ISPOR 2022
May 15-18, 2022

Is the Global Real-World Data (RWD) Supply Chain Broken? Choosing between RWD Quality Versus Locality in Supporting Single Arm Submissions

Issue Panel 304 – May 18, 2022, 8:00 – 9:00 AM

Paradigm Shift in Clinical Trial Development

ISPOR 2022
May 15-18, 2022

Move towards **precision medicine**

Explosion of **innovative technologies**

Increasing Presence of Single-arm Trials

RWE potential to function as external control arms

Challenges for **sourcing an external control group** to establish comparative analysis

Drive for **earlier patient access** especially in rare diseases

Recognition that **RCTs can not answer all efficacy questions**

HTA Trade-Offs

Quality
(fit-for purpose data, biases)

Locality
(representativeness, data availability)

Polling Questions

Question 1: **Which of the following quality elements do you think is most important for choosing an RWE external control in single-arm submissions?**

- ☐ Prospective data collection
- ☐ Population and outcomes comparability
- ☐ Data availability and completeness to allow adjusting for potential confounders
- ☐ Sample size

Polling Questions

Question 2: **Which of the following elements do you think the HTA bodies will trade-off for using <u>local</u> versus international RWE external control in single-arm submissions?**

- ☐ Representative of patients, care settings, pathways
- ☐ Data content and granularity
- ☐ Currency (or timeliness)
- ☐ Sample size and follow up

Polling Questions

Question 3: **What do you think would be the main driver increasing HTA acceptance to international RWE external control data?**

- ☐ Greater availability and higher quality of RWE data
- ☐ Shifting clinical trial development landscape (innovative medicines, precision medicine, single-arm trials)
- ☐ Improved understanding of RWE methods
- ☐ Legislation drive for standardised RWE data collection

Moderator

Grammati Sarri, PhD
Head of RWAA External Research Partnerships/Senior Research Principal

Cytel

Our Panelists

Industry

Luis G. Hernandez, PhD
Global Head of Health Economics

Takeda

Academia

Kristian Thorlund, PhD
Assistant Professor

McMaster University

HTA

Seamus Kent, PhD
Senior Adviser

NICE
National Institute for Health and Care Excellence

Is the Global Real-World Data (RWD) Supply-Chain Broken?
Choosing between RWD Quality Versus Locality in Supporting Single Arm Submissions

ISPOR 2022, May 15-18, Washington DC

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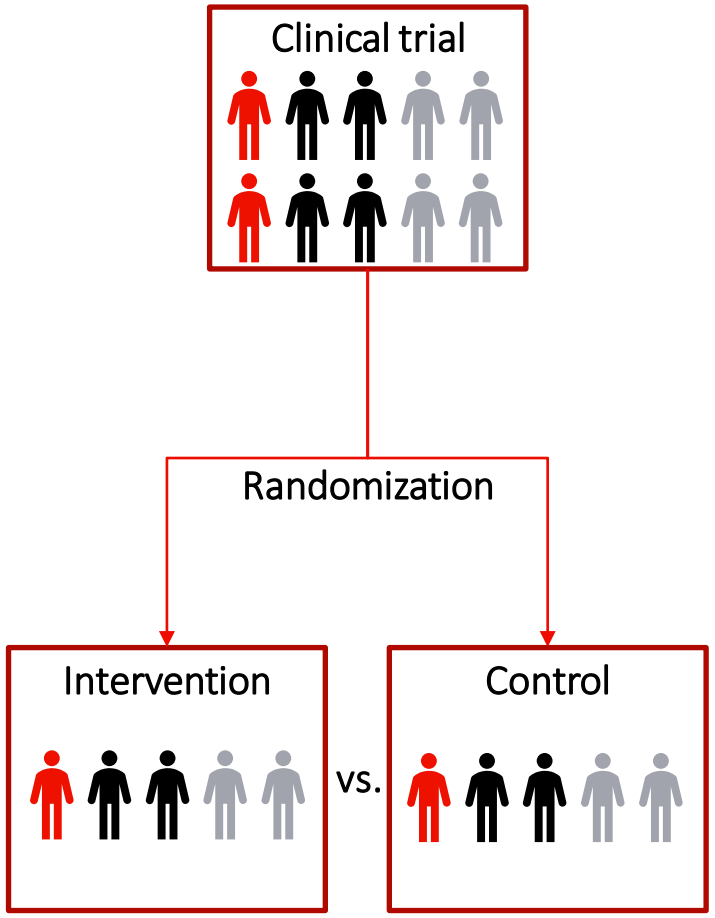
Takeda Oncology

Disclosure

- Employee of Takeda Oncology
- Views and opinions are my own

Context

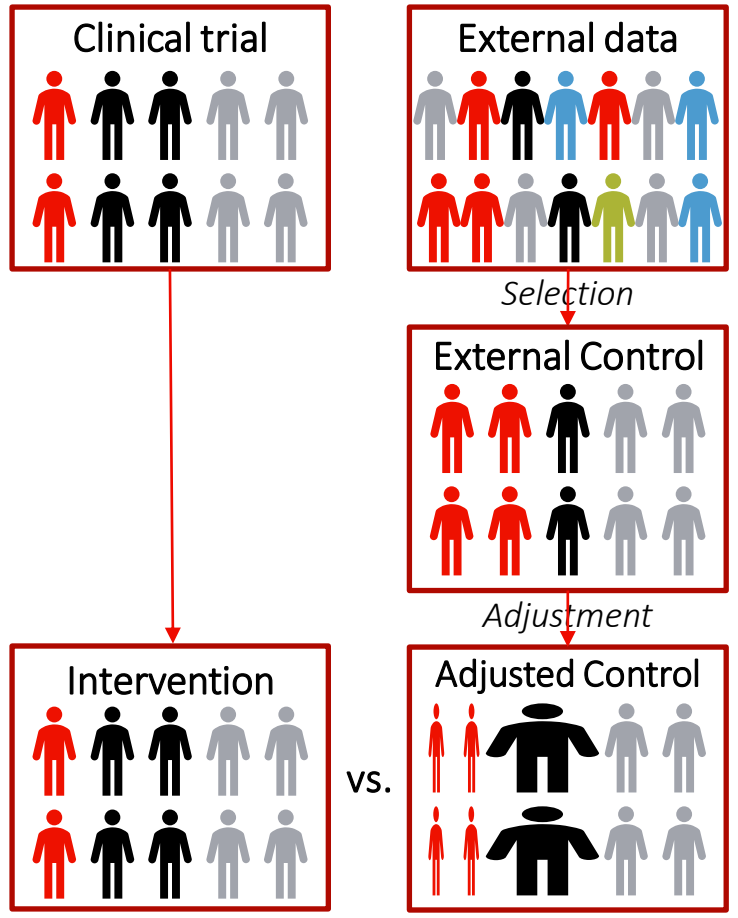
RCTs are the gold standard to evaluate therapies



However, when RCTs are not be ethical, feasible, or practical

- **Areas of high unmet need**
- **Rare or orphan diseases**
- **No established standard of care**
- **Highly specialized or breakthrough therapies, personalized medicine**

Single-arm trial (SAT) + external control arm can be used



Sources of external control arms in SAT-based HTA submissions

433 SAT-based HTA submissions with decision 2011 – 2019 in 21 countries

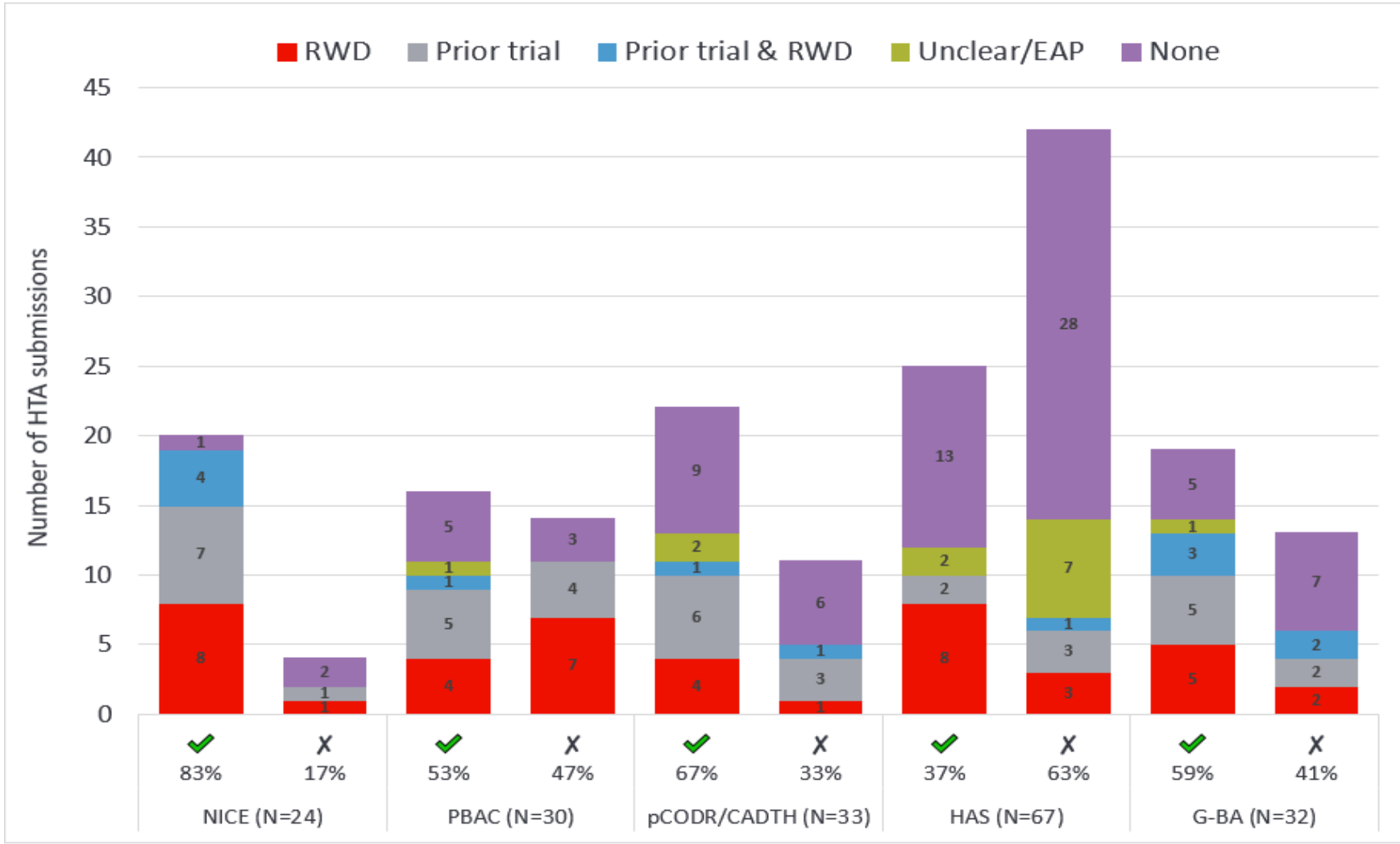
- 5% of total submissions
- 65% being for oncology
- 52.2% included external control; most prior trials (24%) next RWD (20%)

5-year (2015 - 2019) trend

RWD
- Use ↑ 22% (8% to 30%)
- Acceptance ↑ 20% (41% to 61%)

Prior trial
- Use ↓ 14% (33% to 17%)
- Acceptance ↓ 10% (54% to 4%)

No external control
- Acceptance ↓ 15% (49% to 34%)



Source: Patel et al. *Health Policy Analysis*. 2021;24(8):1118-1125

Sources of external control arms, main pros (✓) and cons (✗)

Aggregate data from published literature (prior trials & RWD)	Primary data from prior trials	RWD prospective or from EHR, claims, chart reviews, etc.
✓ Reduced time and cost vs. RWD	✓ Reduced time and cost vs. RWD	✓ Wider heterogeneity of patient (sub)groups; same target population
✓ Earlier access to innovation vs. RWD, if accepted	✓ Earlier access to innovation vs. RWD, if accepted	✓ EHR may be cover historical and concurrent data; potentially, larger sample size (depending on the indication)
✓ Benchmark for rapid assessment	✓ Structured data collection	✓ Often availability of information to conduct extensive adjusted analyses
	✓ Often availability of information to conduct extensive adjusted analyses	
✗ Population, variables, and outcomes may be different	✗ Population, variables, and outcomes may be different	✗ Potential concerns on data quality and bias
✗ Potentially, historical data	✗ Potentially, historical data	✗ Adjusted analyses constrained by the availability of prognostic factors and treatment effect modifiers
✗ Inability to access exhaustive details on outcome definitions and data variables	✗ Accessibility to primary clinical trial data	✗ Accessibility to local or national data
✗ Limited possibility for adjusted analyses		✗ Prospective collection can delay access

Industry perspective: challenges for selecting external control(s) from RWD to support SAT-based HTA submissions in multiple markets?

RWD representative of target patient population and treatment pathways across multiple markets

Quality RWD and **robust analyses**

Enough **sample size** and **follow-up**

Time-relevant data (e.g., current SoC; SoC evolves over time, or may not be defined in some markets)

Multiple market **requirements**

HTA RWE frameworks just started. Guidance or minimum requirements?

Low patient numbers in some indications; need for **blended comparators** and **pooling data** sources

Resources, varying requirements, patients accessing innovation

Moving forward

Recommendations for industry

- Early scientific advice from HTA bodies
- Prognostic factors and effect modifiers across markets
- Good quality RWD
- Apply methods guidelines
- Engage in emerging RWE frameworks development

Recommendations for clear HTA guidance

- Semi-binding commitments from early scientific advice
- Clarity on RWE frameworks guidance vs. minimum requirements
- Expectations for special scenarios (e.g., rare diseases, no SoC)
- Clear quality thresholds for “acceptable” data sources, when locality becomes the main driver for acceptance
- Work with national system to collect data and make it available

Is the global RWD supply chain broken?

Kristian Thorlund
McMaster University
Hamilton, ON

May 18, 2022

Was it ever built properly?

Kristian Thorlund
McMaster University
Hamilton, ON

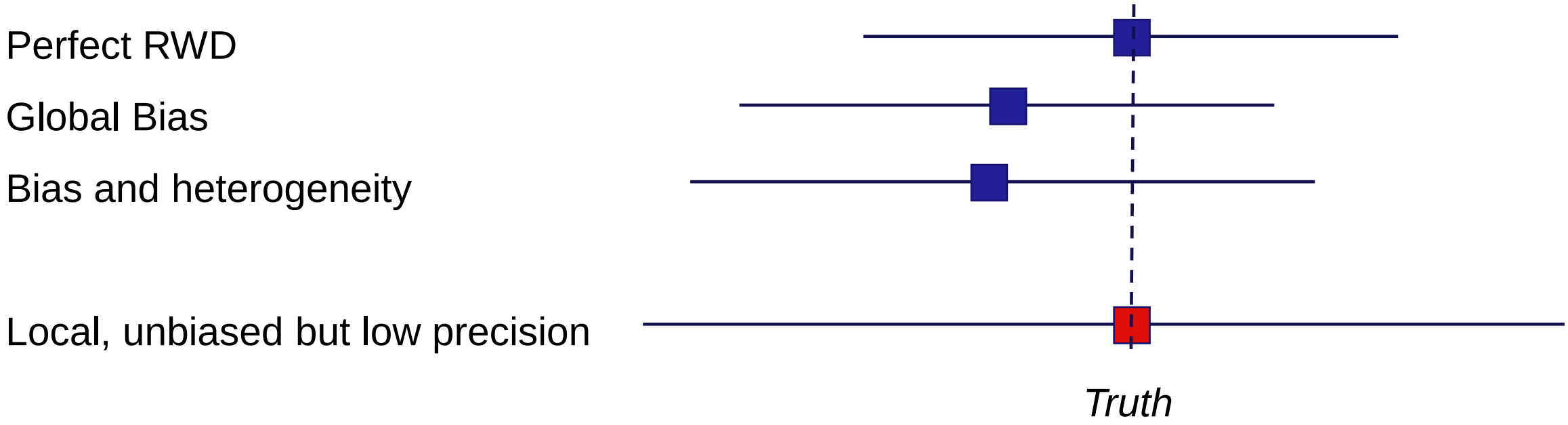
May 18, 2022

RWD Uses and Common Concerns

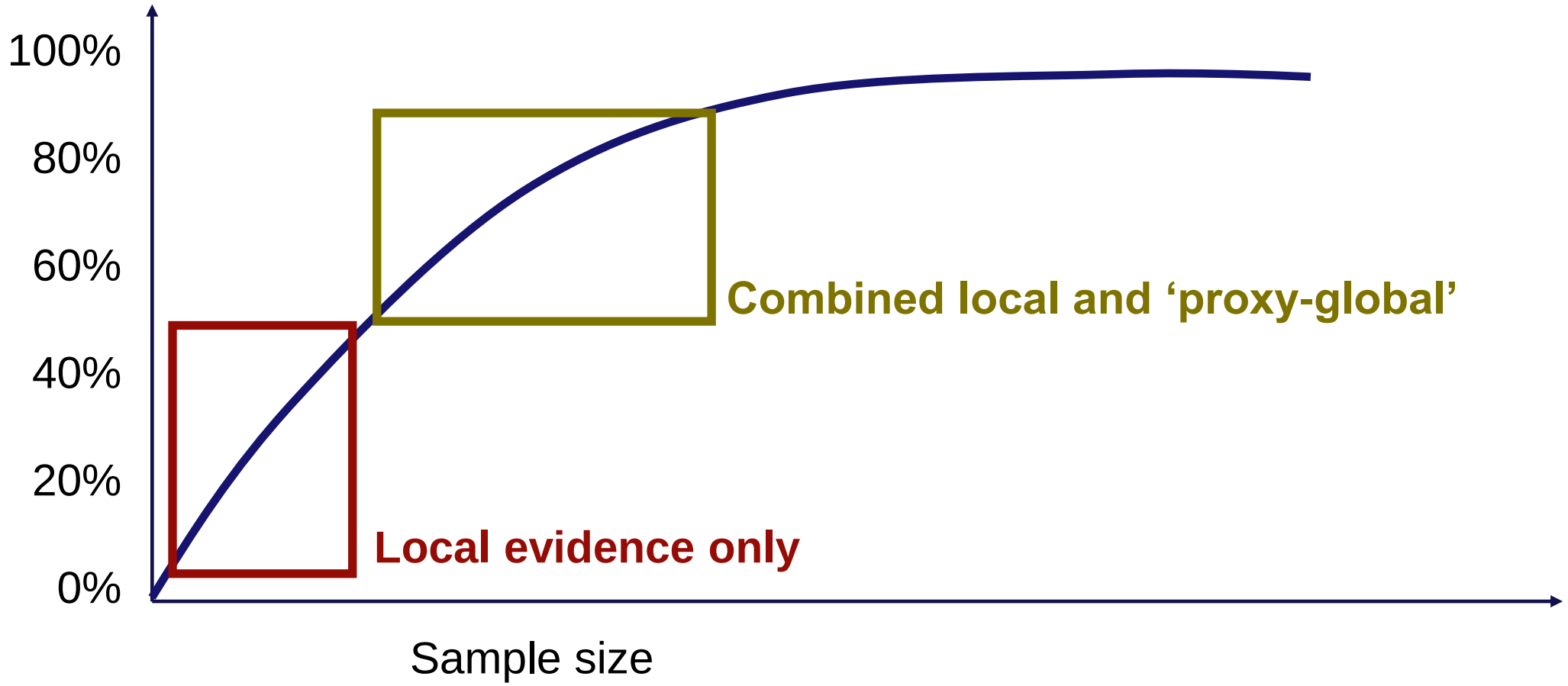
Use: highly unmet need, rare disease, no SOC, breakthrough Tx

Pros: wider heterogeneity (SD+), augmented SS, adjustments feasible

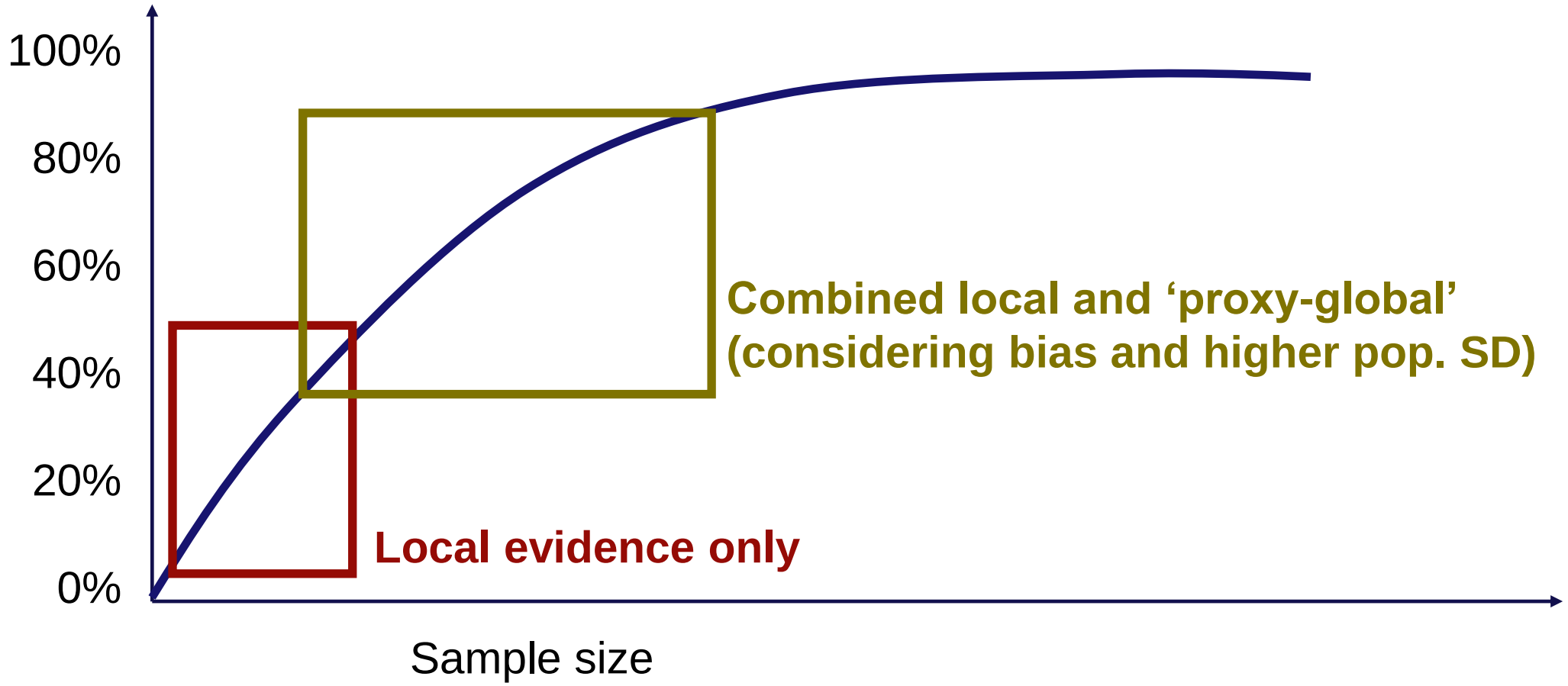
Cons: quality concerns, adjustment feasibility, limited local sample size



Power


100%
80%
60%
40%
20%
0%
Combined local and ‘proxy-global’
Local evidence only
Sample size

Power


100%
80%
60%
40%
20%
0%
Combined local and ‘proxy-global’
(considering bias and higher pop. SD)
Local evidence only
Sample size

Balance

Drugs approval in countries based on clinical trials with only a fraction ‘local patients’

(e.g. molnupiravir approved in US despite MoVE-OUT trial enrolling less than 10% ‘local’ patients)

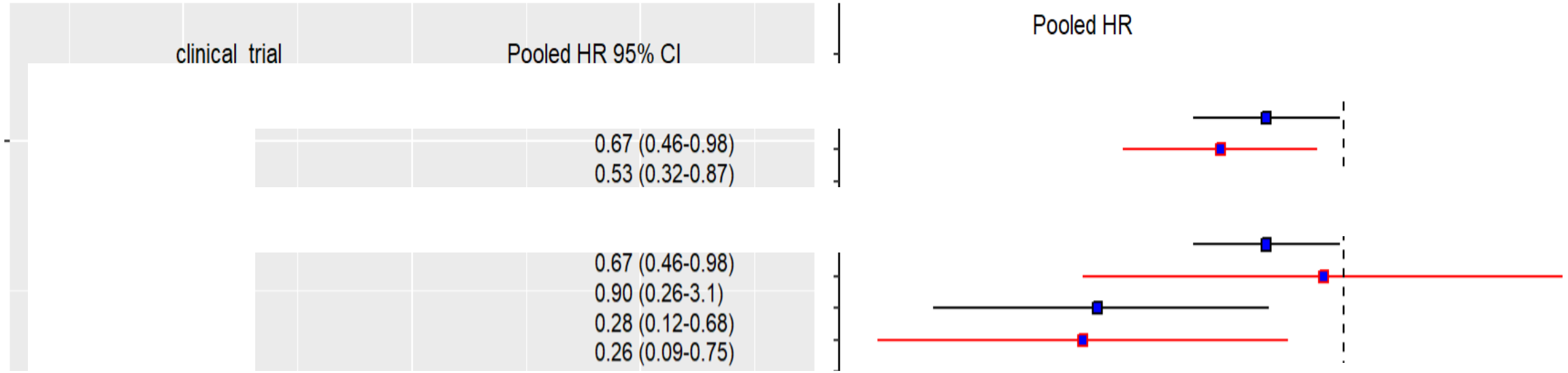
Incidence of hospitalization or death through Day 29 by country
modified Intent-to-Treat population

Country	Participants, n/m (%) Molnupiravir N=709	Placebo N=699	Difference, % (95% CI)
Brazil	1/34 (2.9)	9/40 (22.5)	-19.6 (-35.2, -4.7)
Chile	1/20 (5.0)	2/18 (11.1)	
Colombia	10/136 (7.4)	18/139 (12.9)	-5.6 (-13.1, 1.6)
Guatemala	5/55 (9.1)	0/58 (0.0)	9.1 (2.5, 19.6)
Mexico	4/83 (4.8)	5/66 (7.6)	-2.8 (-12.4, 5.4)
Philippines	4/13 (30.8)	3/13 (23.1)	
Russian Federation	11/155 (7.1)	15/176 (8.5)	-1.4 (-7.4, 4.7)
South Africa	3/89 (3.4)	7/83 (8.4)	-5.1 (-13.5, 2.2)
Ukraine	0/59 (0.0)	2/48 (4.2)	-4.2 (-14.0, 2.1)
United States	4/41 (9.8)	5/45 (11.1)	-1.4 (-15.5, 13.2)

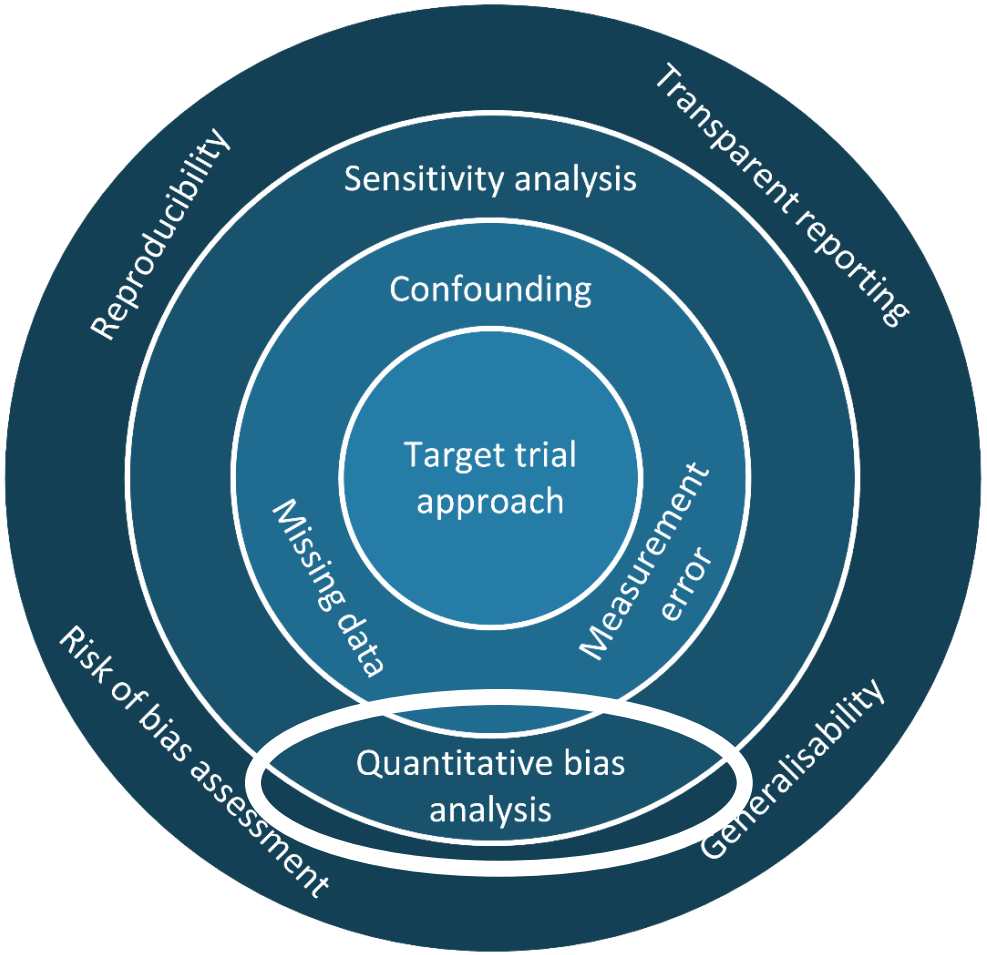
Cross-continent example

Asian ethnicity is a favorable prognostic factor for OS in aNSCLC

ALK-positive aNSCLC: Asian/global trial data (**blue**) vs naïve US RWD (**red**)



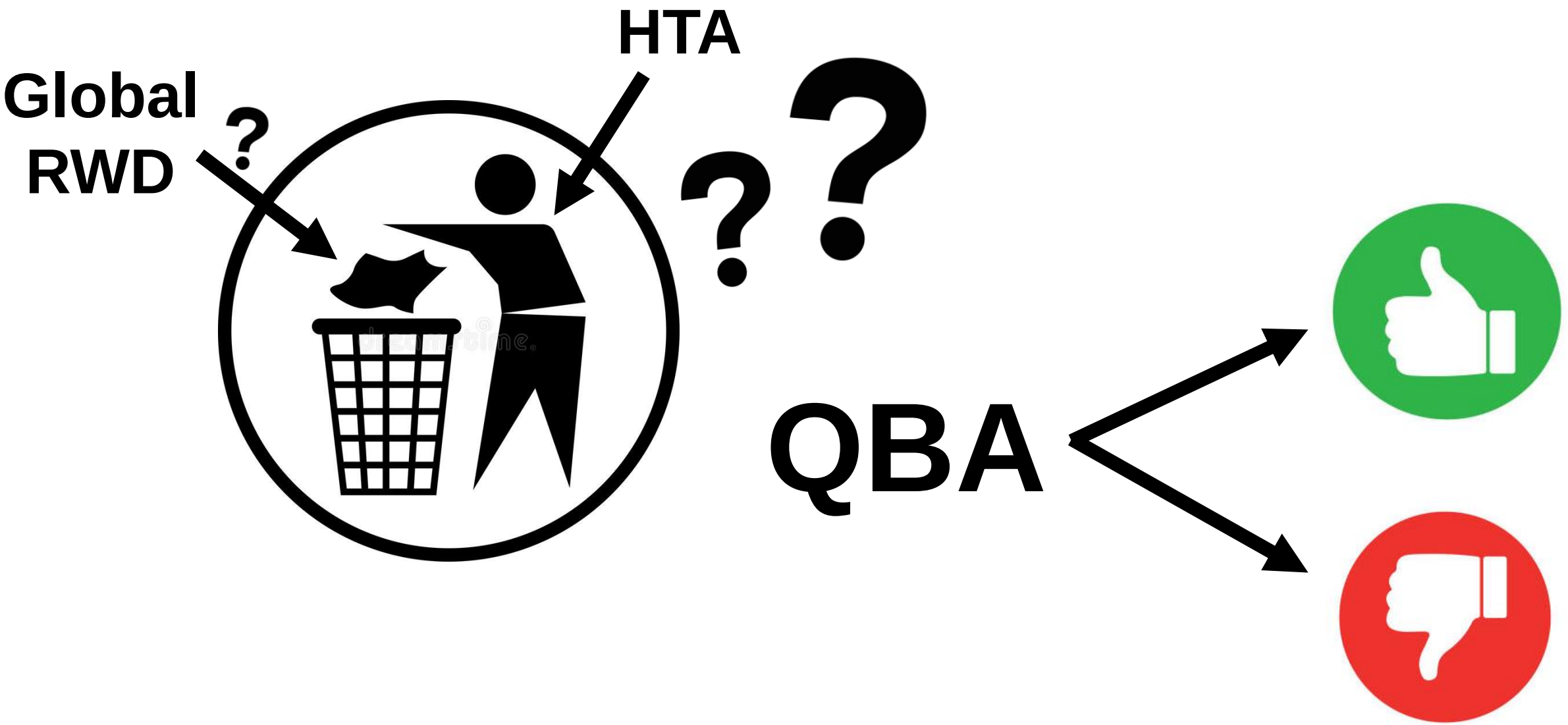
NICE Guidelines



Specific recommendations on comparative effectiveness analyses

- Justify the need for non-randomised evidence
- Provide a study protocol and SAP before performing final analyses
- Design non-randomised studies to emulate the preferred RCT
- Avoid time-related biases
- For studies using external control, minimise differences between data sources
- Systematically identify potential confounders and articulate causal assumptions
- Statistical method that address observed and unobserved confounding
- Consider bias from censoring, missing data, and measurement error
- Use sensitivity and bias analysis to assess the robustness of results
- Report studies in sufficient detail to enable reproduce the study
- Assess the risk of bias and relevance of the study to the research question

Quantitative bias analysis



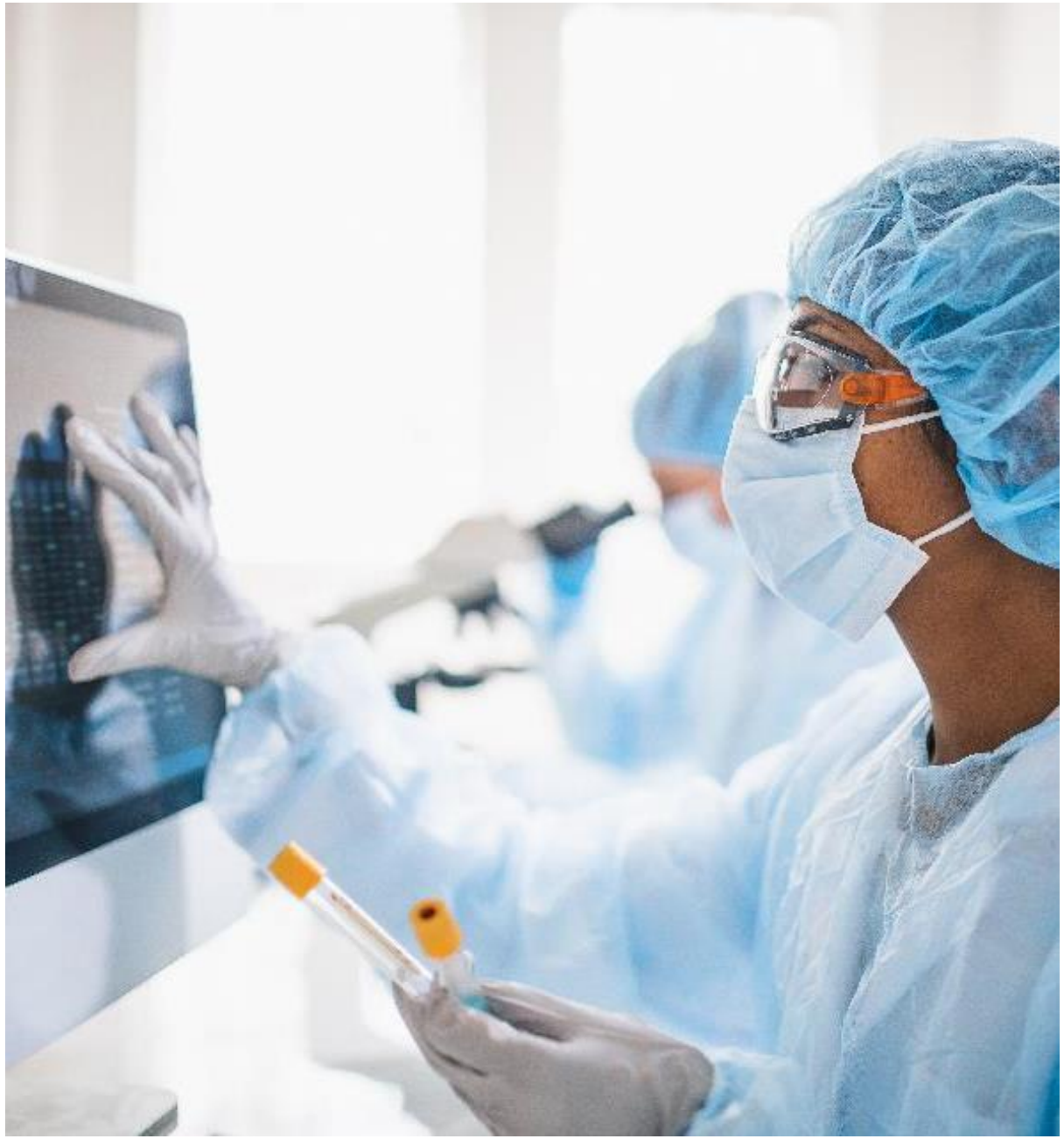
Is the global Real-world data supply chain broken?

Seamus Kent

National Institute for Health and Care Excellence (NICE)

18 May 2022

NICE National Institute for Health and Care Excellence

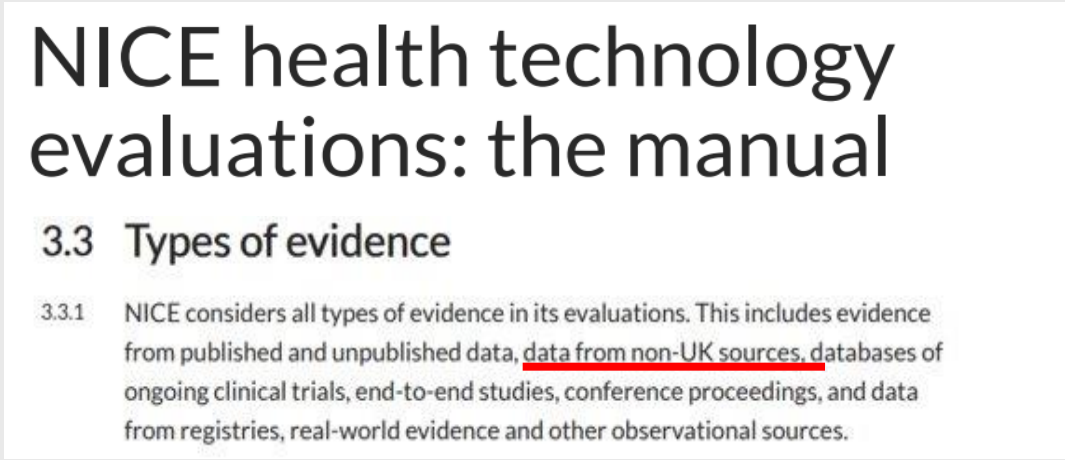


Does data locality matter for HTA?

- Yes – NICE makes decisions about UK patients treated in the NHS (same for other HTAs)

- Differences in populations, healthcare access, treatment patterns/pathways (pre- and post-intervention), outcome rates, etc., can all limit the generalisability of research findings across countries (or even regions)

- Ideally we would always use **national** data, but:
  - There are other dimensions of data suitability
  - Relevant data may not be accessible



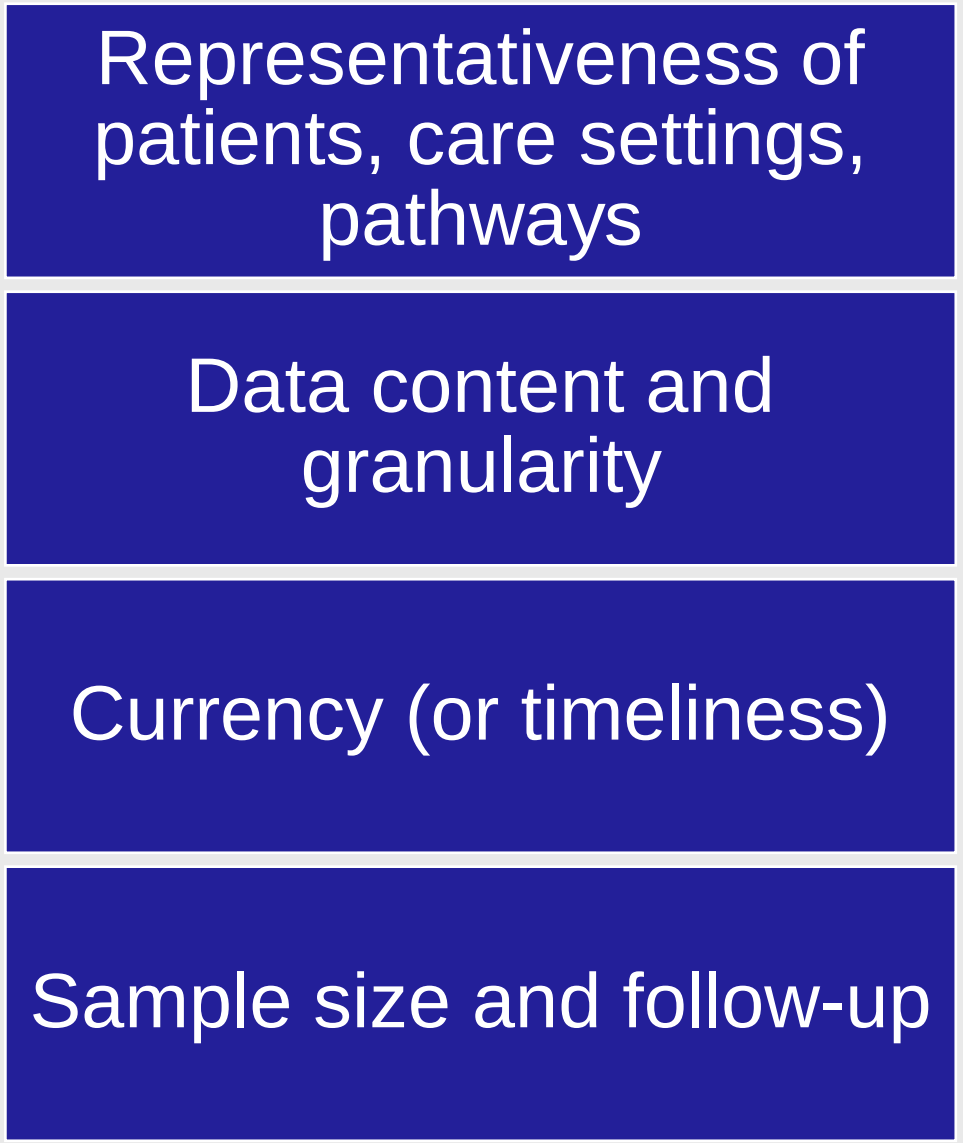
NICE health technology evaluations: the manual

3.3 Types of evidence

3.3.1 NICE considers all types of evidence in its evaluations. This includes evidence from published and unpublished data, data from non-UK sources, databases of ongoing clinical trials, end-to-end studies, conference proceedings, and data from registries, real-world evidence and other observational sources.

Assessing data suitability

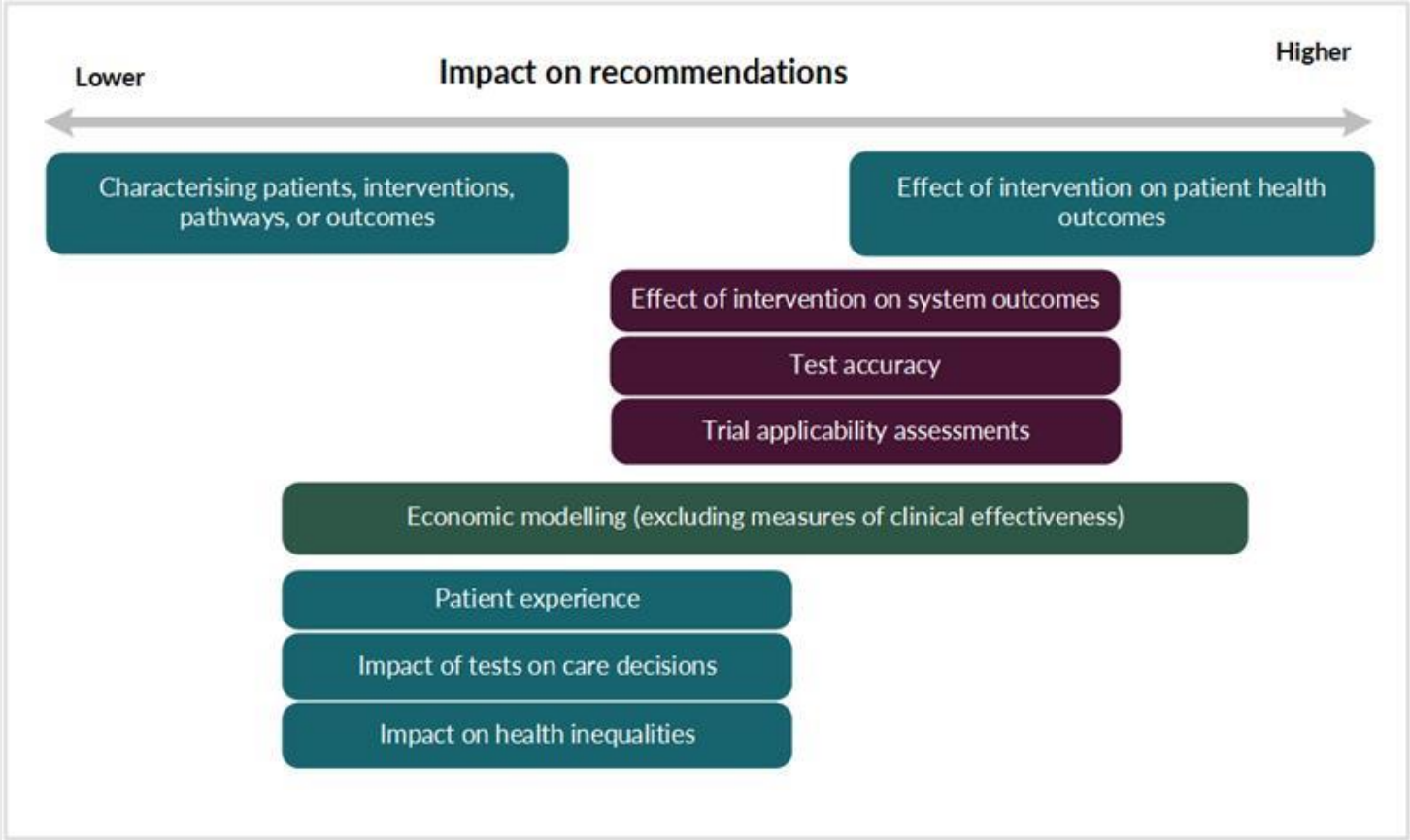
- NICE provides guidance on assessing data suitability in its Real-world evidence framework
- The suitability of data needs to be considered in relation to the intended application
- Suitability depends on quality (completeness, accuracy) and relevance (see figure)
- There is a trade-off between these dimensions of relevance & quality
- **This trade-off depends on the research question**



NICE

Use of real-world data in NICE guidance

- Real world data is widely used in NICE guidance for a range of evidence types (see figure)
- In general, for non-causal questions local data is strongly preferred
- For causal questions, other dimensions may become more important (internal validity)



NICE

International data informs NICE guidance

TA691

Avelumab for untreated metastatic Merkel cell carcinoma

HST12

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

TA589

Blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity

TA491

Ibrutinib for treating Waldenstrom's macroglobulinaemia

How can we move forward?

Guidance

(Real-world evidence framework)

Demonstration projects

Research/infrastructure (common data models, data networks)

International & multi-stakeholder collaboration

NICE

Discussion