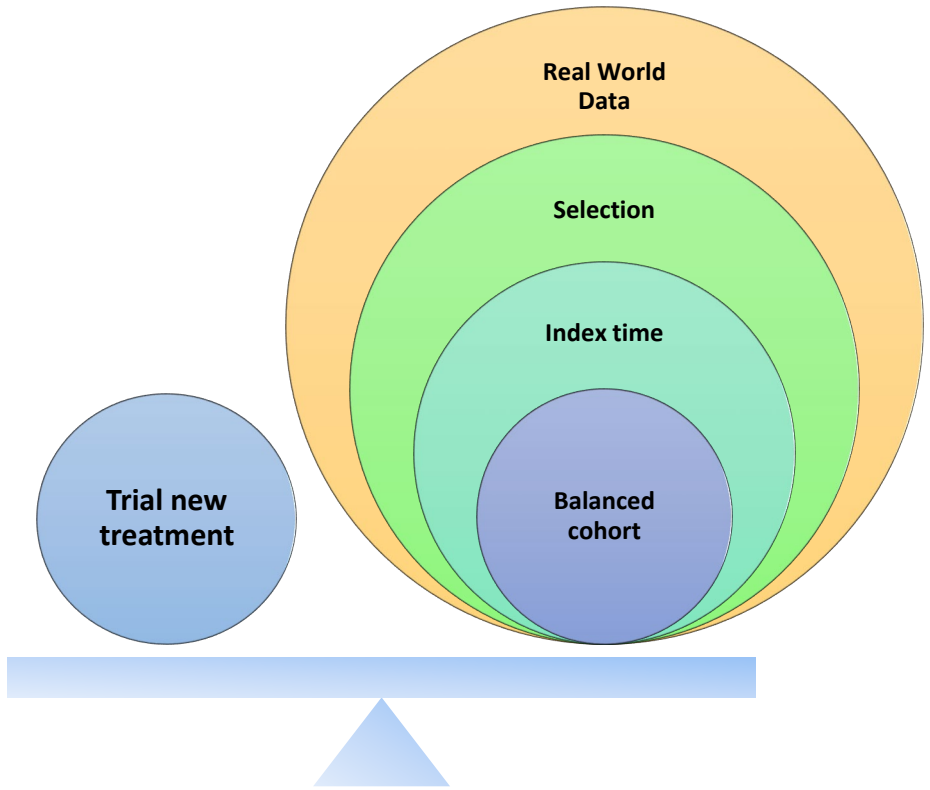
- Apply aligned inclusion/exclusion criteria
- Overlay sites / regions / calendar time

Index Time

- First visit, confirmatory visit, random visit(s), last visit, other methods

Assessment of balance

- pre-specified check and test
- weights: propensity scores, IPTW, ATT, …



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Analysis of time to event

Firewall off
un-blinded for outcome

Rx arm

- Check for informative censoring

Composite endpoint

- Characterize type of events over time in both Rx arm and RWD-selection

Analysis of endpoint

- Kaplan-Meier and Cox regression methods
- Crude effect
- Weighted
- Adjusted for confounders

Sensitivity analyses

- Range of selection of index time
- Pruning of time to avoid immortal time bias

Subgroup analysis

- Concurrent calendar time
- Same region/ sites/or different sites

Lessons learned and discussion points

Pros +

- Enthusiasm for collaboration is huge
- Open for ideas and improvement of methodology
- Improvement of understanding effect size through multiple sensitivity and subgroup analysis
- Validate findings with second RWD

Cons -

- Challenge to asses quality
- No safety data
- Immortal time bias
- Challenge to get all right legally, ethical
- Publication and stakeholders

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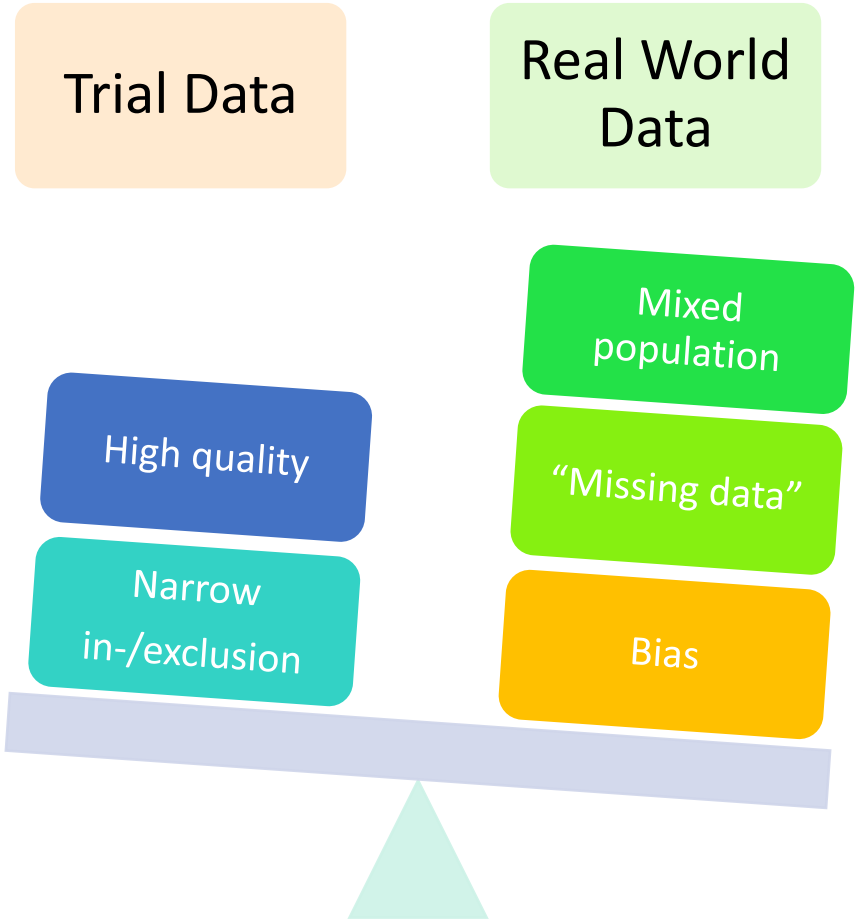

A collaborative strong need to improve methodology

A need for quality measures of RWD

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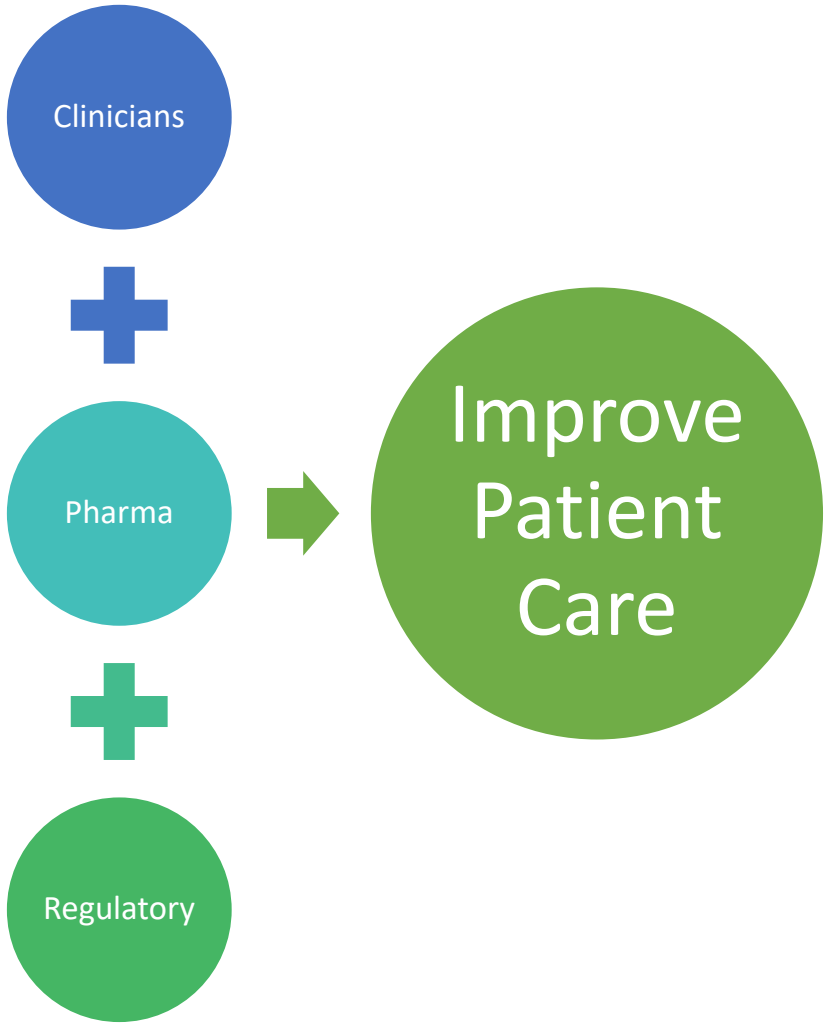

A strong need to create easier pathways for collaboration

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