Real-World Data as External Controls in Clinical Trials

PSC Partners

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THE FORUM
For Collaborative Research℠

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TORONTO CENTRE FOR LIVER DISEASE

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Motivation 1: rare chronic disease

Primary Biliary Cholangitis (PBC)

- Rare chronic autoimmune liver disease affecting bile ducts
- Affects 1 in 1,000 women over age 40
- First line therapy Ursodeoxycholic acid (UDCA)
- A need for effective second-line therapy for patients with insufficient biochemical response to UDCA
- Accelerated approval of OCA 2016: new treatment shows lowering of ALP in patients not responding to UDCA[1, 2]

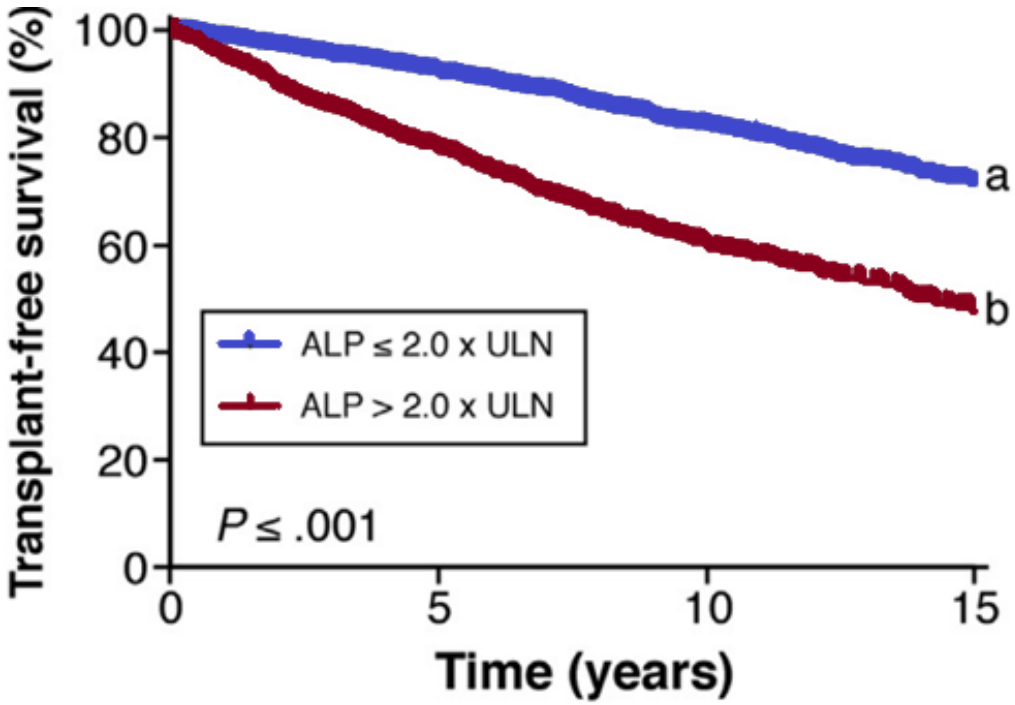
→ ***Does treatment improve event free survival?***

- *Trial duration 10-15 years, biased dropout in placebo arm*

Global PBC Study Group[3]

ALP associated with liver transplantation and death

PBC patients treated with UDCA (N=4655)



1. Nevens et al. N Engl J Med. 2016 Aug 18;375(7):631-43
2. Ocaliva Prescribing Information

3. Lammers et al., Gastroenterology 2014

Motivation 2: rare chronic disease

Paediatric disease: Alagille Syndrome (ALGS)

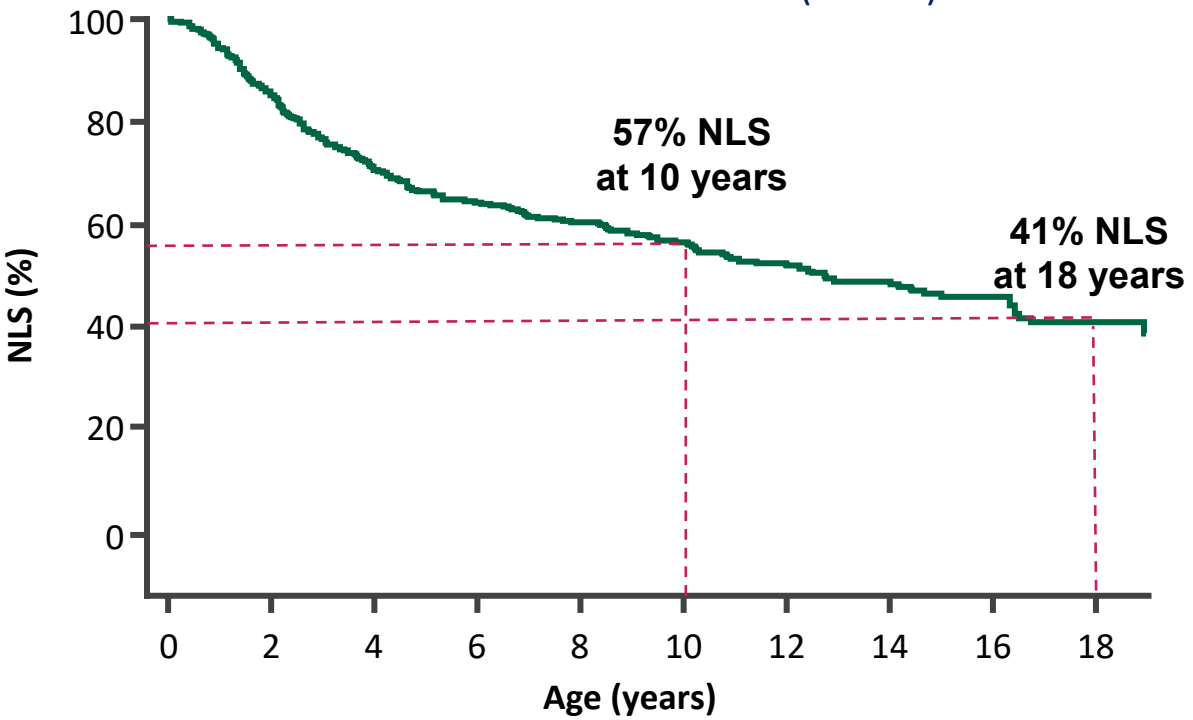
- a rare, genetic disorder characterized by bile duct paucity and extrahepatic clinical manifestations
- Key clinical features: cholestasis, xanthomas and severe debilitating pruritus
- Complications of cholestasis and severe pruritus are the leading indications for liver transplantation
- 2021&2022: Livmarli™ recently received FDA&EMA approval for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older[1,2]

→ ***Does treatment improve event free survival?***

- *Long term RCT not ethical*

GALA[3] (Global)

Native liver survival (NLS) in patients with ALGS presenting with neonatal cholestasis (N=911)



1. Gonzales E, et al. *Lancet* 2021; In press;
2. Mirum Pharmaceuticals, Inc. LIVMARLI™ (maralixibat) Prescribing Information. 2021.

Native Liver Survival = Transplant-Free Survival

3. Vandriel SM, et al. Hepatology 2022

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

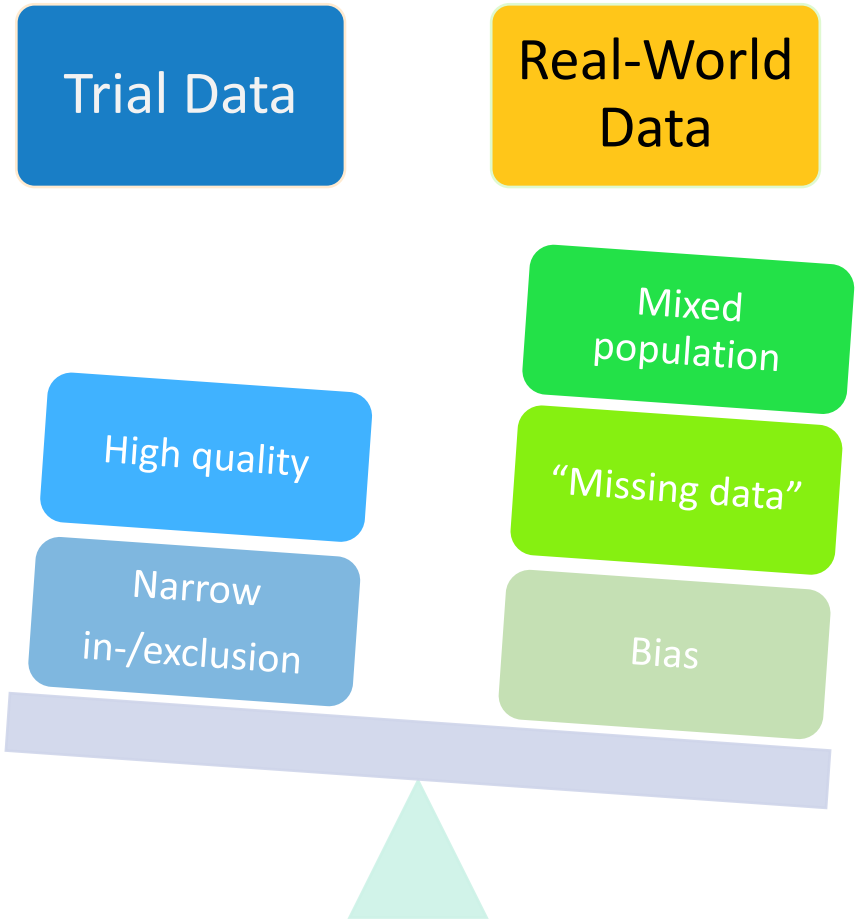
Examples: treated patients without control arm

- Phase 3 study of OCA in PBC
  - placebo roll over after end phase 3
  - all treated with OCA
  - extended long term follow-up
- Phase 2 studies of Livmarli in children with Alagille syndrome
  - all treated with Livmarli
  - extended long term follow-up

→ External Control comparisons needed to understand if treatment improves event free survival

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)

Is it feasible to use Real-World Data as external controls?



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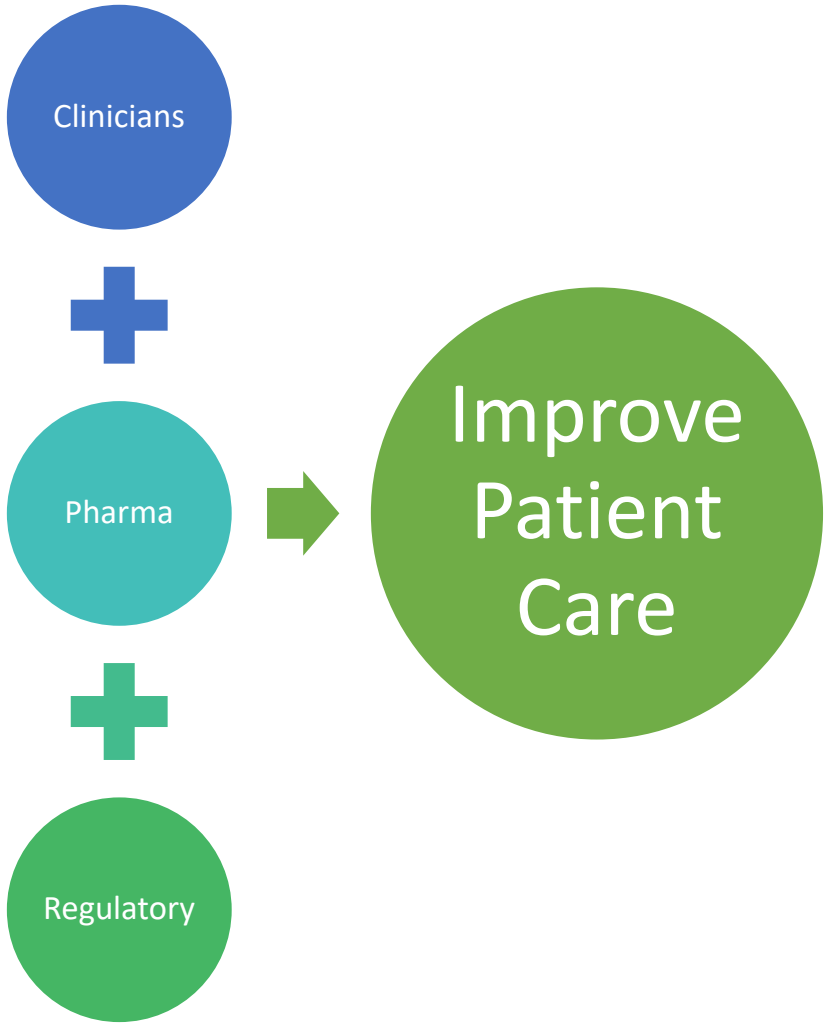

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Stakeholders

- Pharma: trial data
- Independent researchers / scientists: RWD
- Regulatory: advance treatment while guarding the integrity
- Patients

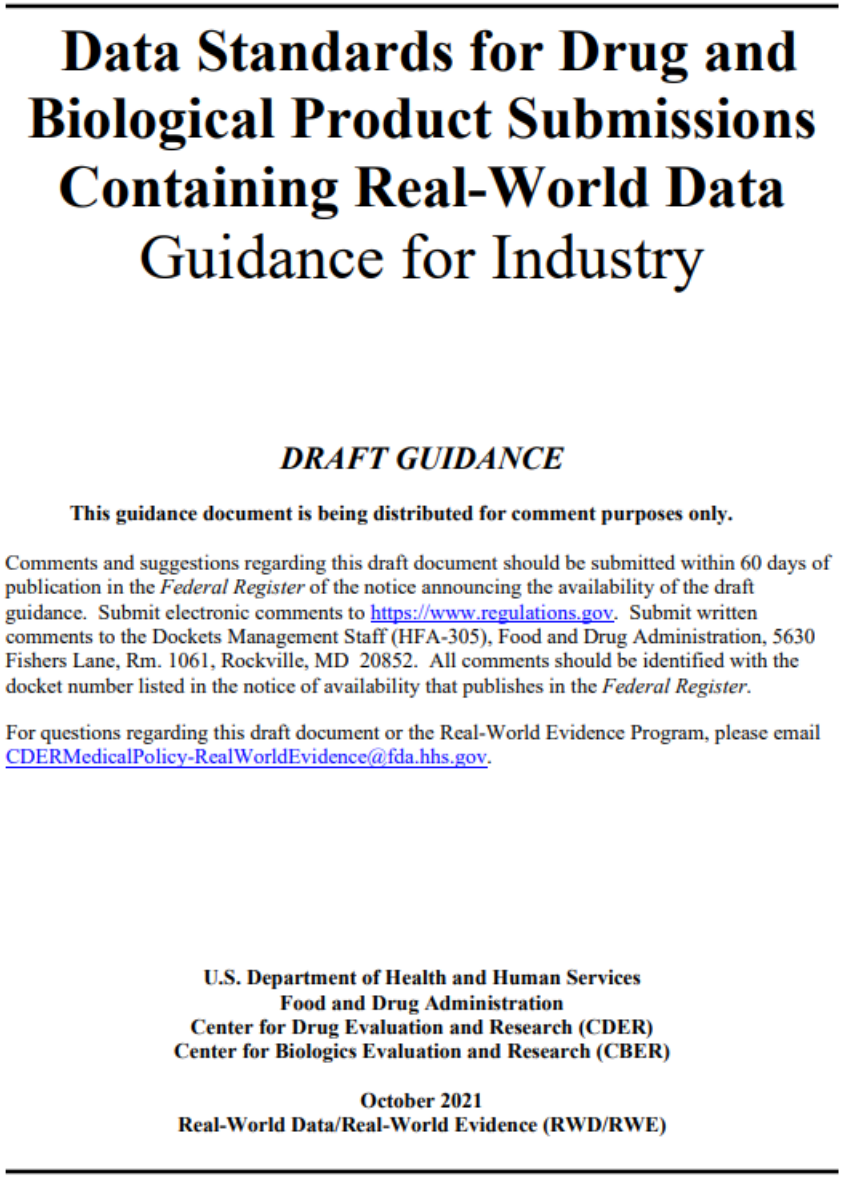
Collaboration: willingness, transparency and trust

- Data sharing
- Protocol
- Statistical Analysis Plan

Real-World Data (RWD)

High bar of standardization and quality[1]

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



Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document or the Real-World Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2021
Real-World Data/Real-World Evidence (RWD/RWE)

1. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory. Accessed on November 2, 2021.

Examples Real-World Data

Launched in 2012

PBC ongoing registry, retrospective[1]

>6000 patients, >40.000 visits,

25 sites from 18 countries

Launched in 2012

PBC ongoing registry [2]

6900 patients,

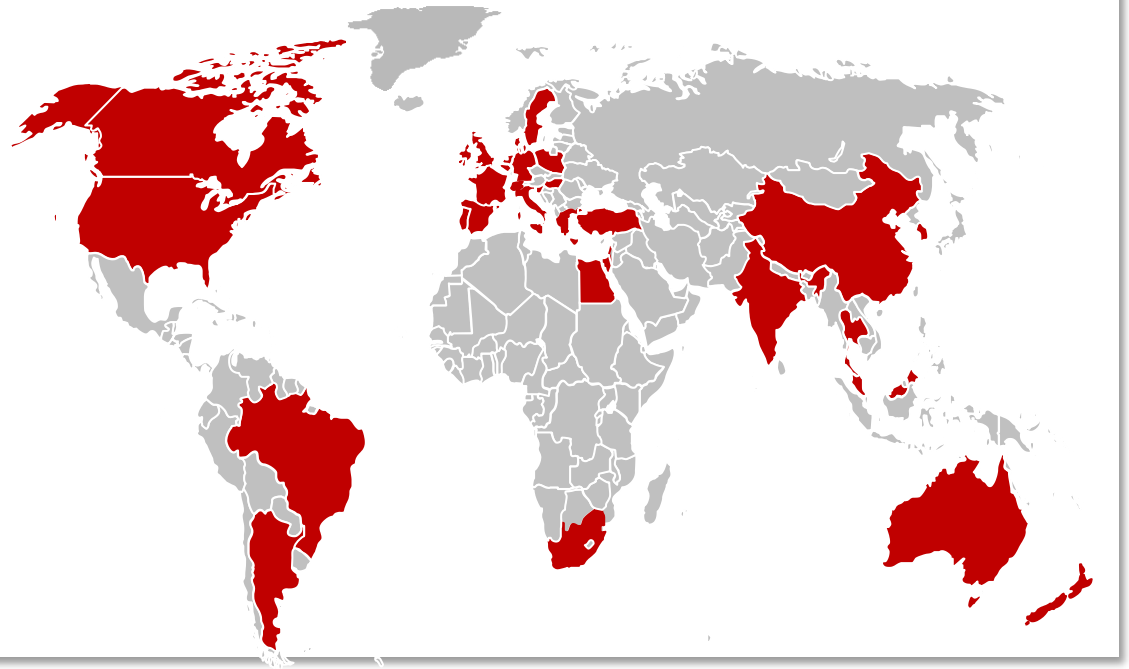
161 UK centres

Launched in 2018

the global Alagille Alliance Study

Retrospective, >1400 patients, >12.000 visits,

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



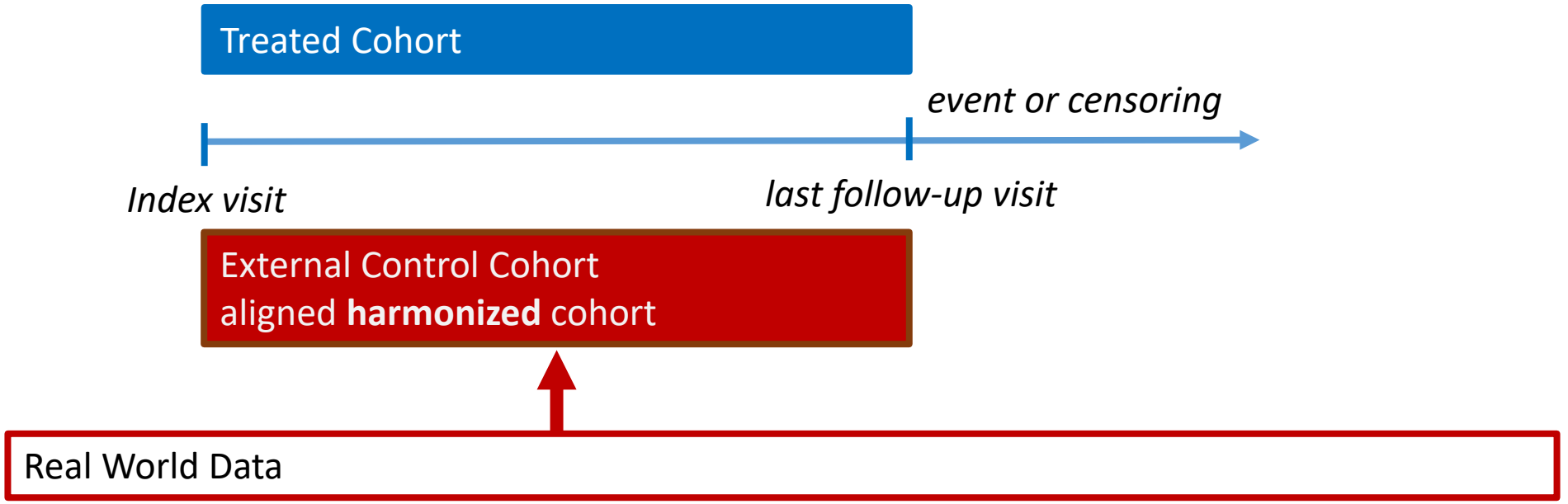
1. Lammers et al., *Gastroenterlogy* 2014 2. Carbone et al. Hepatology. 2016;63(3):930-950.

3. Vandriel SM, et al. EASL 2020 (oral presentation) 4. Vandriel SM, et al Hepatology 2022

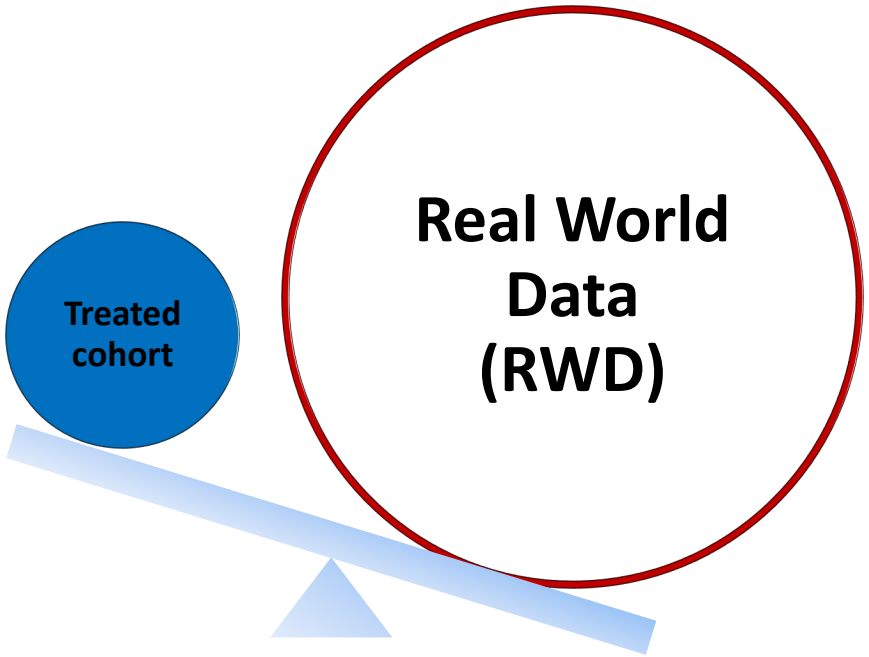
Primary aim

To compare time to clinical event in treated patients from an open label extension study with external controls

Example: PBC open label extension study of OCA: Event defined as liver transplantation or death
Example: Alagille open label extension study of Livmarli: Event defined as clinical event



Harmonize Design

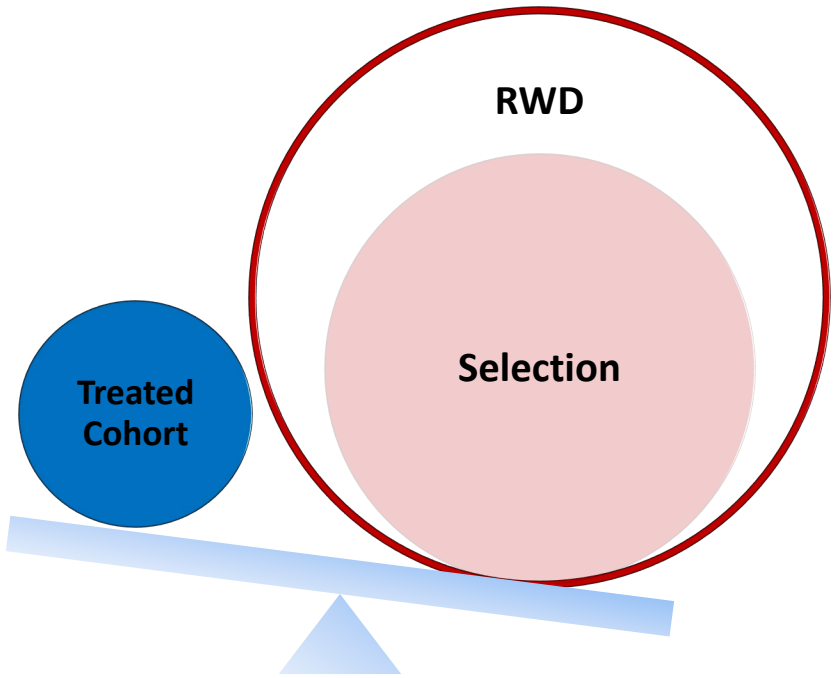


Fit for Purpose

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

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

Identification of patients & visits



Selection process

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

RWD = Real-World Data

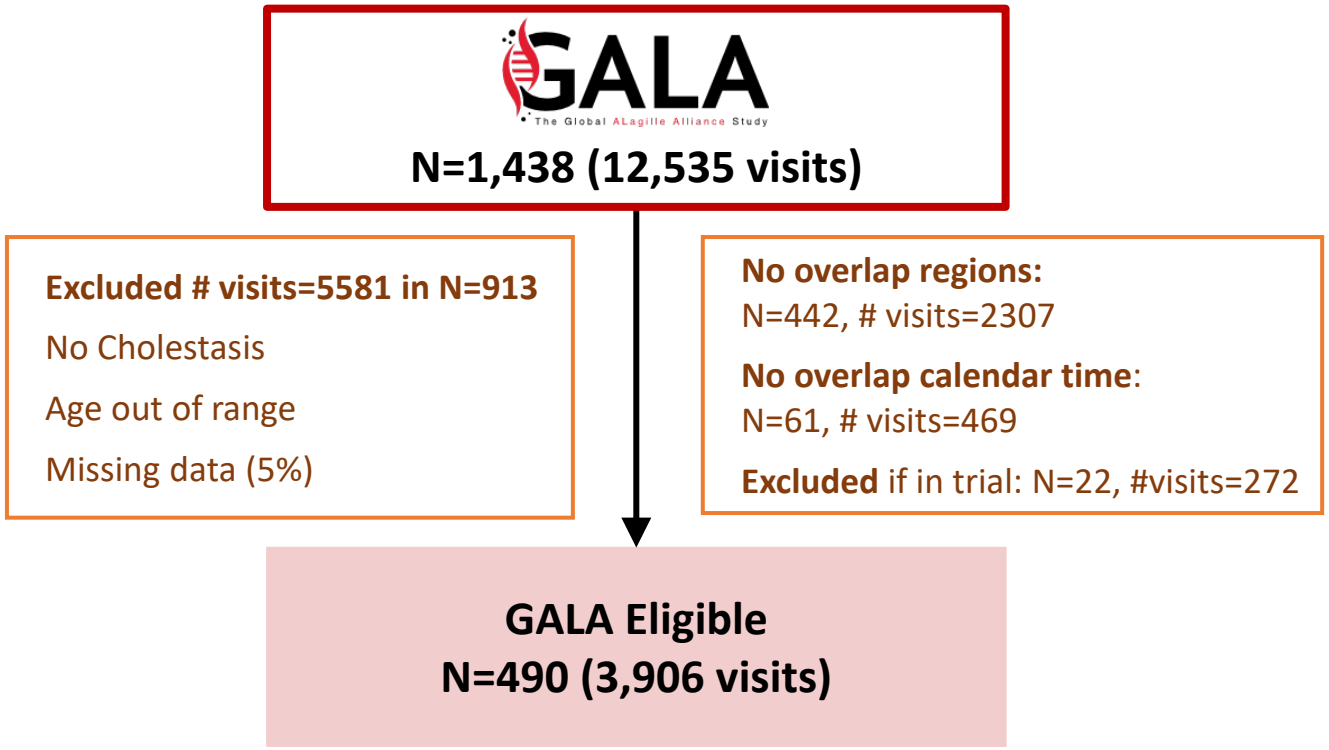
Example external controls selection Alagille syndrome

Treated cohort: Alagille phase 2 open label extension of Livmarli: inclusion severe cholestasis, age 1-18yr

Real-World Data: External controls from GALA

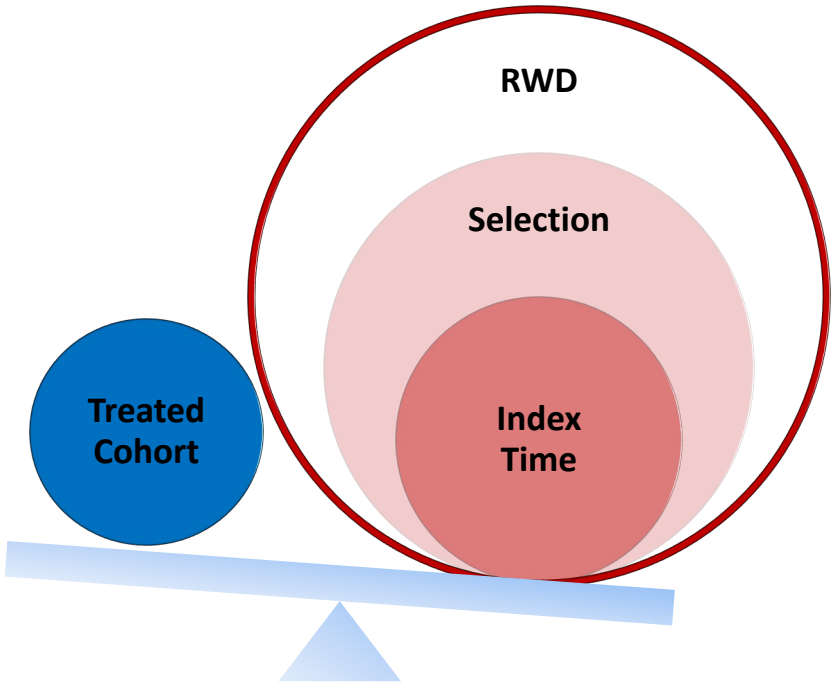
Identification of patients and visits:

- A patient may be eligible with multiple visits



Hansen et al., AASLD 2021

Index visit

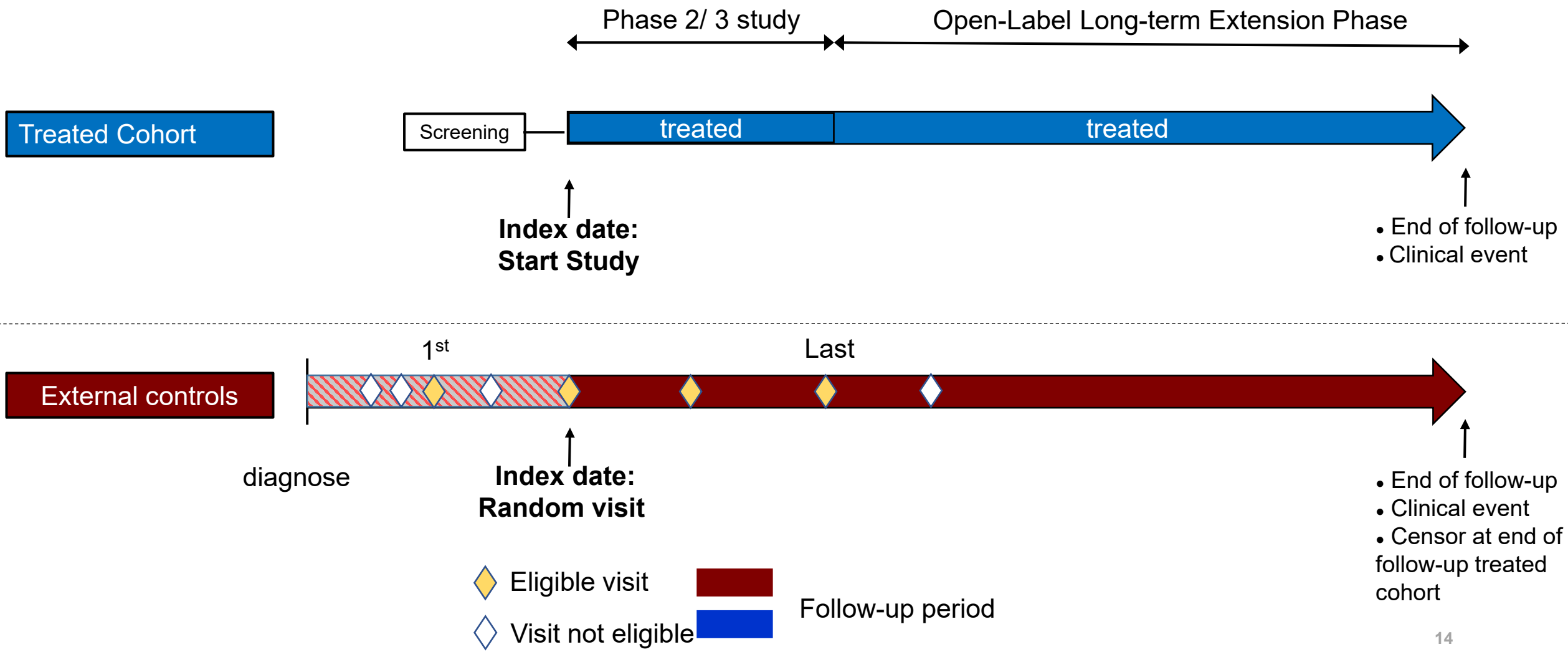


RWD = Real-World Data

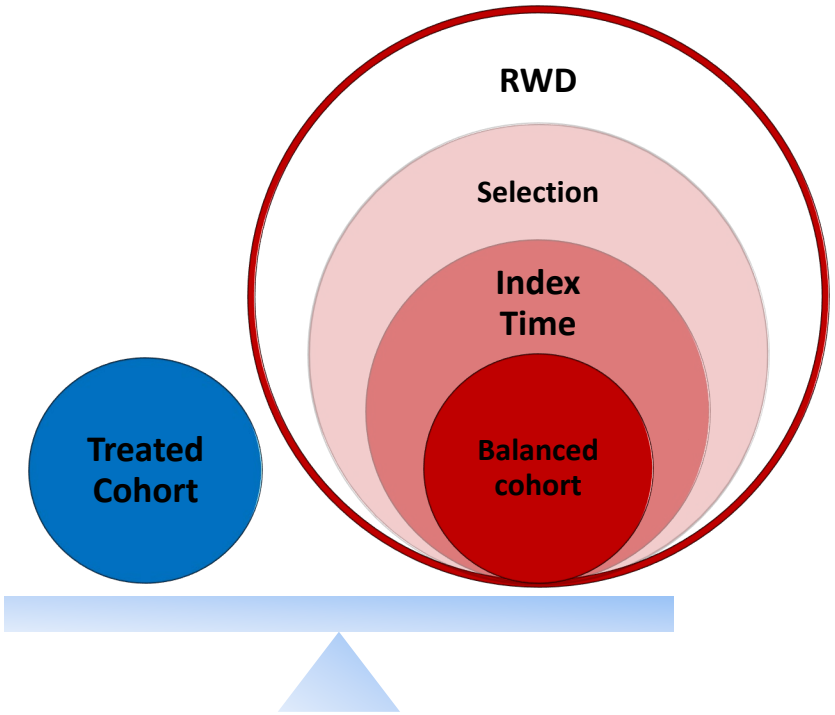
Choice of Index Time (start of follow-up)

- First visit
- Random visit(s)
- Last visit
- Other methods:
  - Confirmatory visit
  - Multiple visits – weighted
  - ML-method
  - …

Careful selection of comparable index date



Balanced design using weights

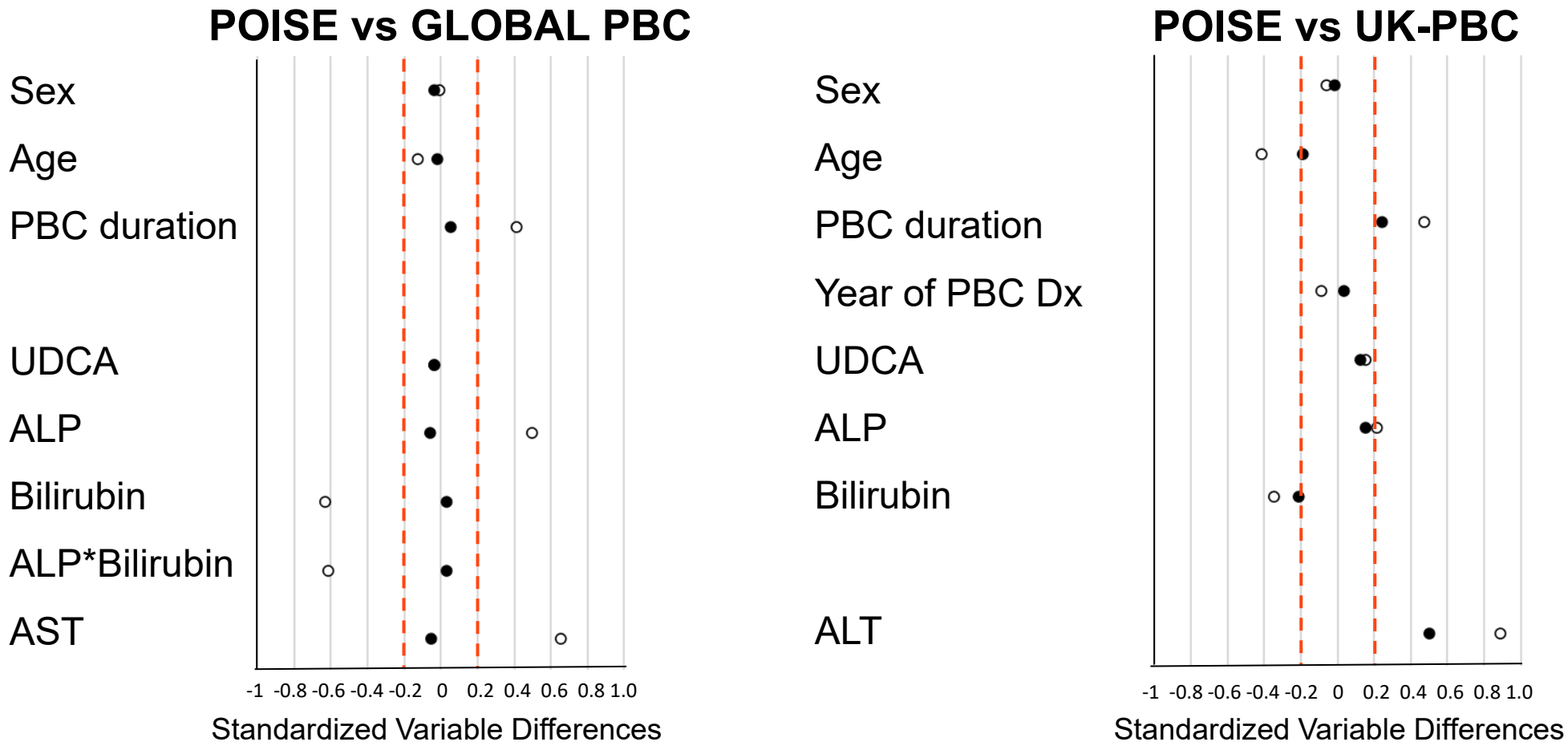


Assessment of balance

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

RWD = Real-World Data

PBC: POISE OCA-Treated and External Controls Balance assessment



Murillo-Perez et al., *Gastroenterlogy* 2022

Harmonize Design

Firewall:
blinded for outcome

Fit for purpose

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

Selection

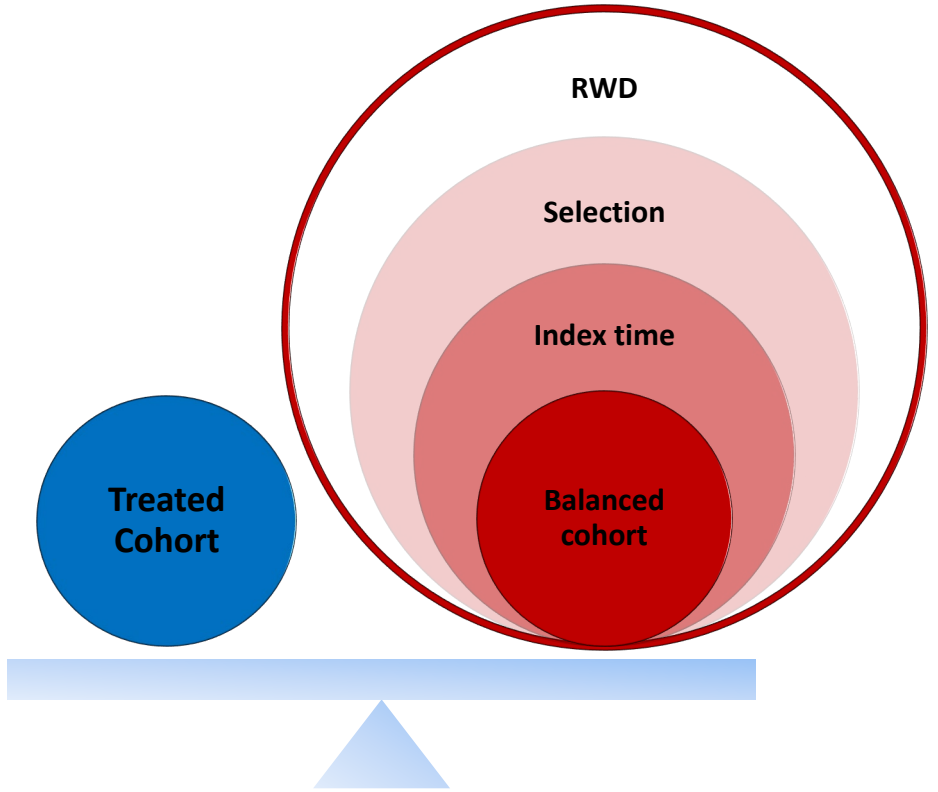
- Apply aligned inclusion/exclusion criteria
- Overlay sites / regions / calendar time

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, …



RWD = Real-World Data

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

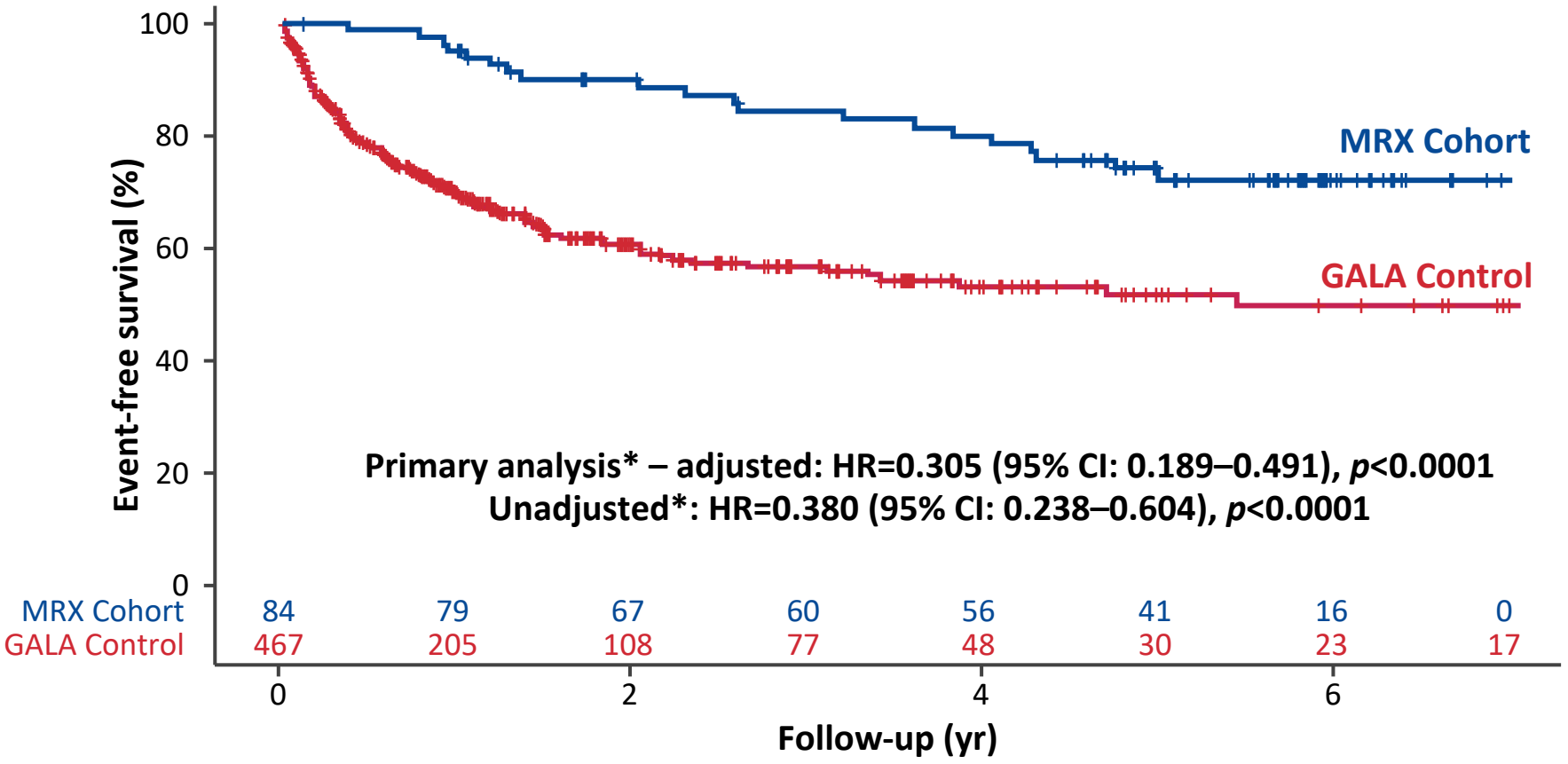
Sensitivity analyses

- 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

Alagille: Livmarli shows significant improvement in event free survival
(biliary diversion surgery, decompensation event, liver transplantation, or death)



Conclusions

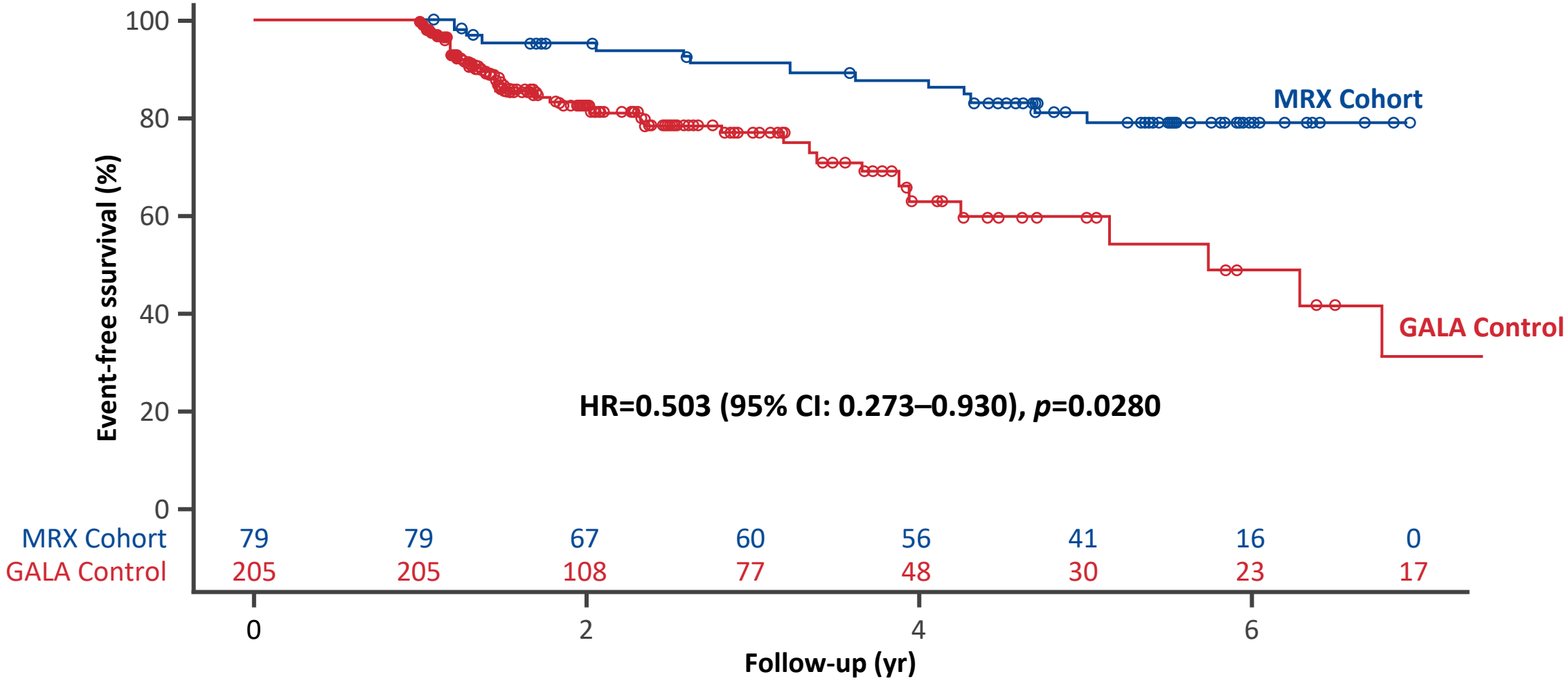
Using this real-world evidence analytical method, a significant reduction in clinical outcomes was observed in MRX-treated ALGS patients compared with controls from the GALA database.

Hansen et al., AASLD 2021

ALT, alanine aminotransferase; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ML, maximum likelihood; MRX, maralixibat; SAP, statistical analysis plan.
* Cox regression models: Primary: Cox regression - effect of MRX vs. GALA log likelihood test adjusted for age, sex, bilirubin, and ALT (according to the SAP).

Alagille: Livmarli shows significant improvement in EFS

Pruning for events occurring in the first 12 months

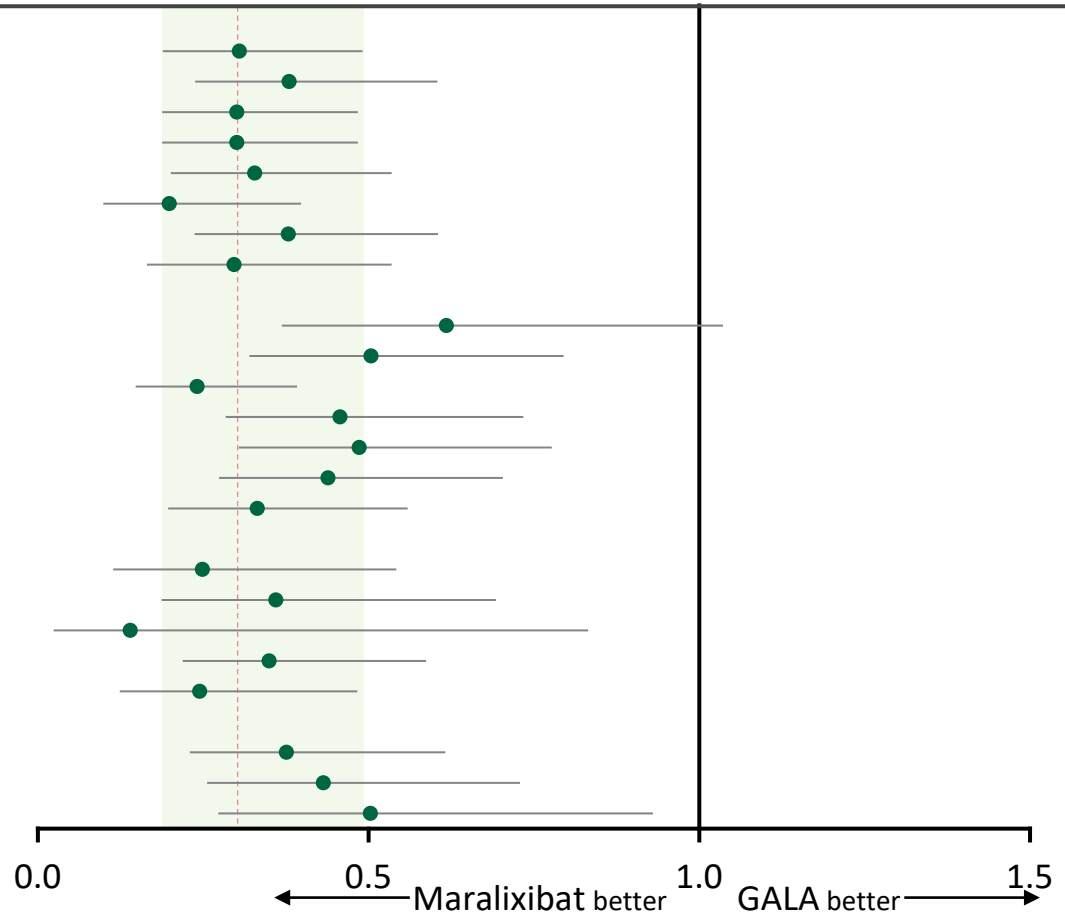


Hansen et al., AASLD 2021

CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ML, maximum likelihood; MRX, maralixibat.

Alagille: Consistent results observed across several sensitivity analyses

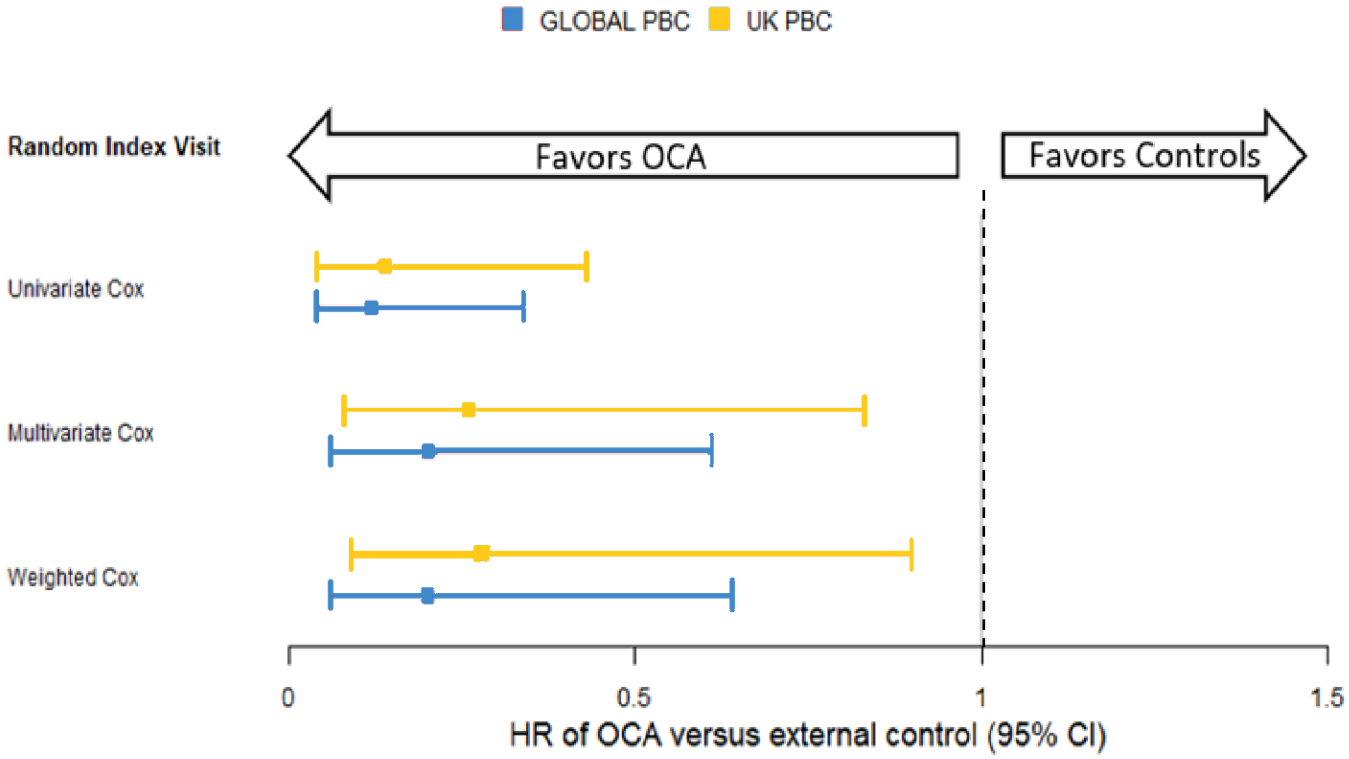
Estimated HR (95% CI) of EFS in MRX Cohort vs. GALA Control



	HR	95% CI	*p*-value
Primary comparison			
SAP specified	0.305	(0.189, 0.491)	<.0001
Unadjusted	0.380	(0.238, 0.604)	<.0001
Adjusted 1	0.301	(0.188, 0.484)	<.0001
Adjusted 2	0.301	(0.188, 0.484)	<.0001
Adjusted 3	0.328	(0.201, 0.535)	<.0001
Adjusted 4	0.199	(0.099, 0.398)	<.0001
Weighted Std IPTW	0.379	(0.237, 0.605)	<.0001
Weighted ATT	0.297	(0.165, 0.535)	<.0001
Sensitivity analyses			
First eligible visit	0.618	(0.369, 1.036)	0.0680
Date of birth	0.504	(0.320, 0.795)	0.0032
Last eligible visit	0.241	(0.148, 0.392)	<.0001
Random visit 1	0.457	(0.284, 0.734)	0.0012
Random visit 2	0.486	(0.304, 0.777)	0.0026
Random visit, Method 2	0.439	(0.274, 0.703)	0.0006
Liver transplant-free survival	0.332	(0.197, 0.559)	<.0001
Subgroup analyses			
By region North America	0.249	(0.114, 0.542)	0.0005
By region Europe	0.360	(0.187, 0.693)	0.0022
By region Australia	0.140	(0.024, 0.832)	0.0306
By site overlap	0.350	(0.219, 0.587)	<.0001
With sBA available	0.245	(0.124, 0.483)	<.0001
Pruning analyses			
Pruning 3 month	0.376	(0.230, 0.616)	0.0001
Pruning 6 month	0.432	(0.256, 0.729)	0.0017
Pruning 12 month	0.503	(0.273, 0.930)	0.0284

Hansen et al., AASLD 2021

PBC: OCA associated with lower risk for liver transplant or death



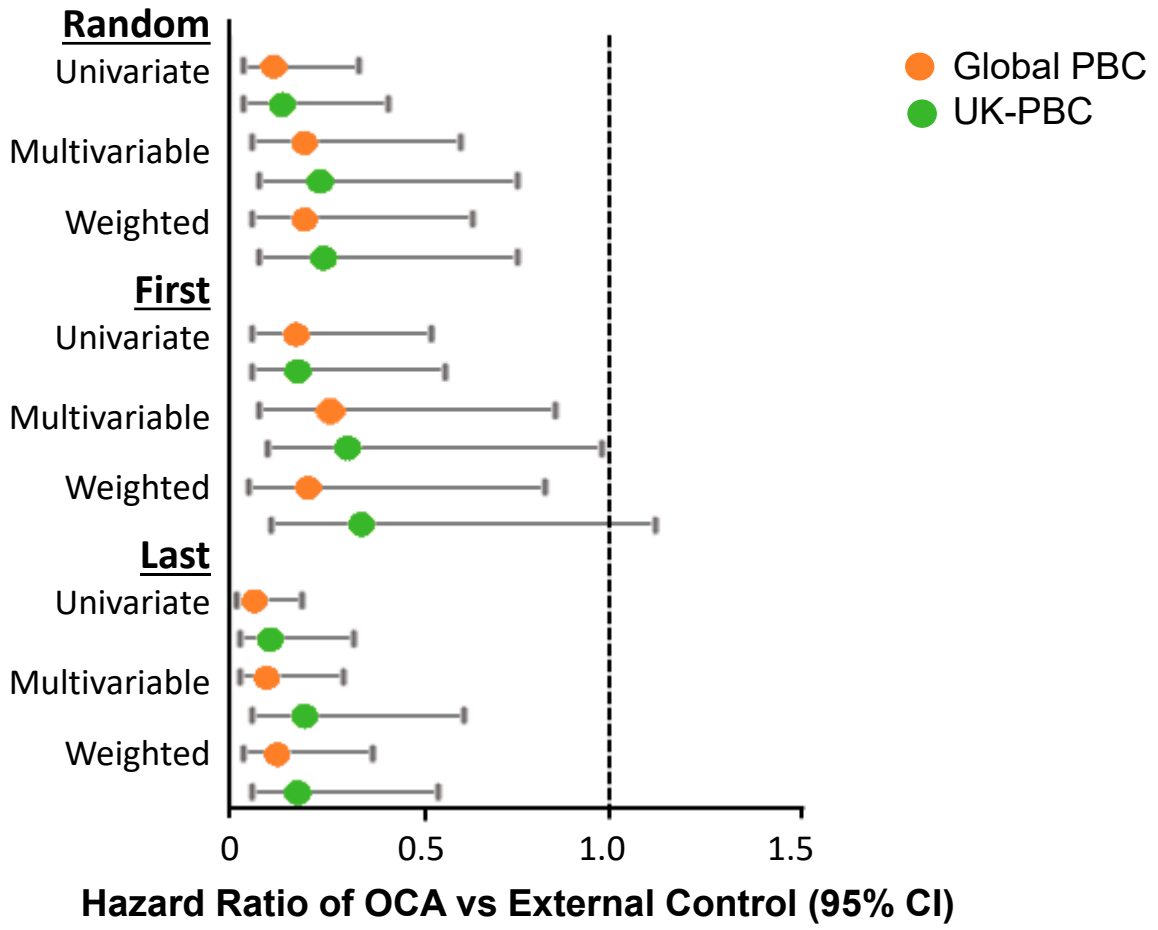
	HR (95%CI)	P value
Univariate Cox	0.14 (0.04-0.42)	<0.001
	0.12 (0.04-0.34)	<0.001
Multivariate Cox	0.24 (0.08-0.76)	0.015
	0.20 (0.06-0.61)	0.005
Weighted Cox	0.28 (0.09-0.91)	0.034
	0.20 (0.06-0.64)	0.007

Conclusions

These are the first data showing improvement in the occurrence of clinically important outcomes with obeticholic acid in patients with PBC

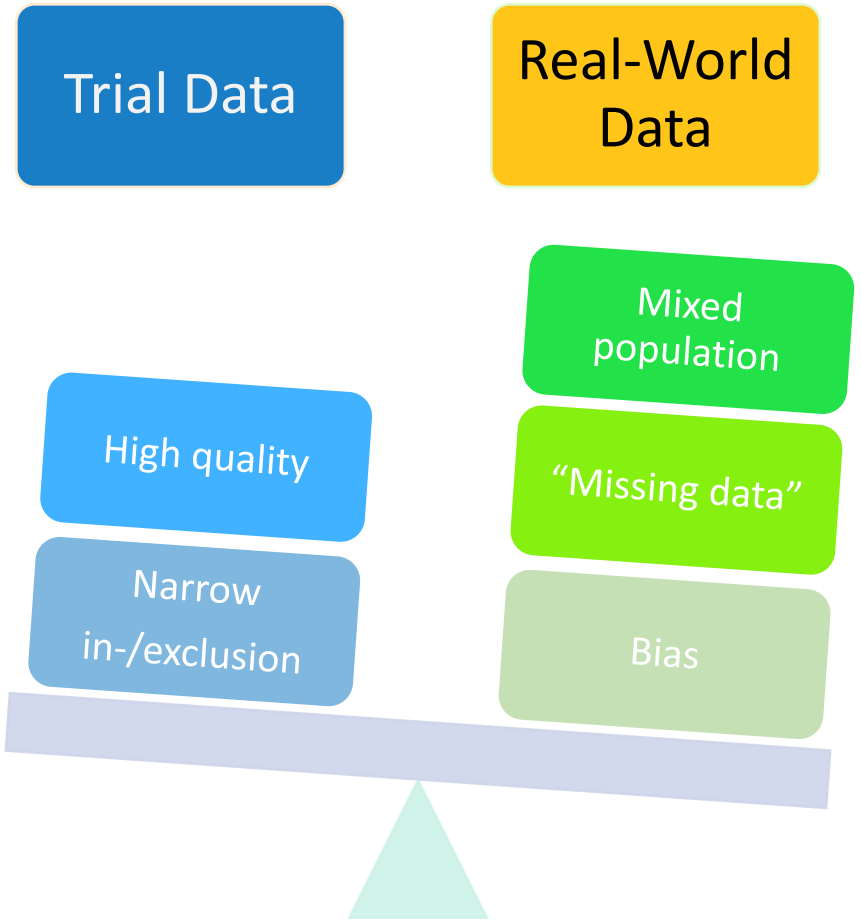
Murillo-Perez et al., *Gastroenterlogy* 2022

Sensitivity Analyses: Alternative Index Visits Demonstrate Consistent Findings



Murillo-Perez et al., *Gastroenterlogy* 2022

Is it feasible to use RWD as External Controls? Yes



*A collaborative strong need to **improve** methodology*

*A need for **quality measures** of Real-World Data*

Key Takeaways

- There is benefit in using real-world data and innovative methodology to study interventions
- Methodology can be successfully implemented to show benefit/harm of new intervention in a multitude of diseases

Lessons learned and discussion points

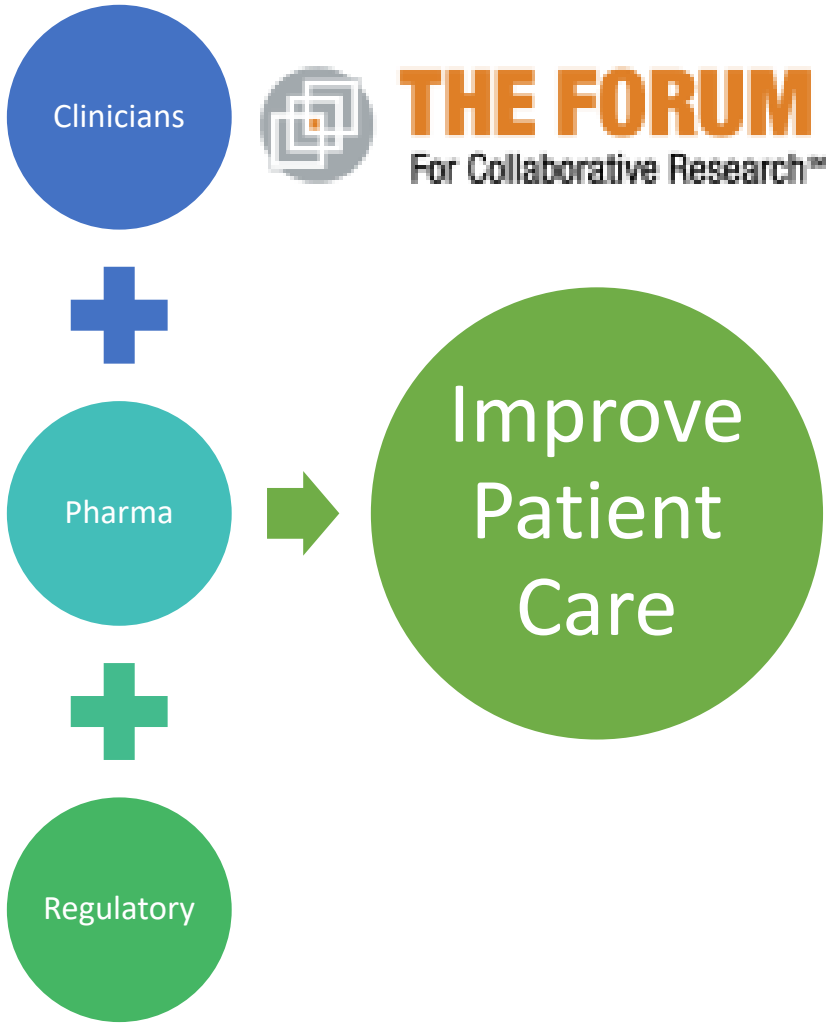
Pros +

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

Cons -

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

Is it feasible to use RWD as External Controls?



A strong need to create easier pathways for collaboration

Thank you