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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Is it feasible to use RWD as External Controls?

Trial Data
- High quality
- Narrow in-/exclusion

Real World Data
- Mixed population
- “Missing data”
- Bias
Is it feasible to use RWD as External Controls?

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)*
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

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
Launched in 2012

Retrospective, >6000 patients, 40,000 visits, 40 sites from 18 countries (1,2)

Launched in 2018

Retrospective, >1400 patients, 12,000 visits, 56 sites from all regions of the world (3,4)

Transplantation-free Survival (%)

Follow up (years)

ALP<1.67 Normal bilirubin
ALP>1.67 Abnormal bilirubin
ALP<1.67
ALP>1.67

57% NLS at 10 years
41% NLS at 18 years

Native Liver Survival (NLS) (%)

Age (years)

0 5 10 15

0 20 40 60 80 100

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

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 completeness
- 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
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

- Excluded # visits=5581 in N=913
  - No Cholestasis
  - Age out of range
  - Missing data (5%)

- No overlap regions:
  - N=442, # visits=2307

- No overlap calendar time:
  - N=61, # visits=469

- Excluded if in trial: N=22, visits=272

GALA Total
N=1,438 (12,535 visits)

GALA Eligible
N=490 (3,906 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**
Selection of index time

Rx

period eligible and eligible visits = *

Follow-up

event / end of follow-up

treatment follow-up

screening period

index time

1st index time

RWD

diagnose

Follow-up

event / end of follow-up

period eligible and eligible visits = *

for Collaborative Research
Selection of index time

Rx

RWD

* * * * * * *

screening period

index time

treatment
follow-up

event / end of follow-up

period eligible and eligible visits = *

Follow-up
Immortal time bias – too frail for inclusion?

Rx

screening period

index time

treatment follow-up

event / end of follow-up

Follow-up event / end of follow-up

RWD

follow-up to short ?

index time

* * *

diagnose

* * *

period eligible and eligible visits = *

Follow-up
Balanced design using weights

Assessment of balance
- pre-specified check and tests
- Estimate weights
  - Propensity scores
  - IPTW
  - ATT weights
Harmonize Design

**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, ...

**Firewall:** blinded for outcome
Analysis of time to event

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

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<thead>
<tr>
<th><strong>Pros +</strong></th>
<th><strong>Cons -</strong></th>
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<tbody>
<tr>
<td>• Enthusiasm for collaboration is huge</td>
<td>• Challenge to assess quality</td>
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<tr>
<td>• Open for ideas and improvement of methodology</td>
<td>• No safety data</td>
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<td>• Improvement of understanding effect size through multiple sensitivity and subgroup analysis</td>
<td>• Immortal time bias</td>
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<tr>
<td>• Validate findings with second RWD</td>
<td>• Challenge to get all right legally, ethical</td>
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<td>• Publication and stakeholders</td>
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Is it feasible to use RWD as External Controls?

A collaborative strong need to improve methodology

A need for quality measures of RWD
Is it feasible to use RWD as External Controls?

A strong need to create easier pathways for collaboration