Analysis and interpretation of real-world data: a 5-year outlook

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Disclosure

Opinions are my own, and do not necessarily reflect those of Janssen R&D, Columbia University or OHDSI community

Clinical Pharmacology & Therapeutics

PERSPECTIVE

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

Peter Arlett[1,*], Jesper Kjær[2], Karl Broich[3] and Emer Cooke[1]

We outline our vision that by 2025 the use of real-world evidence will have been enabled and the value will have been established across the spectrum of regulatory use cases. We are working to deliver this vision through collaboration where we leverage the best that different stakeholders can bring. This vision will support the development and use of better medicines for patients.

Real-world data (RWD) and real-world evidence (RWE) are already used in the regulation of the development, authorization, and supervision of medicines in the European Union. Their place in safety monitoring and disease epidemiology are well-established while their evidentiary value for additional use cases, notably for demonstrating efficacy, requires further evaluation.[1] During the coronavirus disease 2019 (COVID-19) pandemic, RWE rapidly provided impactful evidence on drug safety, vaccine safety, and effectiveness and we were reminded of the importance of robust study methods and transparency.[2] Our vision, anchored in the European Medicines Regulatory Network (EMRN) strategy to 2025, is that by 2025 the use of RWE will have been enabled and the value will have been established across the spectrum of regulatory use cases.[3] Delivering this vision will support the development and use of better medicines for patients.

In December 2018, the US Food and Drug Administration (FDA) published its framework for RWE underpinned by three pillars: whether RWD are fit for use, whether the study design can provide adequate evidence, and whether the study conduct meets regulatory requirements.[4] In 2019 in the European Union, we published the OPTIMAL framework for RWE also consisting of three pillars: operational, technical, and methodological.[5] More recently, the EU approach places RWE in the wider context of big data and is guided by the priority recommendations of the Big Data Task Force. These recommendations are being implemented through the Big Data Steering Group and the second multi-annual work plan was published in August 2021.[6] **Figure 1** represents the workplan with its 11 workstreams which will deliver our vision for RWE by 2025. The workplan places emphasis on collaboration across stakeholders and with international regulatory partners. This work also needs to be seen in the wider EU policy context, most notably the European Commission's plans for a European Health Data Space.[7]

Acknowledging different frameworks to conceptualize the challenges and opportunities of RWE, we believe the two main priorities for the European Union are to enable its use and establish its value for regulatory decision making. The EMRN is working to deliver on both priorities through a collaborative approach where we leverage the best that different stakeholders can bring, and where those stakeholders can complement the central role of industry in generating evidence.

ENABLING USE

To enable use, we are working on multiple fronts with our stakeholders, including patients, healthcare professionals, industry, regulatory and public health agencies, health technology assessment bodies, payers, and academia. We are initiating work to establish a data quality framework, not just for RWD but for all data used in regulatory decision making. We are striving to improve the discoverability (findability) of RWD through agreement of metadata for RWD and through a public catalogue of RWD sources[8] that builds on the early work of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP Guide on Methodological Standards in Pharmacoepidemiology,[9] extensively updated in 2021, is the core of our efforts to drive up the standards of study methods for RWE, and this is complemented by recently published guidance on conducting studies based on patient registries.[10]

The European Medicines Agency (EMA) and some national medicines agencies

[1]European Medicines Agency, Amsterdam, Netherlands; [2]Danish Medicines Agency, Copenhagen, Denmark; [3]BfArM, Bonn, Germany. *Correspondence: Peter Arlett (Peter.Arlett@ema.europa.eu)

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1. DARWIN EU
2. Data quality
3. Data discoverability
4. Skills
5. Business processes
6. Analytics capability
7. Expert advice
8. Data governance
9. International collaboration
10. Stakeholder engagement
11. Veterinary data strategy

Figure 1 Big Data Steering Group workplan to 2023. Eleven workstreams to progress the real-world evidence (RWE) vision.[5]

PERSPECTIVES

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"Our vision is that by 2025 the use of RWE will have been enabled and its value will have been established across the spectrum of regulatory use cases. We are committed to working with stakeholders to deliver this vision and in turn to support the development and use of better medicines for patients."

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Ensuring the appropriate use of real-world evidence to inform regulatory decision-making is not just a European regulatory responsibility…

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OHDSI community

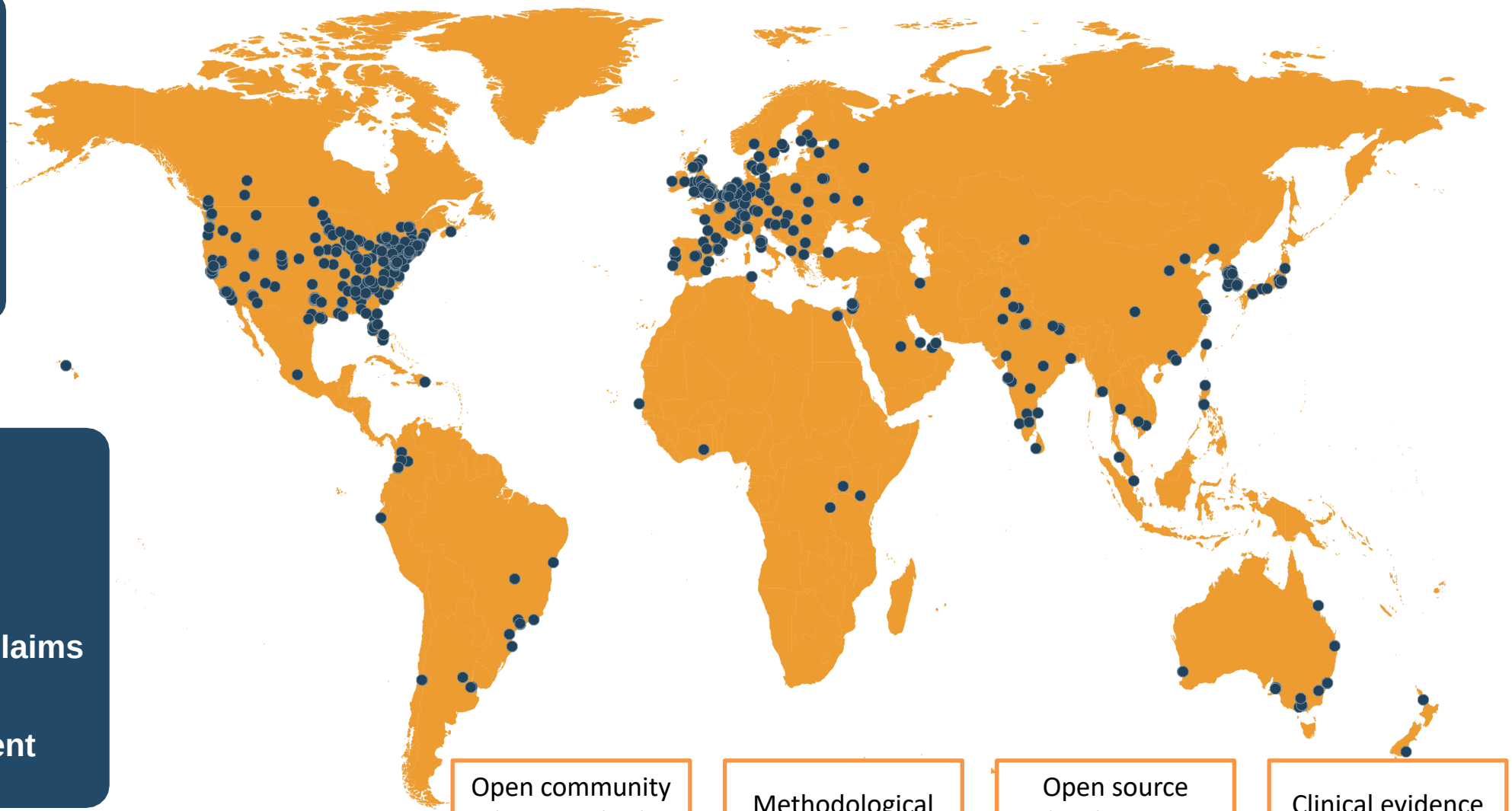
We're all in this journey together…

OHDSI Collaborators

- 2,367 collaborators
- 74 countries
- 21 time zones
- 6 continents

OHDSI Data Network

- 331 data sources
  - 284 EHRs
  - 28 administrative claims
- 34 countries
- 810 million unique patient records

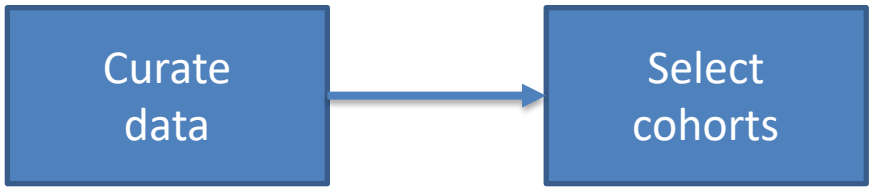


Open community data standards (OMOP CDM) ↔ Methodological research ↔ Open source development (OHDSI tools) ↔ Clinical evidence generation

Current status quo in observational research makes it challenging to build trust in evidence

Curate data

Current status quo in observational research makes it challenging to build trust in evidence



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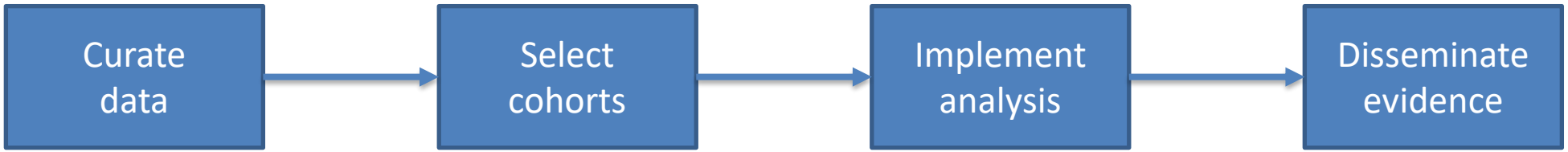

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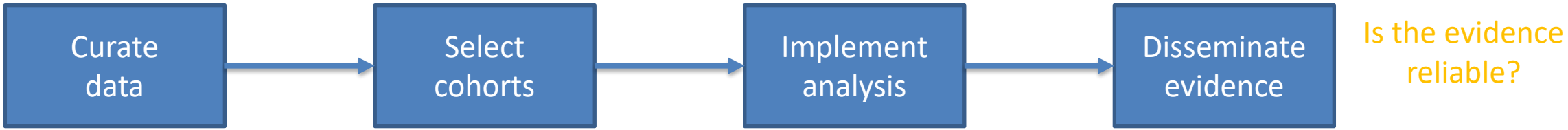

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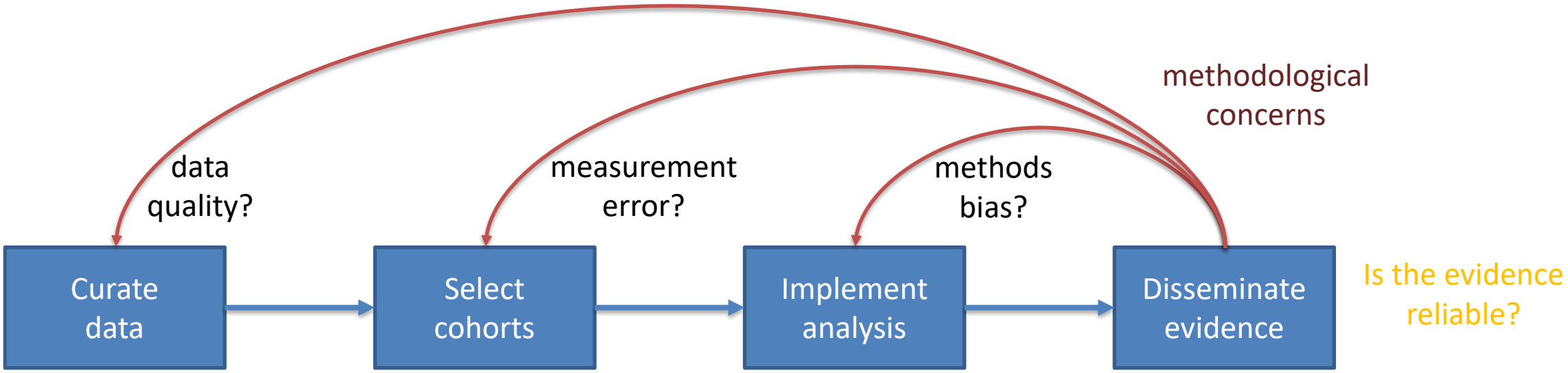

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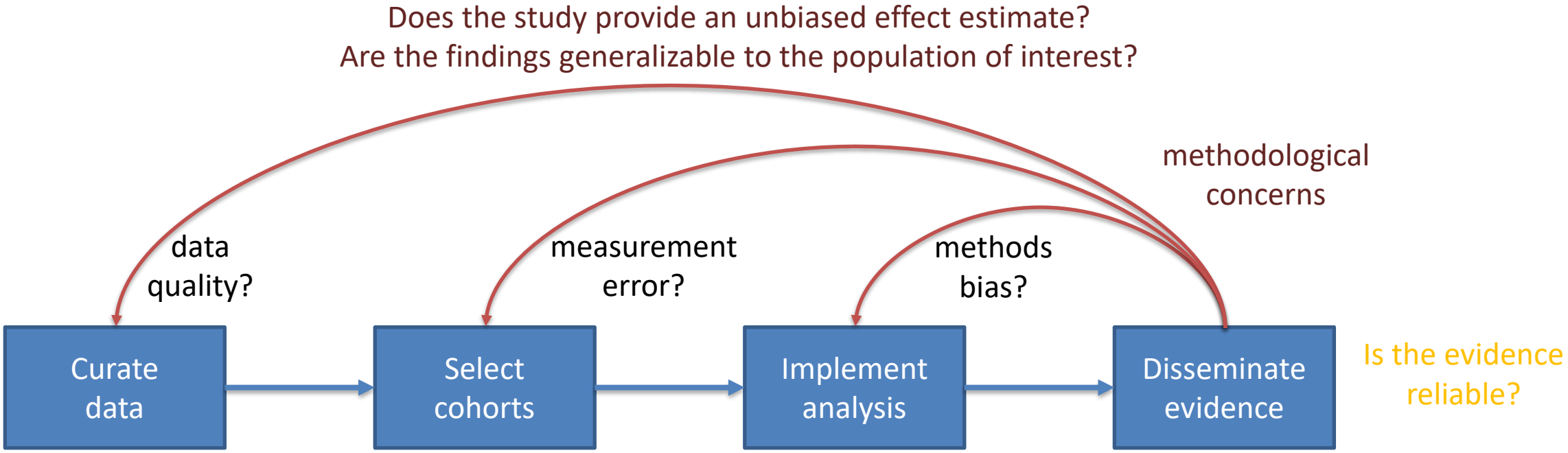

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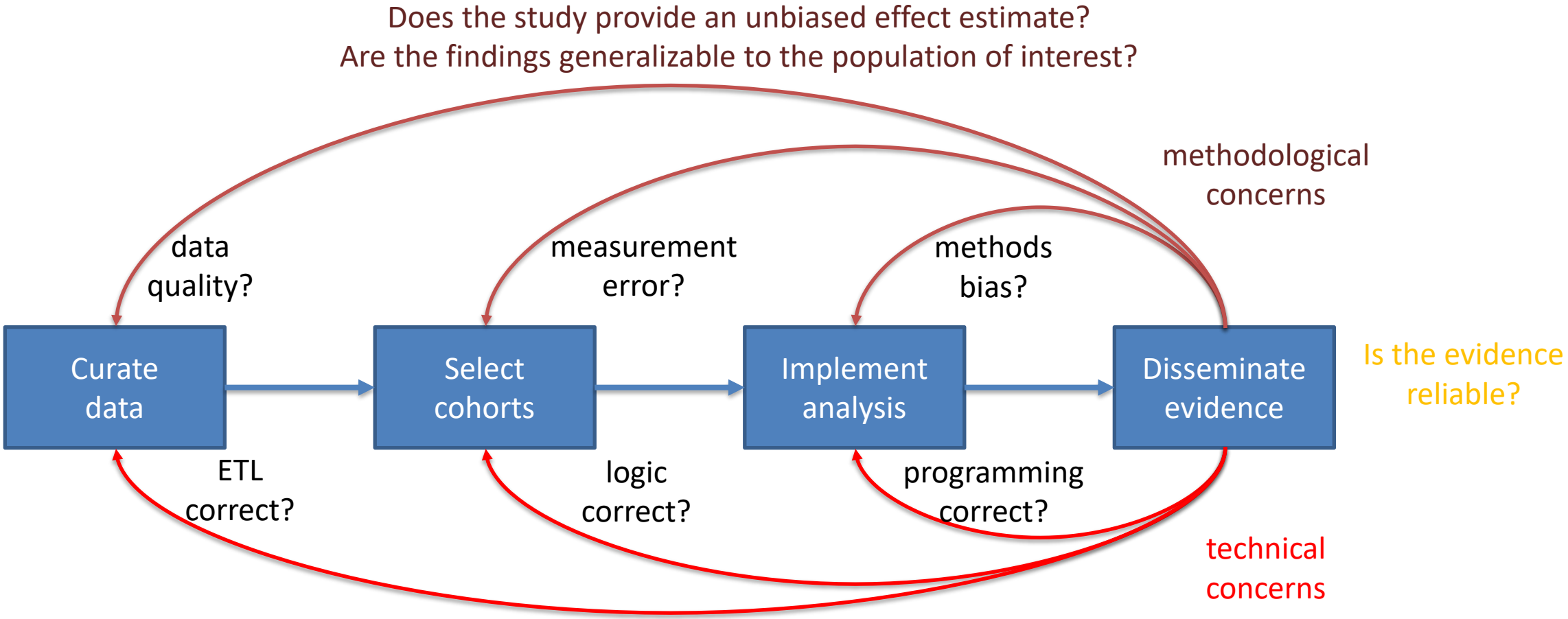

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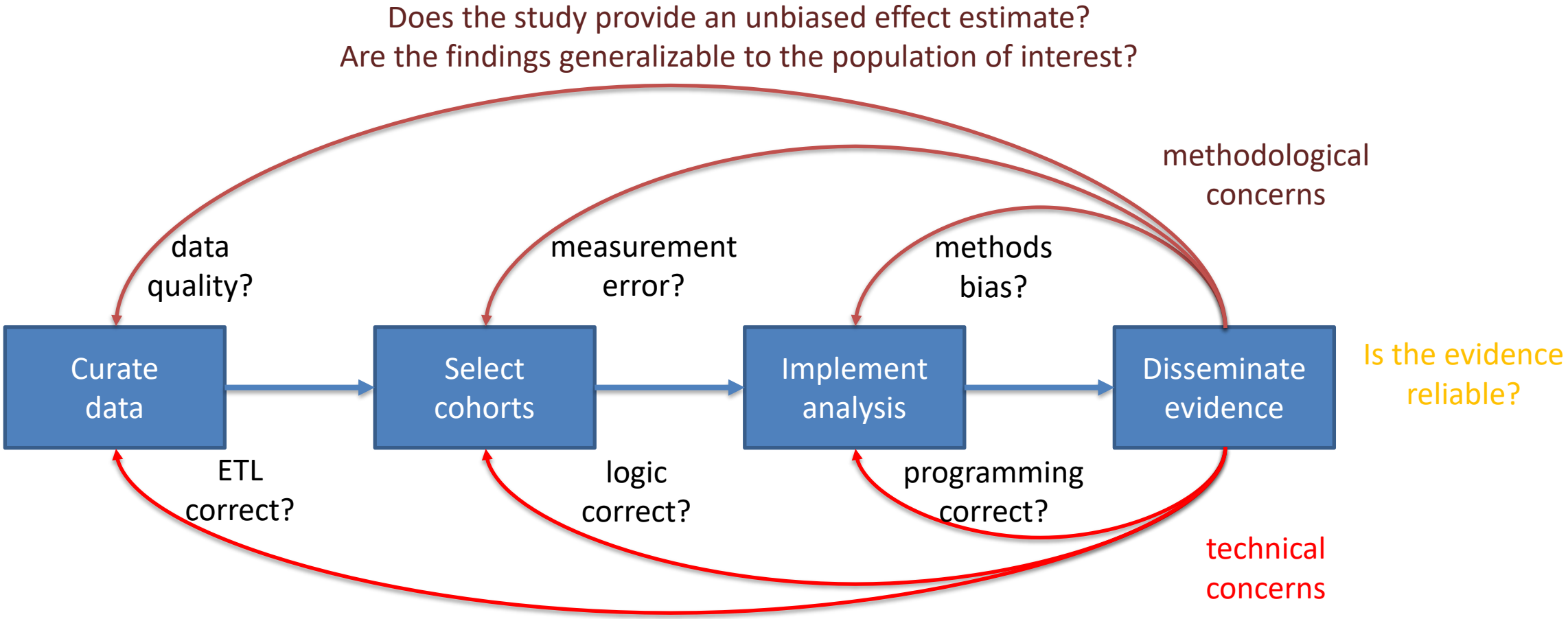
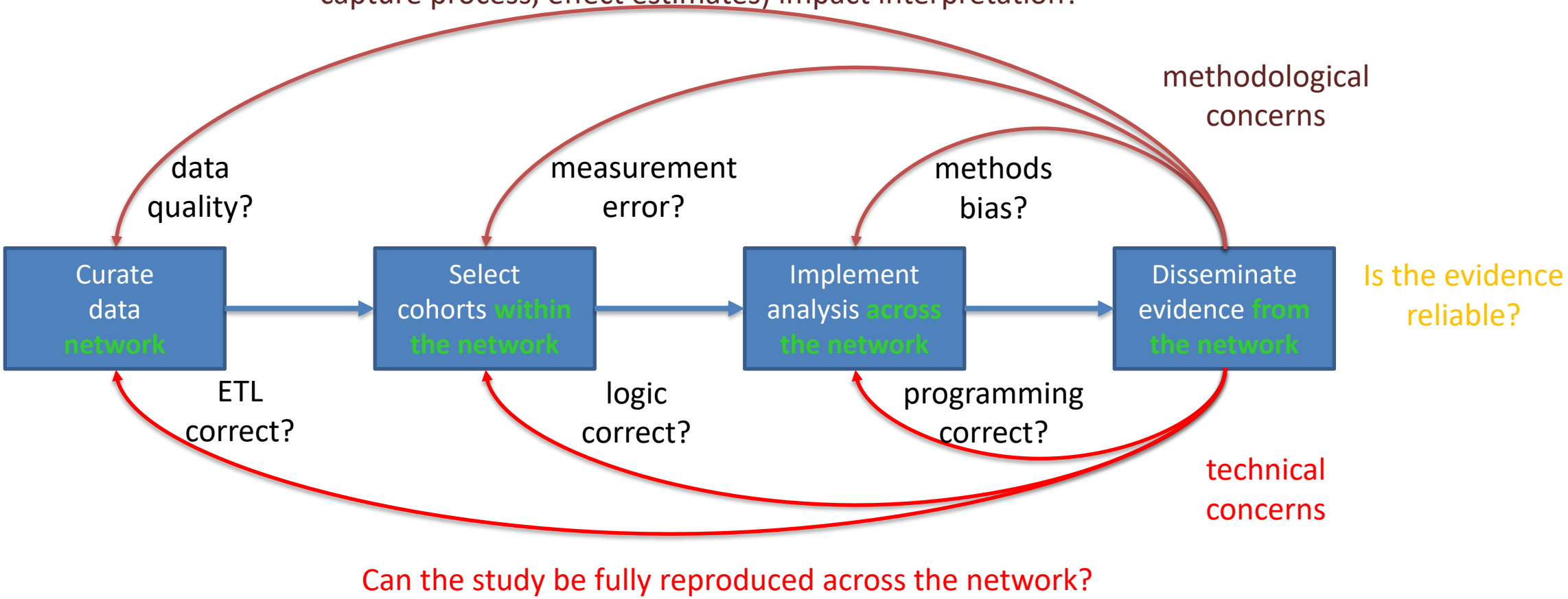


Observational research across data networks increases complexity and raises new questions



Desired attributes for reliable evidence

Desired attribute	Question	Researcher	Data	Analysis		Result
Repeatable	Identical	Identical	Identical	Identical	=	Identical
Reproducible	Identical	Different	Identical	Identical	=	Identical
Replicable	Identical	Same or different	Similar	Identical	=	Similar
Generalizable	Identical	Same or different	Different	Identical	=	Similar
Robust	Identical	Same or different	Same or different	Different	=	Similar
Calibrated	Similar (controls)	Identical	Identical	Identical	=	Statistically consistent

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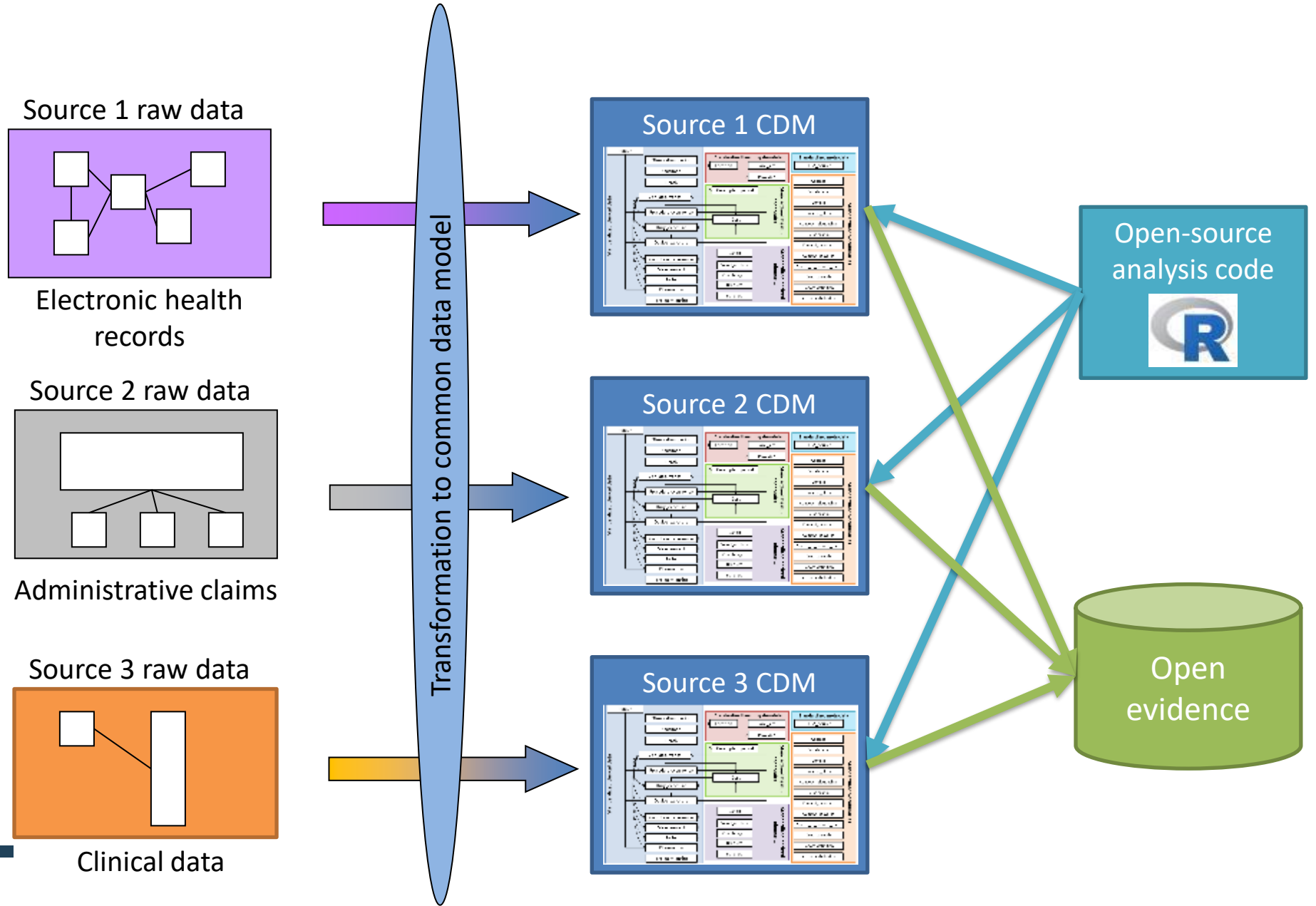
A system for real-world evidence generation based on consistent application of standardized analytics across a standardized data network can be empirically demonstrated to be reliable

Common data model can enable standardized analytics across a distributed data network



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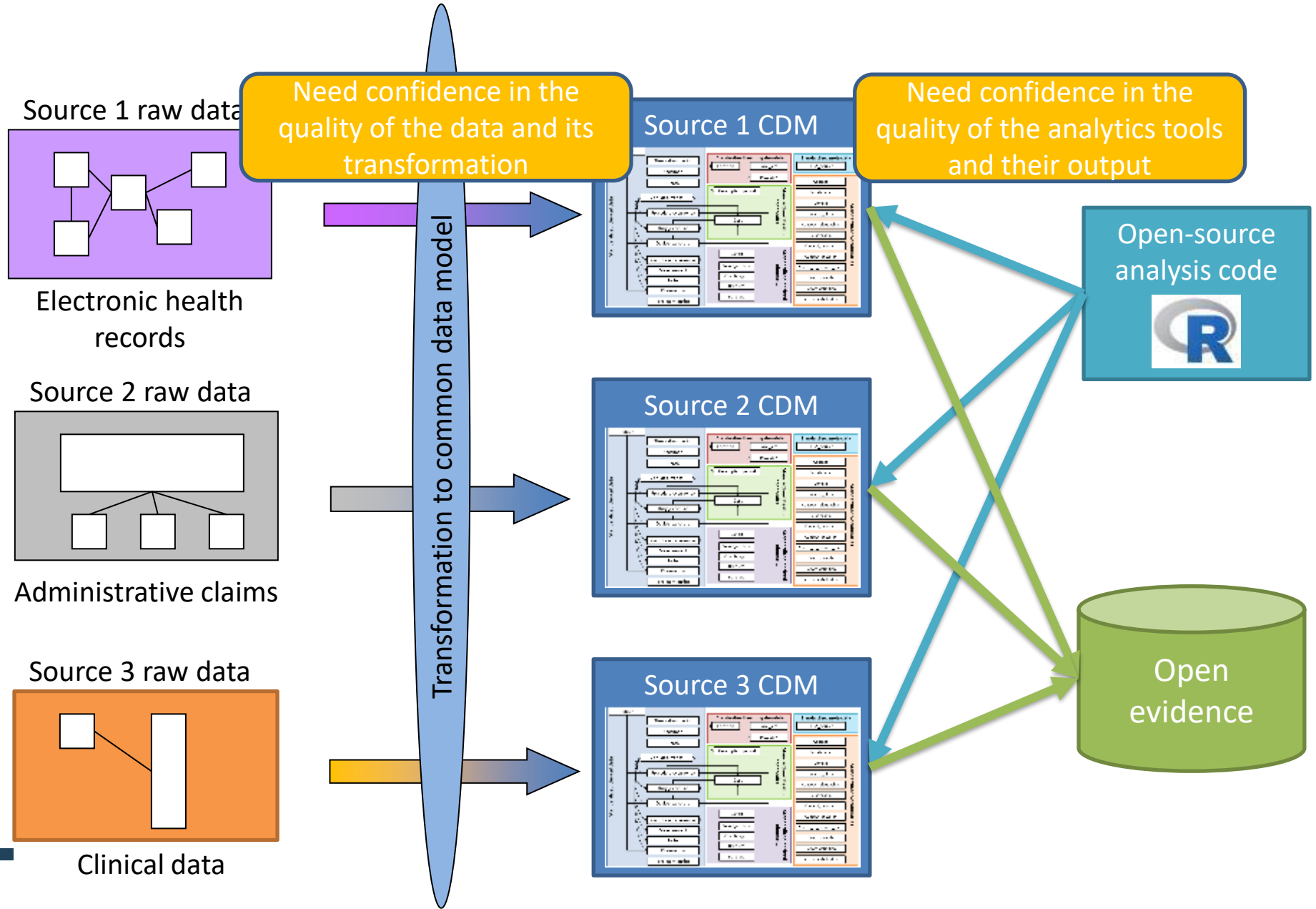
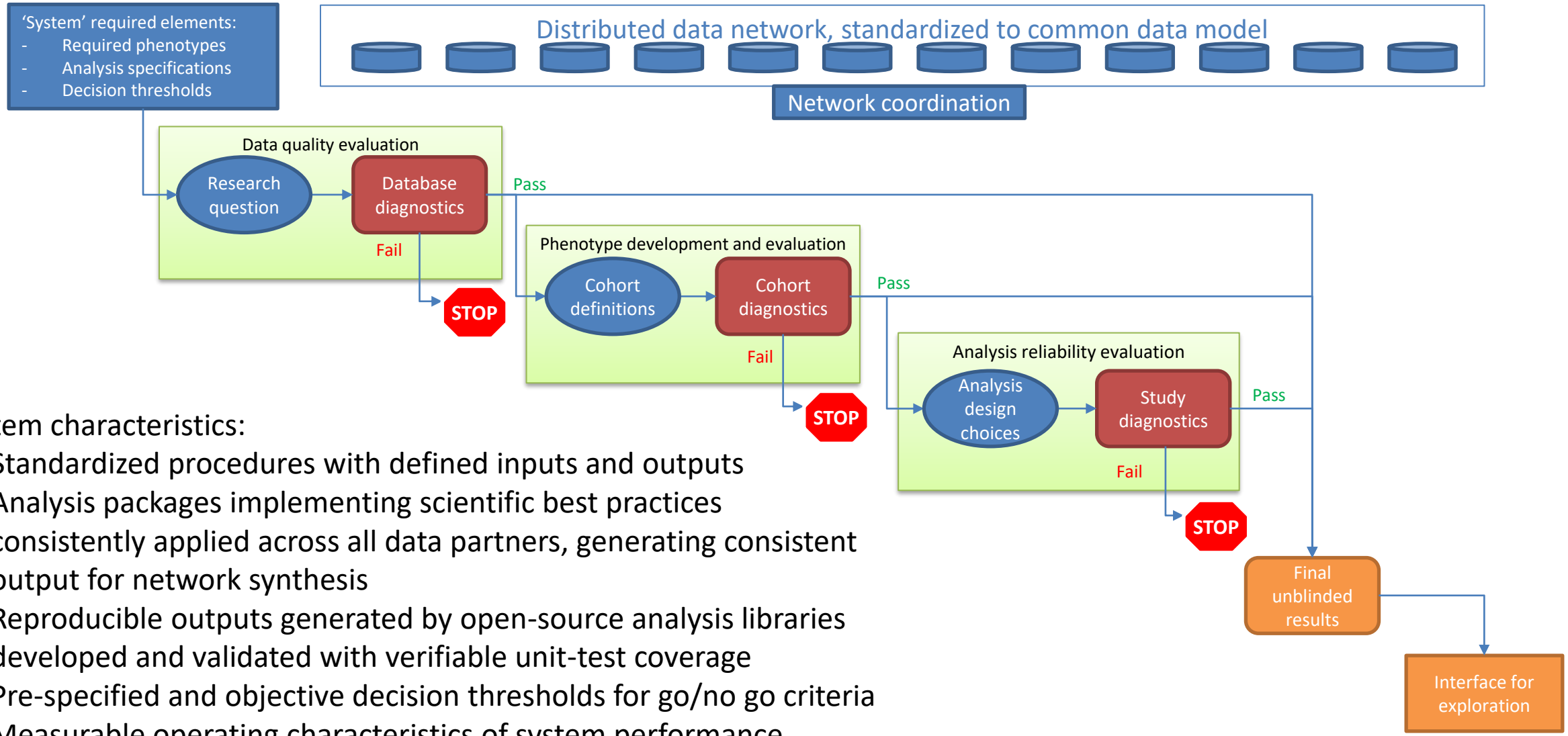


Engineering open science systems that build trust into the real-world evidence generation and dissemination process



System characteristics:

- Standardized procedures with defined inputs and outputs
- Analysis packages implementing scientific best practices consistently applied across all data partners, generating consistent output for network synthesis
- Reproducible outputs generated by open-source analysis libraries developed and validated with verifiable unit-test coverage
- Pre-specified and objective decision thresholds for go/no go criteria
- Measurable operating characteristics of system performance

Engineering open science systems that build trust into the real-world evidence generation and dissemination process

'System' required elements:
- Required phenotypes
- Analysis specifications
- Decision thresholds

Distributed data network, standardized to common data model

Network coordination

Data quality evaluation

Research question

Database diagnostics

Fail

STOP

Pass

Phenotype development and evaluation

Cohort definitions

Cohort diagnostics

Fail

STOP

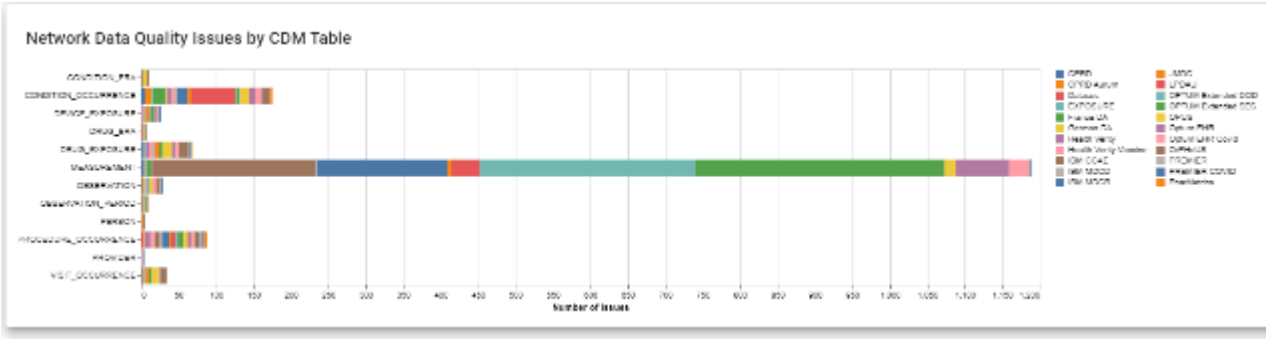
Pass

Analysis reliability evaluation

Analysis design choices

Study diagnostics

Pass



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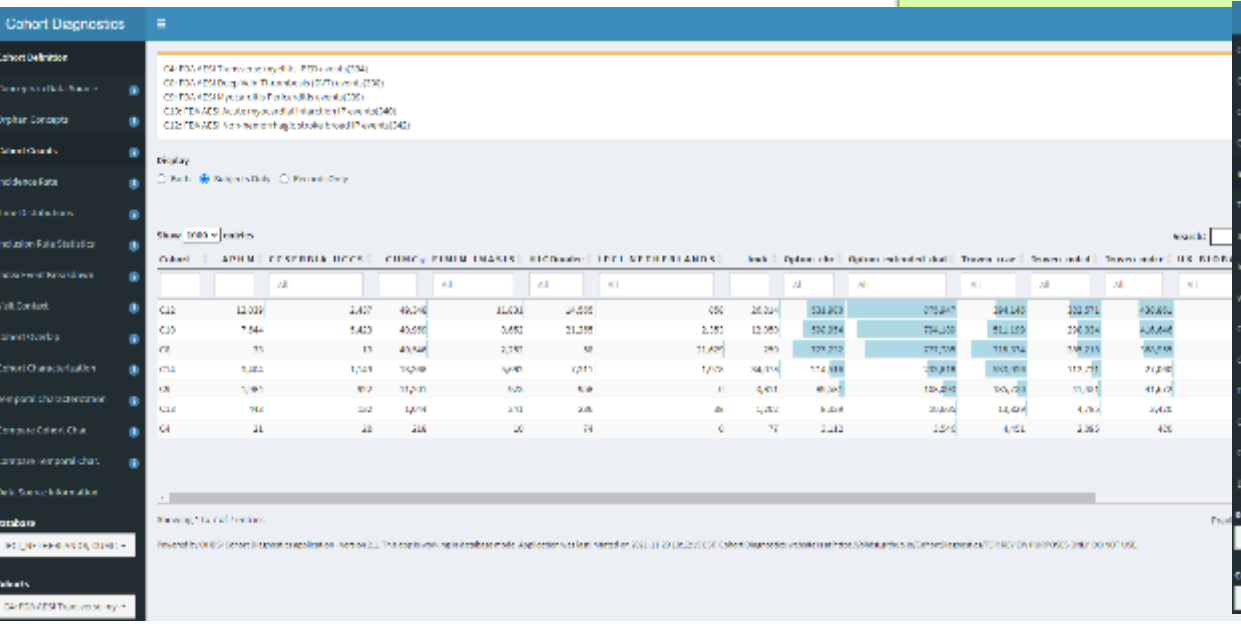

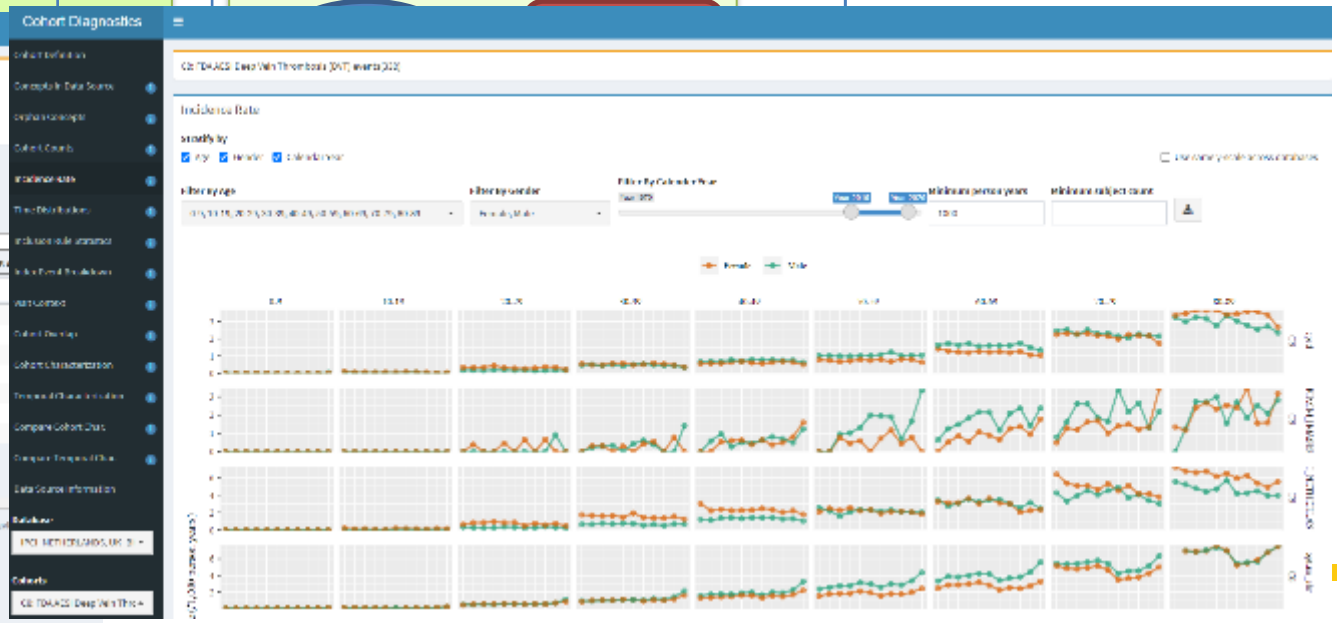

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Research question → Database diagnostics

Database diagnostics: Pass → Phenotype development and evaluation; Fail → STOP

Phenotype development and evaluation

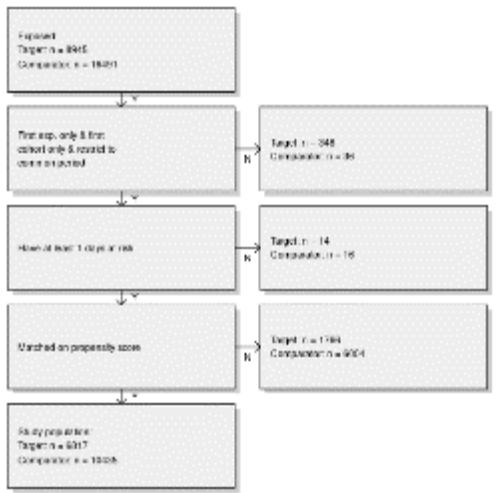
Cohort definitions → Cohort diagnostics

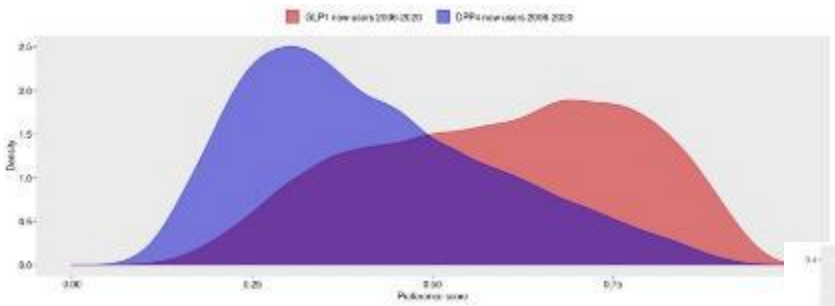
Cohort diagnostics: Pass → Analysis reliability evaluation; Fail → STOP

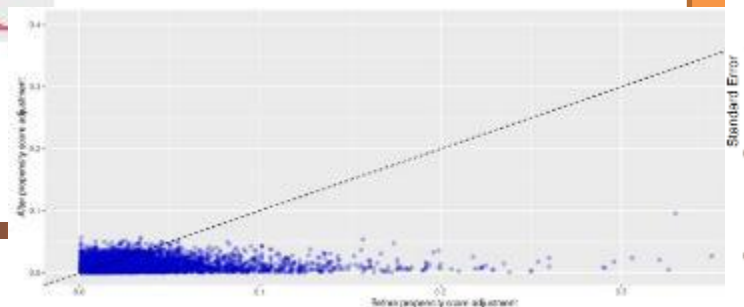
Analysis reliability evaluation

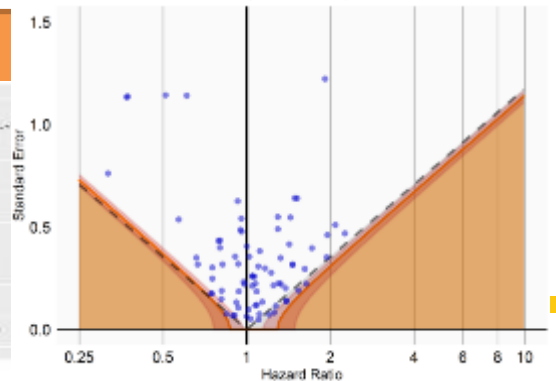
Analysis design choices → Study diagnostics

Study diagnostics: Pass; Fail → STOP









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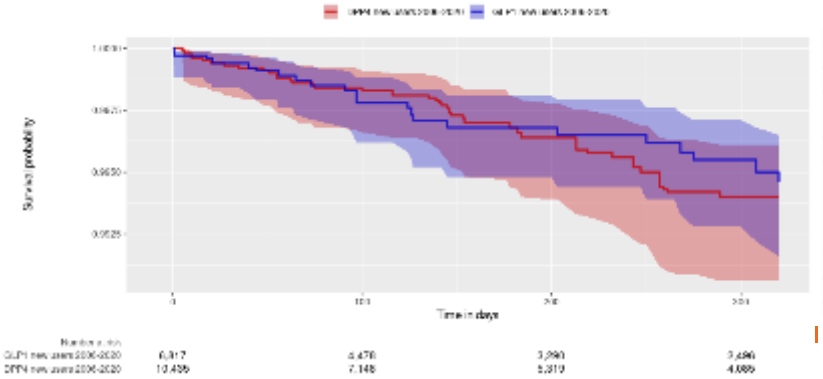
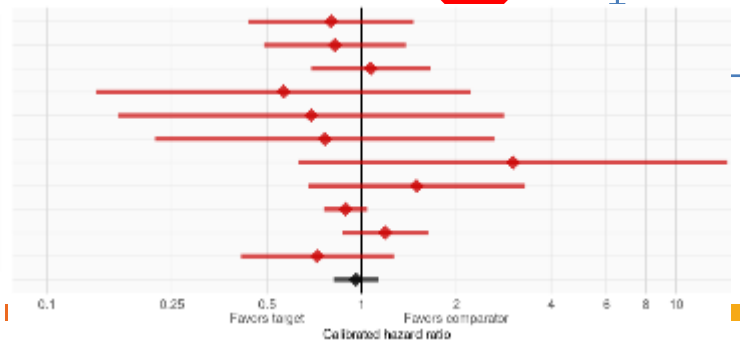
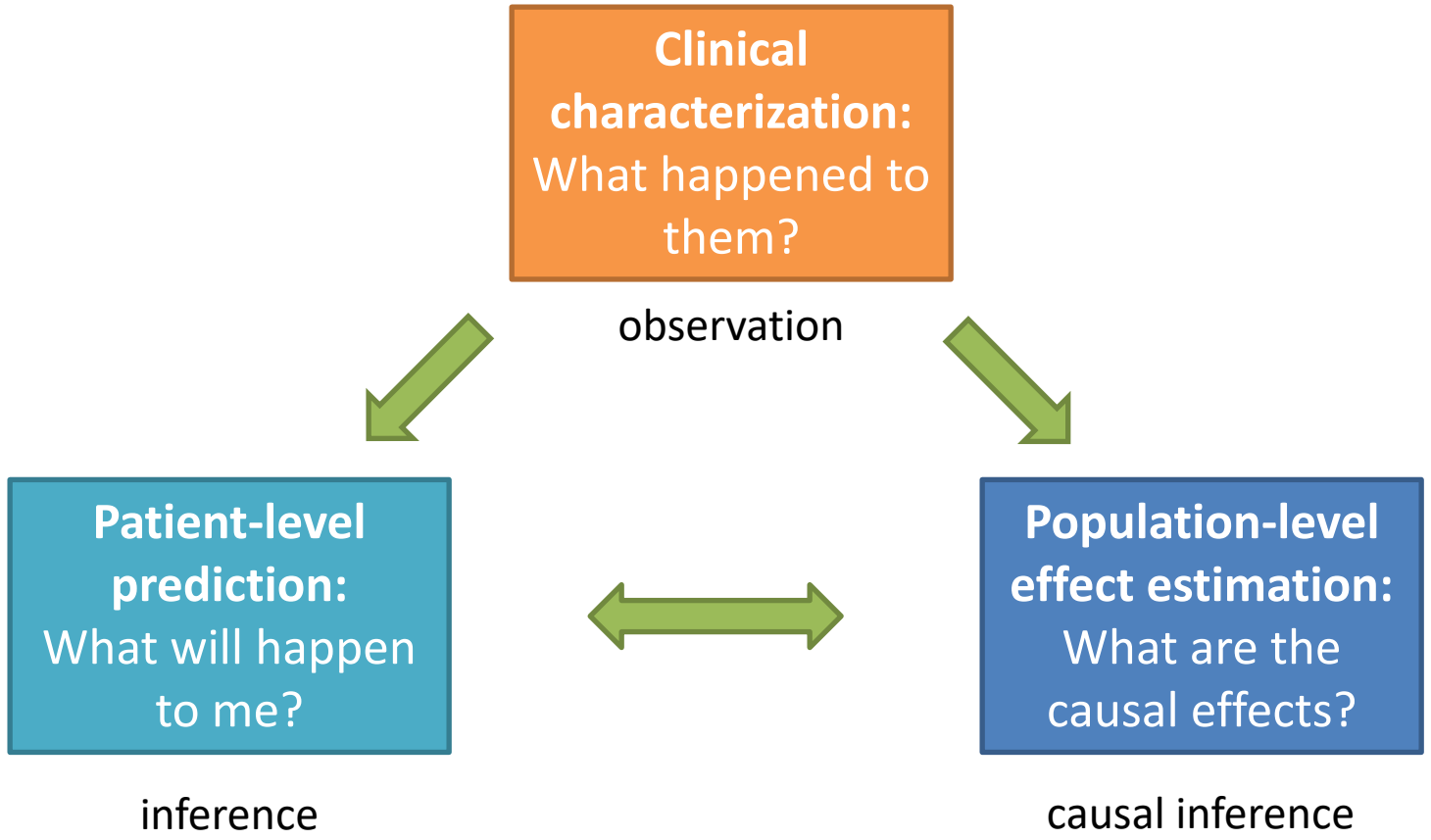




Interface for exploration

Complementary types of evidence to generate from real-world data



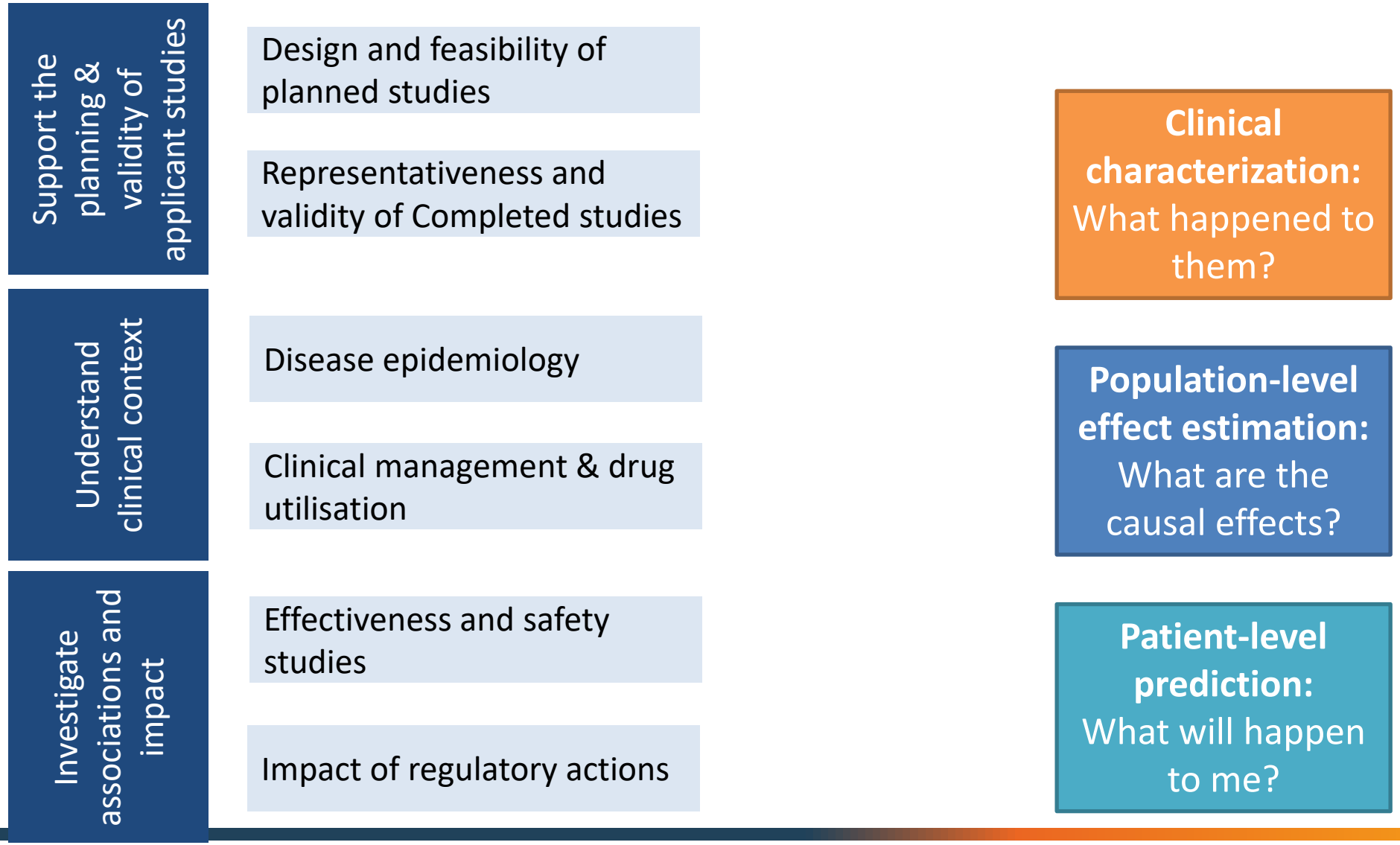
Three potential use cases for the support to committees' decision-making

From a regulatory perspective, RWE aims to support committees' decision-making in three main areas

Use case objective	**Support the planning & validity of applicant studies**	**Understand clinical context**	**Investigate associations and impact**
Use case category	Design and feasibility of planned studies	Disease epidemiology	Effectiveness and safety studies
	Representativeness and validity of Completed studies	Clinical management & drug utilisation	Impact of regulatory actions

with permission from Peter Arlett

Mapping regulatory use cases to evidence types



Mapping regulatory use cases to evidence types

Support the planning & validity of applicant studies	Design and feasibility of planned studies	**Clinical characterization:** What happened to them?	Who are the patients with disease eligible for treatment? Who are the patients exposed to those treatments? How often do outcomes occur amongst those patients?
	Representativeness and validity of Completed studies		
Understand clinical context	Disease epidemiology	**Population-level effect estimation:** What are the causal effects?	Is the outcome causally related to exposure to treatment? How does the risk compare with alternative treatments?
	Clinical management & drug utilisation		
Investigate associations and impact	Effectiveness and safety studies	**Patient-level prediction:** What will happen to me?	Which risks can be actionably predicted with available data? Which patients are at highest risk of adverse events?
	Impact of regulatory actions		

Questions that can be informed with real world evidence:

Mapping regulatory use cases to evidence types

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Design and feasibility of planned studies

Representativeness and validity of Completed studies

Disease epidemiology

Clinical management & drug utilisation

Effectiveness and safety studies

Impact of regulatory actions

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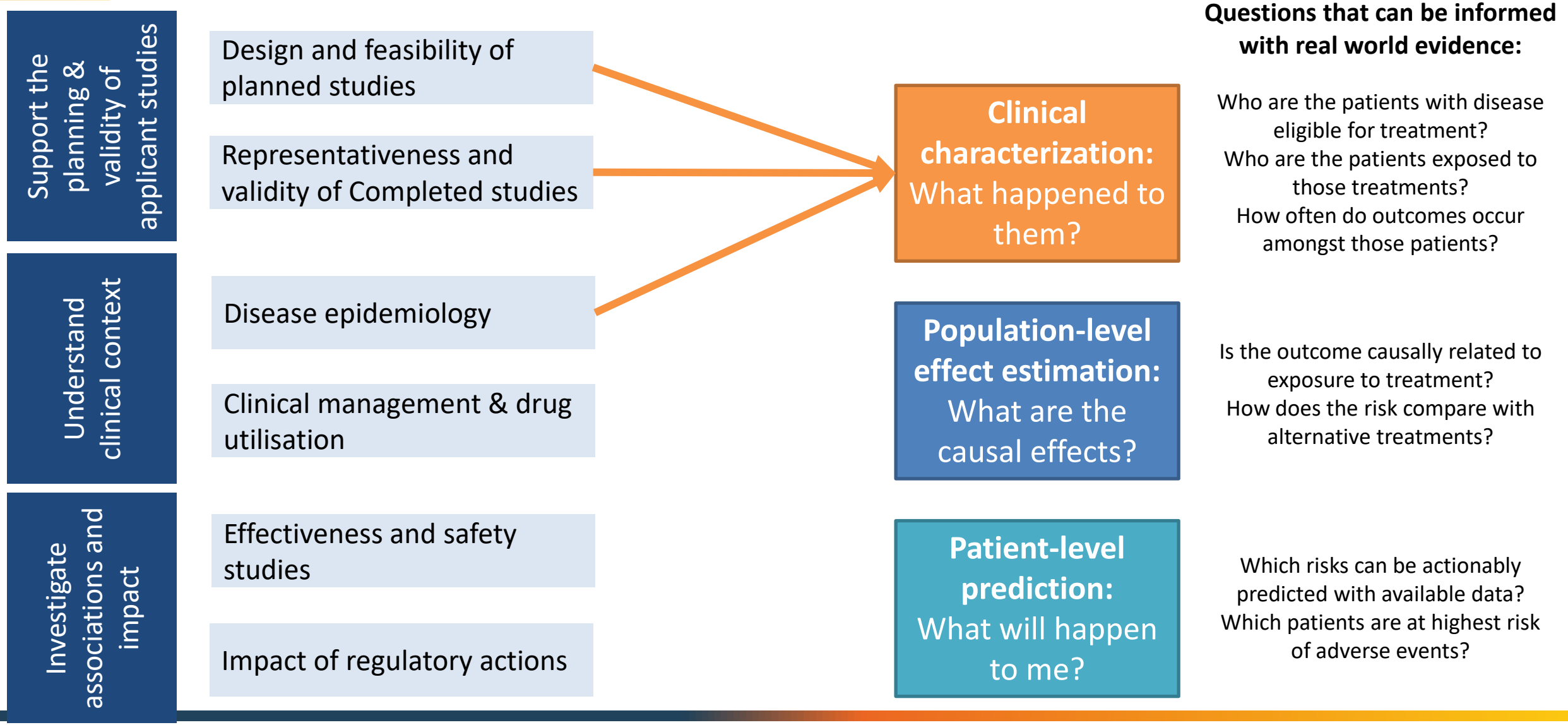

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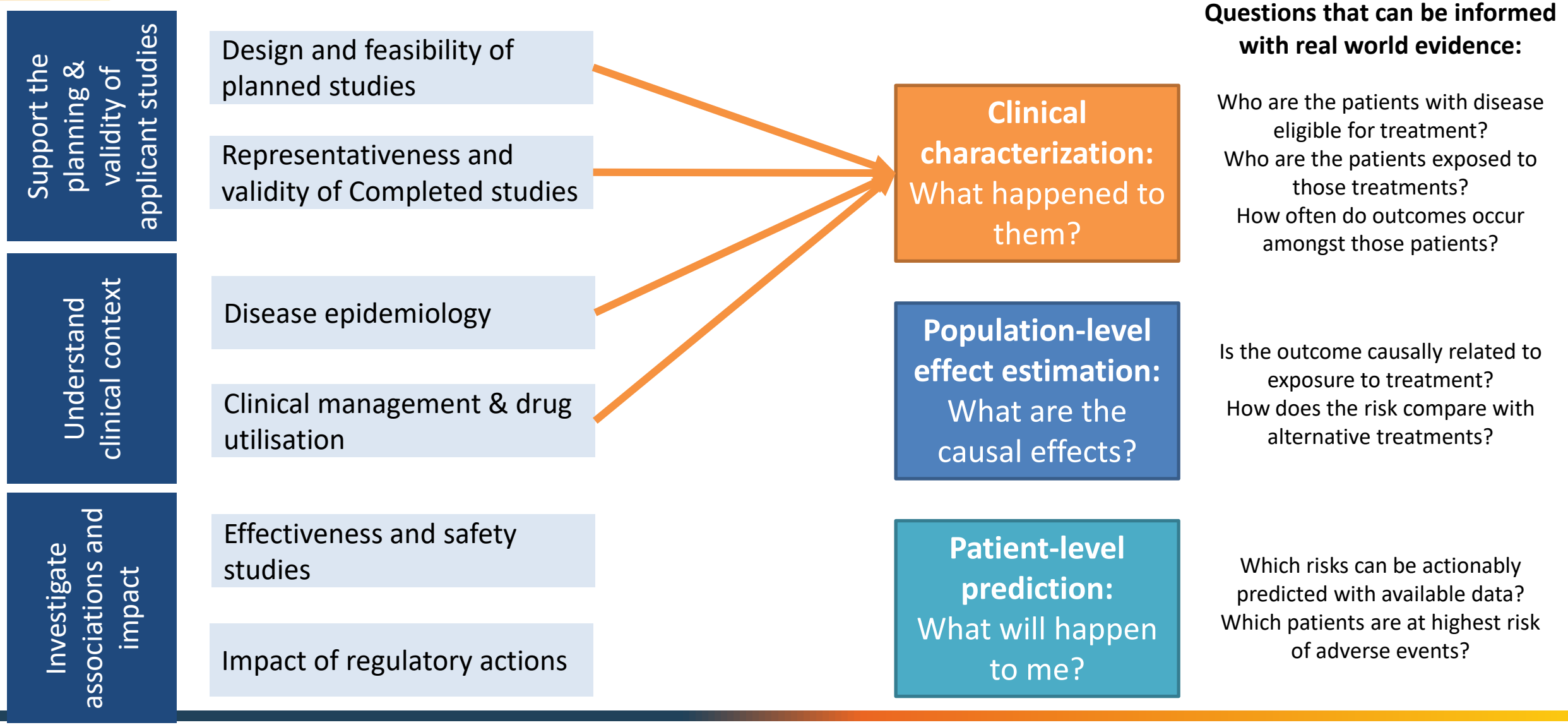

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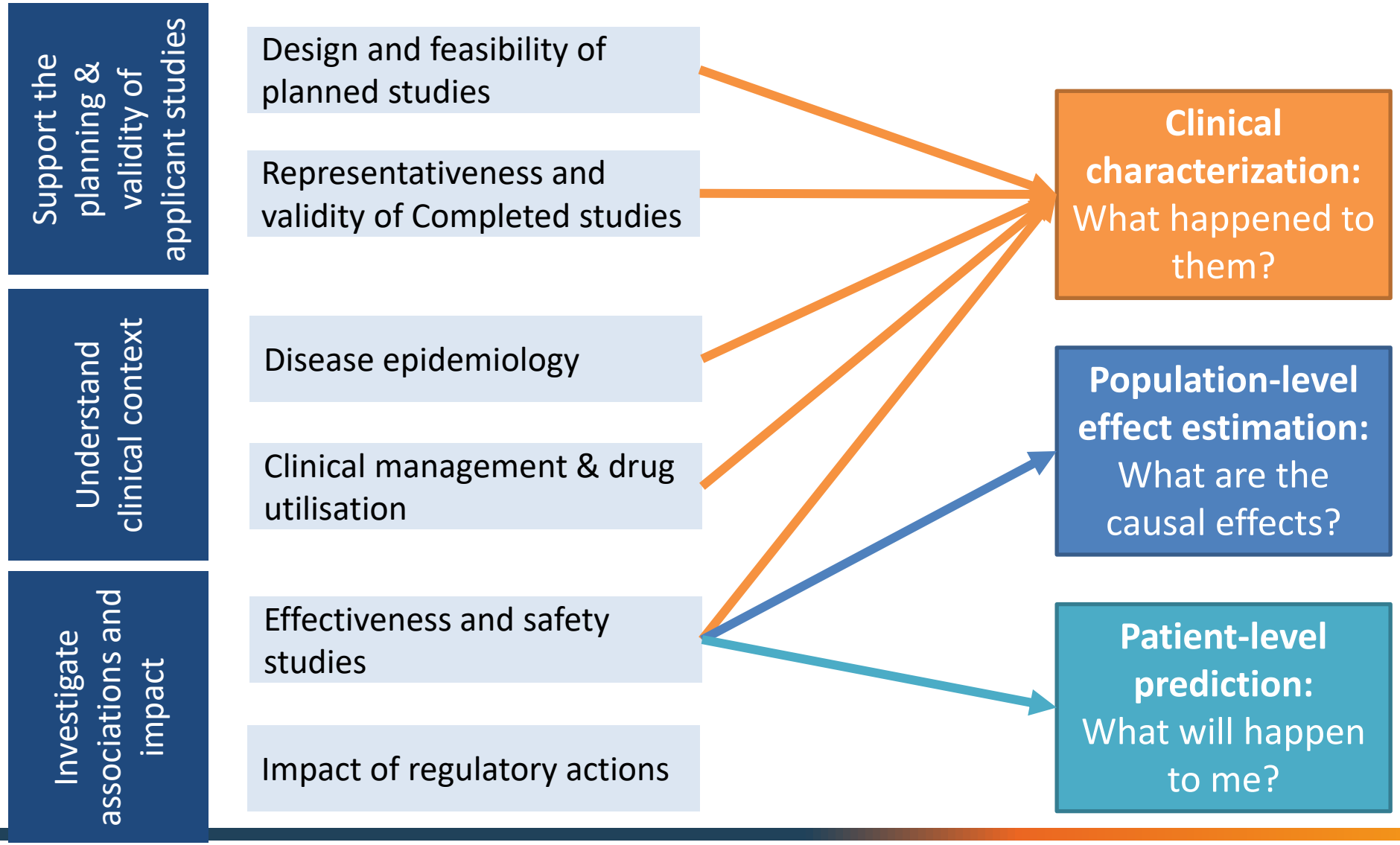

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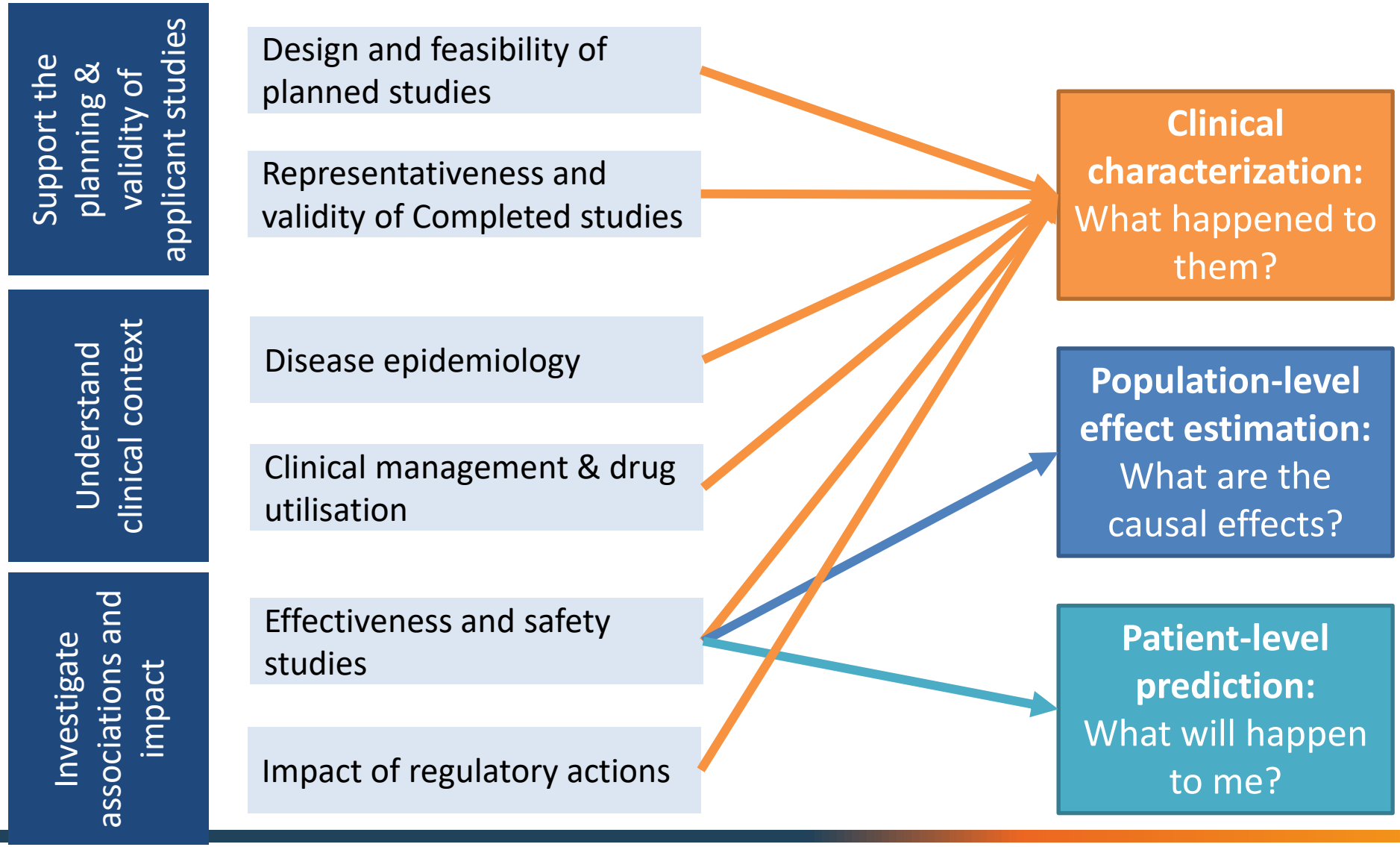

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Level of proactivity in delivering real-world evidence

Service bespoke project requests by convening team to align on problem statement, author protocol/analysis plan documents, implement statistical programming code to custom specification, execute analysis across databases, iteratively review results and request post hoc analyses, write summary of results as report, and deliver to decision-maker to ensure it meets their needs

Level of proactivity in delivering real-world evidence

Enabled

Design and execute standardized analysis packages that apply validated statistical libraries with defined input parameters and fixed output to compile summary results across a network standardized to a common data model

Reactive Bespoke

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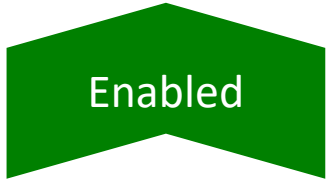
Level of proactivity in delivering real-world evidence

Enable fast evidence generation by using interface that allow qualified users to set defined input parameters, execute standardized analyses, and view results upon request.



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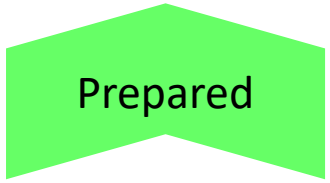
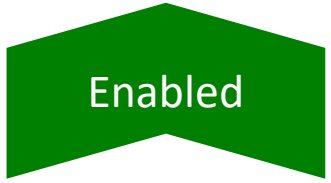


Produce pre-computed evidence to enable answer retrieval in ‘real time’ by qualified users when requested; standardized analysis packages executed across network generate results ‘at-scale’ across many target, outcome cohorts

Enable fast evidence generation by using interface that allow qualified users to set defined input parameters, execute standardized analyses, and view results upon request.

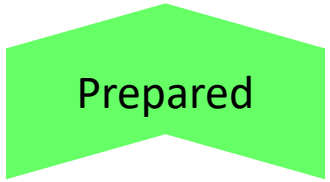


Design and execute standardized analysis packages that apply validated statistical libraries with defined input parameters and fixed output to compile summary results across a network standardized to a common data model

Service bespoke project requests by convening team to align on problem statement, author protocol/analysis plan documents, implement statistical programming code to custom specification, execute analysis across databases, iteratively review results and request post hoc analyses, write summary of results as report, and deliver to decision-maker to ensure it meets their needs

Level of proactivity in delivering real-world evidence

Generate and deliver insights without being asked; answer questions before requested by ‘pushing’ relevant pre-computed evidence to potential evidence consumers



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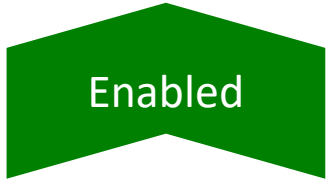

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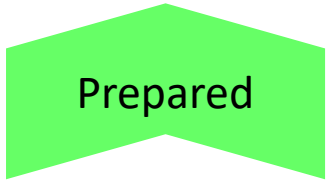

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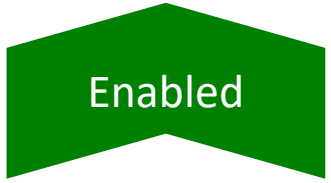

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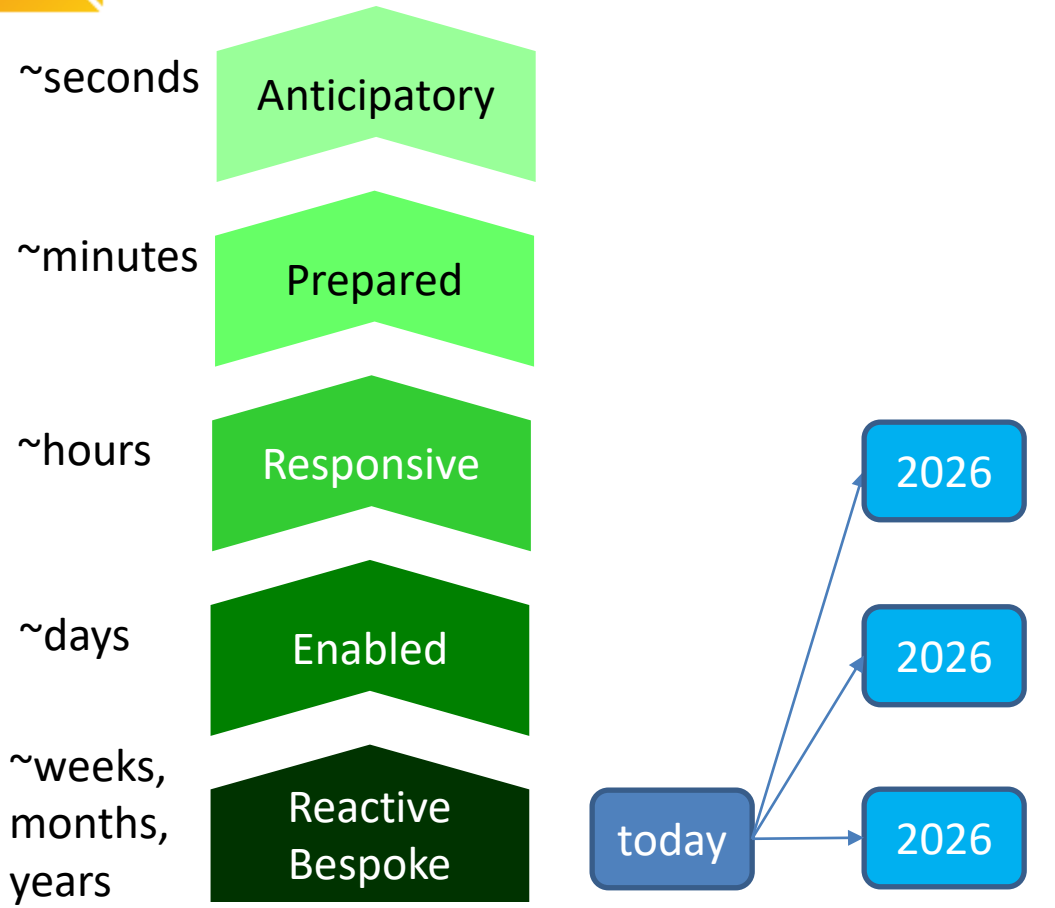
Standardized dissemination
+
Standardized analysis configurations
+
Standardized analysis tools
+
Standardized data, network execution

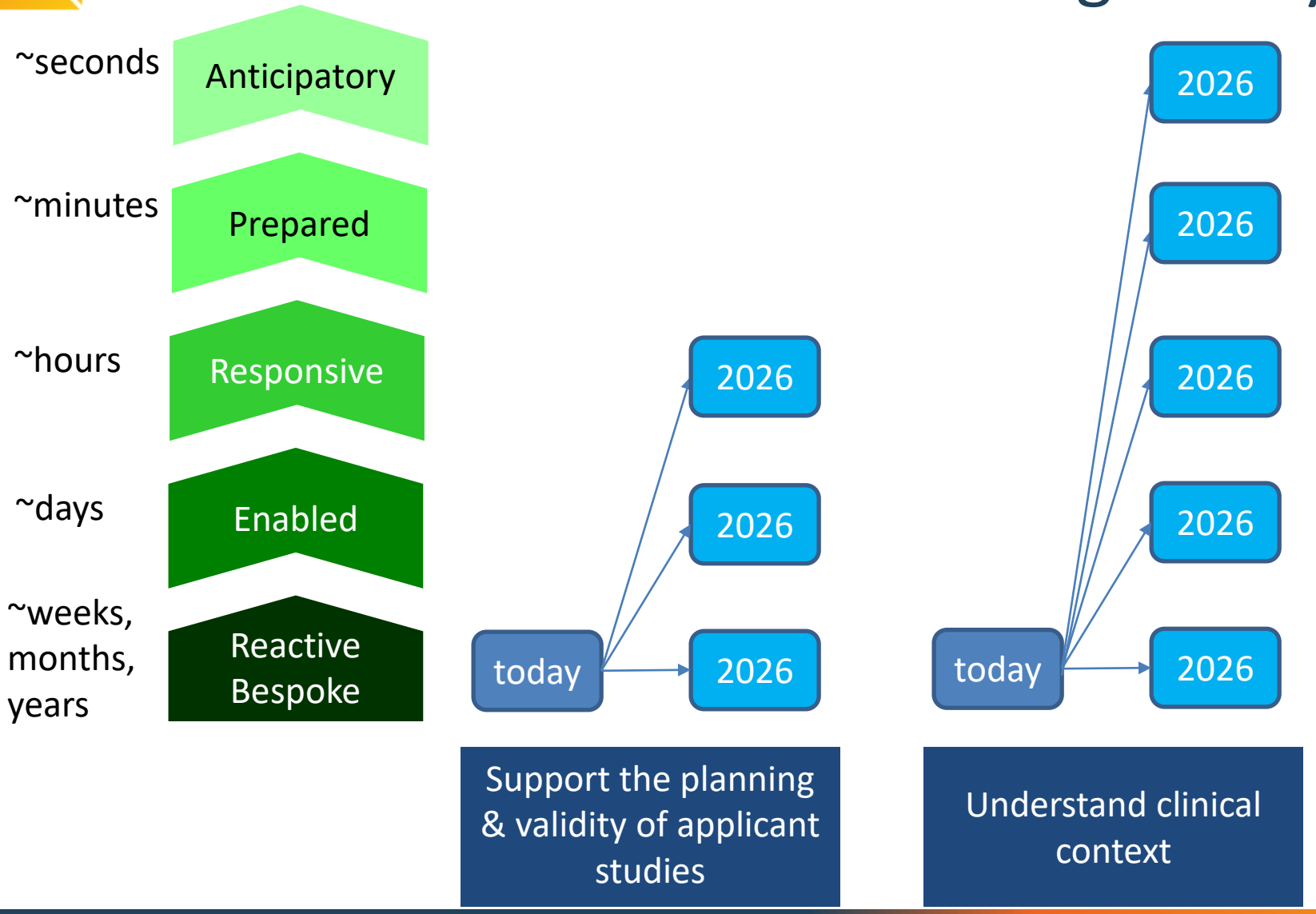
Level of proactivity in delivering real-world evidence

Time-to-evidence			
~seconds	Anticipatory	Generate and deliver insights without being asked; answer questions before requested by 'pushing' relevant pre-computed evidence to potential evidence consumers	Standardized dissemination +
~minutes	Prepared	Produce pre-computed evidence to enable answer retrieval in 'real time' by qualified users when requested; standardized analysis packages executed across network generate results 'at-scale' across many target, outcome cohorts	Standardized analysis configurations +
~hours	Responsive	Enable fast evidence generation by using interface that allow qualified users to set defined input parameters, execute standardized analyses, and view results upon request.	Standardized analysis tools +
~days	Enabled	Design and execute standardized analysis packages that apply validated statistical libraries with defined input parameters and fixed output to compile summary results across a network standardized to a common data model	Standardized data, network execution
~weeks, months, years	Reactive Bespoke	Service bespoke project requests by convening team to align on problem statement, author protocol/analysis plan documents, implement statistical programming code to custom specification, execute analysis across databases, iteratively review results and request post hoc analyses, write summary of results as report, and deliver to decision-maker to ensure it meets their needs	

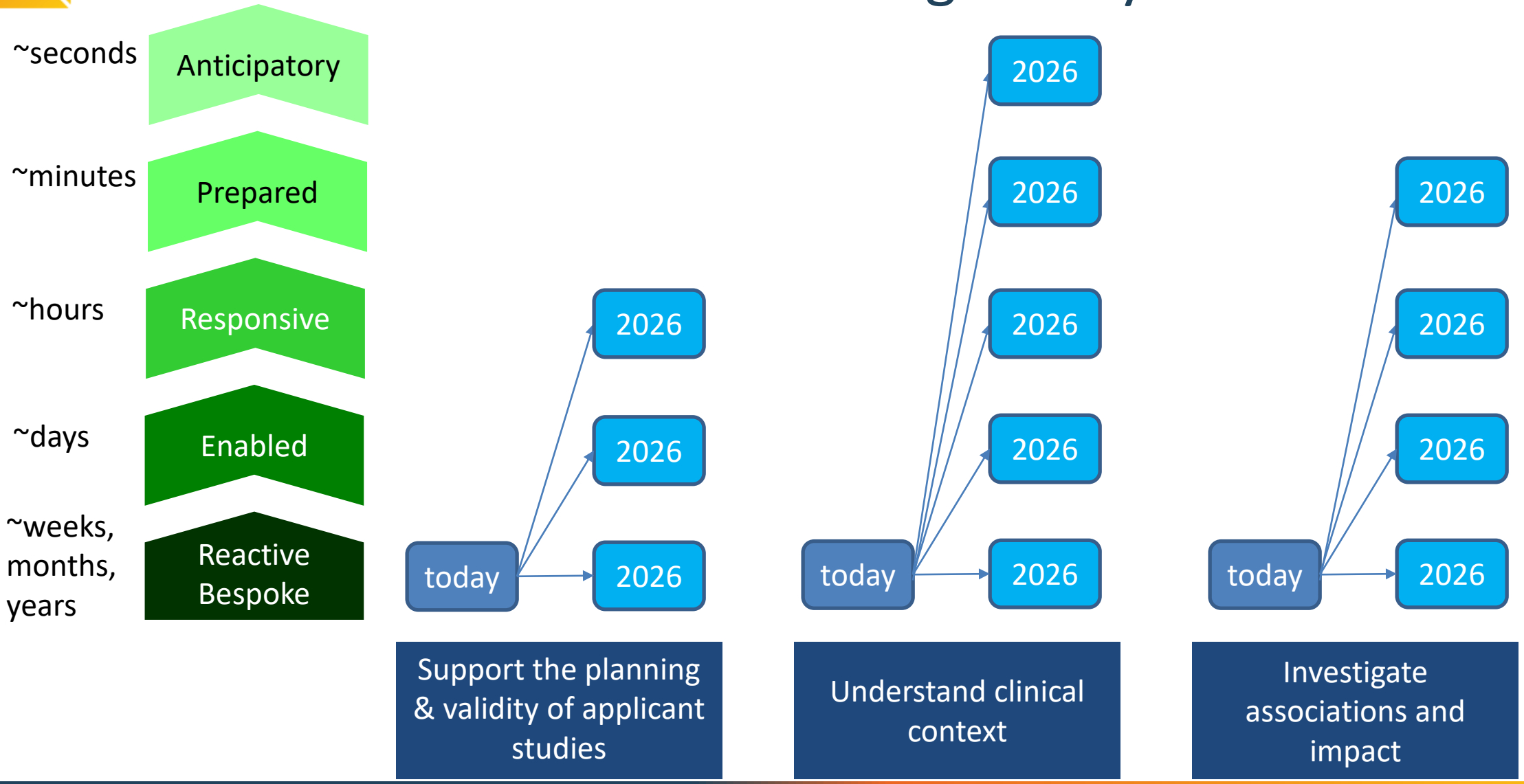
A 5-year vision for expanding the proactive use of real-world evidence across regulatory use cases



A 5-year vision for expanding the proactive use of real-world evidence across regulatory use cases



A 5-year vision for expanding the proactive use of real-world evidence across regulatory use cases



Expanding the proactive use of real-world evidence for study planning and validity

~seconds — Anticipatory

~minutes — Prepared

~hours — Responsive

~days — Enabled

~weeks, months, years — Reactive Bespoke

today → 2026

today → 2026

today → 2026

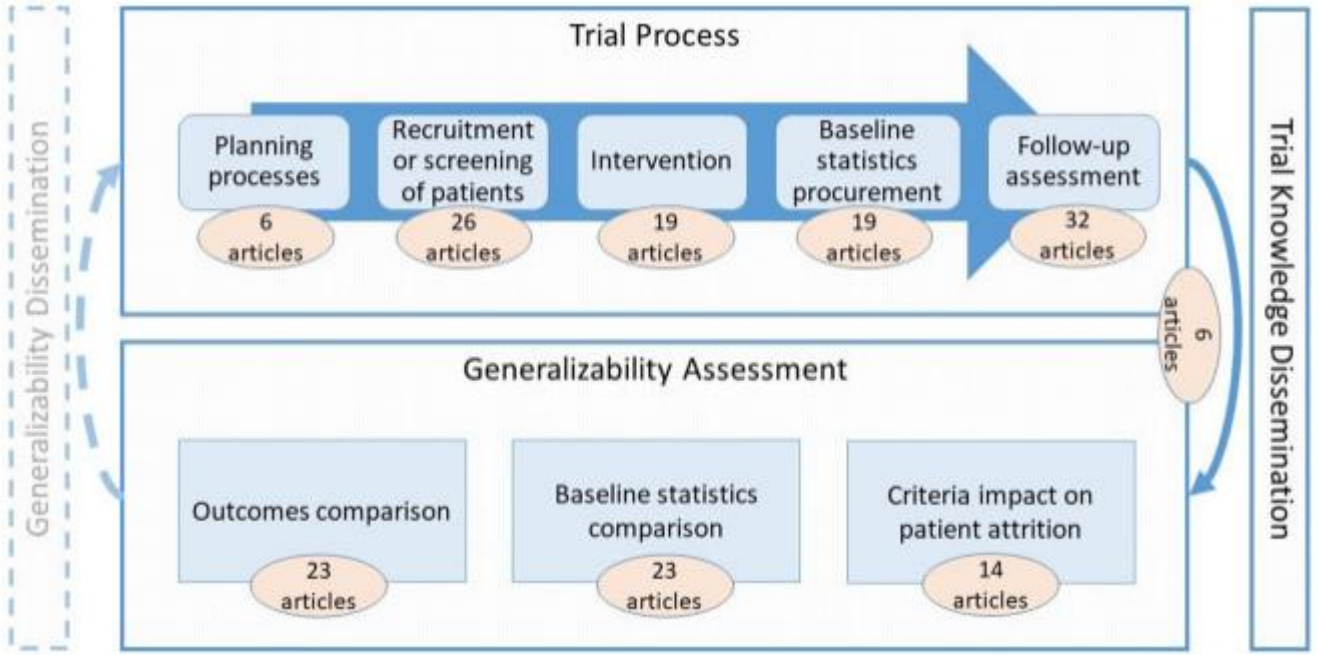
Support the planning & validity of applicant studies

Journal of the American Medical Informatics Association, 28(1), 2021, 144–154
doi: 10.1093/jamia/ocaa224
Advance Access Publication Date: 4 November 2020
Review

Review

Contemporary use of real-world data for clinical trial conduct in the United States: a scoping review

James R. Rogers,[1] Junghwan Lee,[1] Ziheng Zhou,[2] Ying Kuen Cheung,[3] George Hripcsak,[1,4] and Chunhua Weng[1]



Expanding the proactive use of real-world evidence for study planning and validity

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~weeks, months, years — Reactive Bespoke

today → 2026 | 2026 | 2026

Support the planning & validity of applicant studies

Journal of Biomedical Informatics 119 (2021) 103822

Contents lists available at ScienceDirect

Journal of Biomedical Informatics

journal homepage: www.elsevier.com/locate/yjbin

Original Research

Clinical comparison between trial participants and potentially eligible patients using electronic health record data: A generalizability assessment method

James R. Rogers [a], George Hripcsak [a,b], Ying Kuen Cheung [c], Chunhua Weng [a,*]

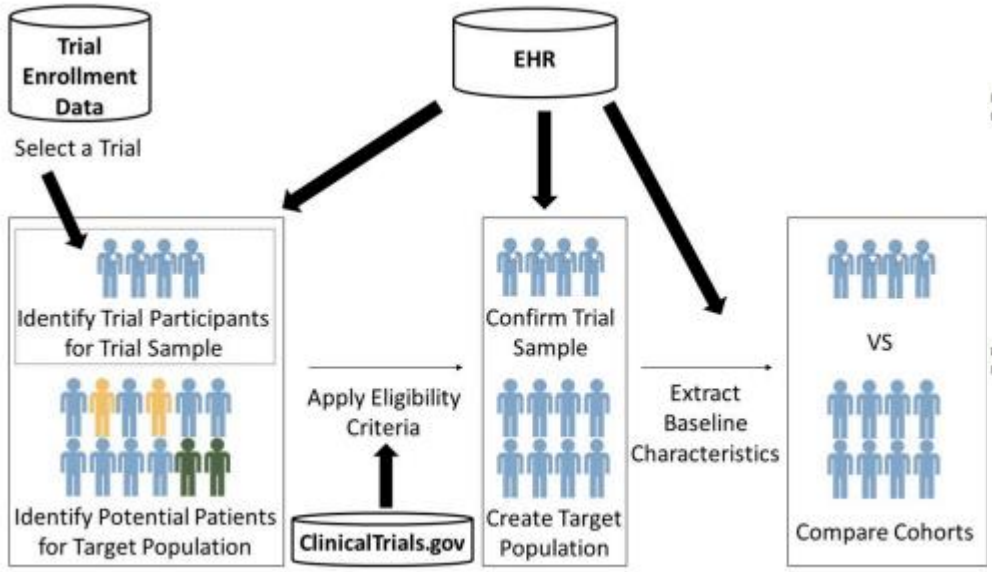
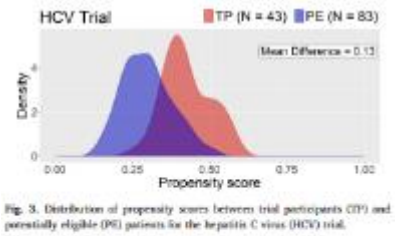
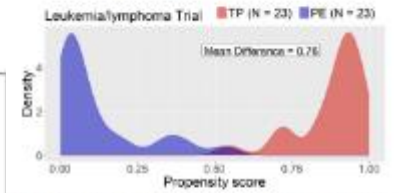
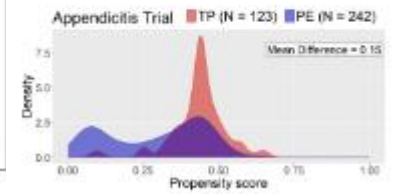


Fig. 1. Overview of study methodology.







Expanding the proactive use of real-world evidence for understanding clinical context

~seconds — Anticipatory

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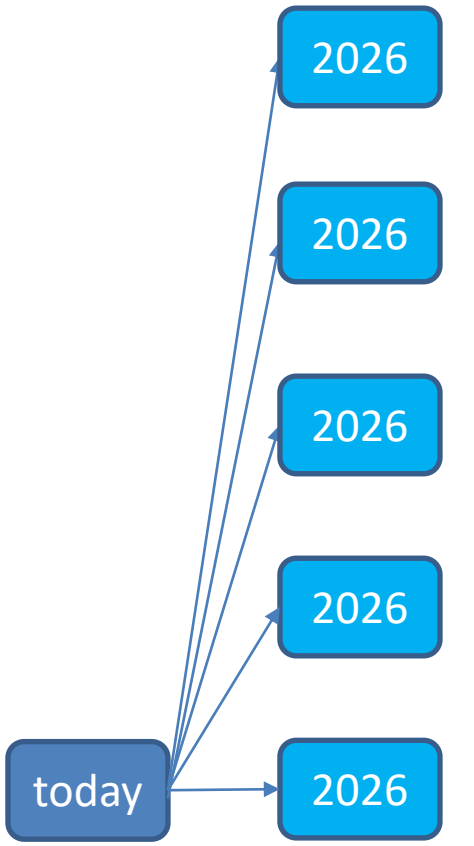
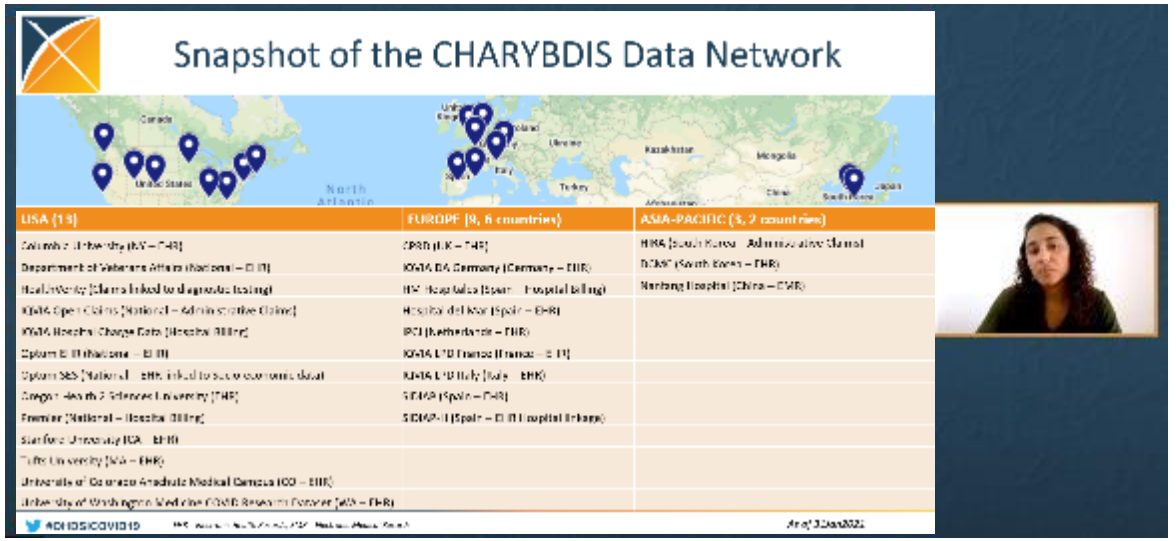
~hours — Responsive

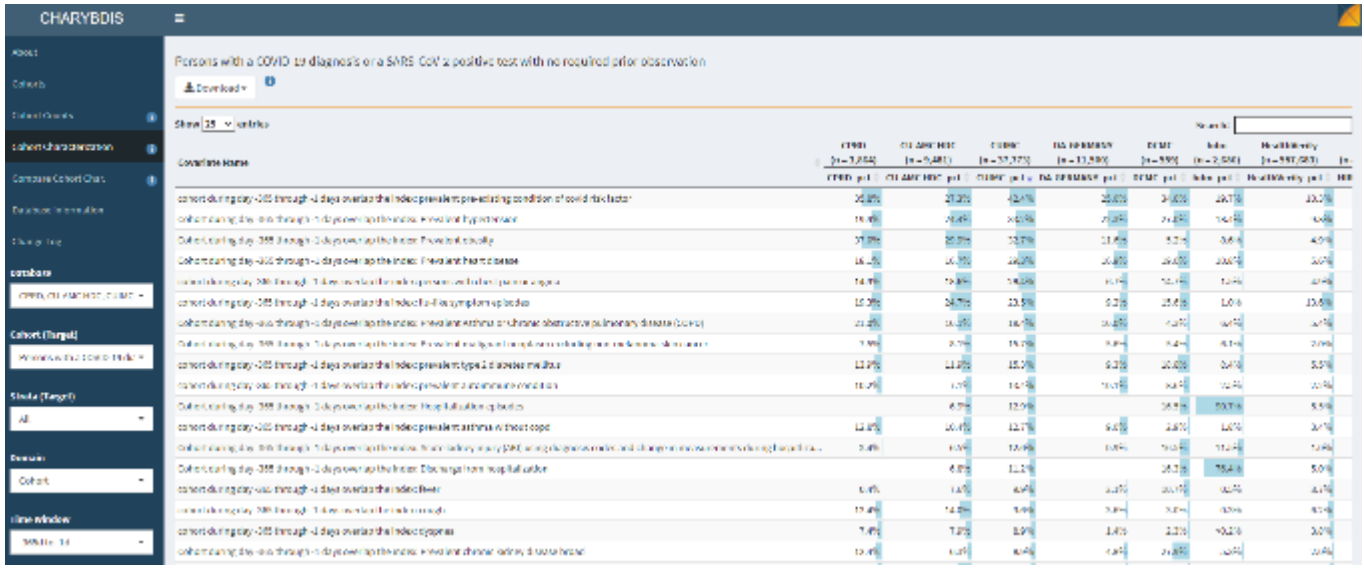
~days — Enabled

~weeks, months, years — Reactive Bespoke



Understand clinical context





https://data.ohdsi.org/Covid19CharacterizationCharybdis/

Expanding the proactive use of real-world evidence for understanding clinical context

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~hours — Responsive

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~weeks, months, years — Reactive Bespoke

today → 2026 | 2026 | 2026 | 2026 | 2026

Understand clinical context

thebmj

RESEARCH: SPECIAL PAPER

FAST TRACK

Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study

Xintong Li,[1] Anna Ostropolets,[2] Rupa Makadia,[3] Azza Shoaibi,[3] Gowtham Rao,[3] Anthony G Sena,[3,6] Eugenia Martinez-Hernandez,[4] Antonella Delmestri,[1] Katia Verhamme,[6,7] Peter R Rijnbeek,[6] Talita Duarte-Salles,[5] Marc A Suchard,[8,9] Patrick B Ryan,[2,3] George Hripcsak,[2] Daniel Prieto-Alhambra[1,6]

For numbered affiliations see end of the article.

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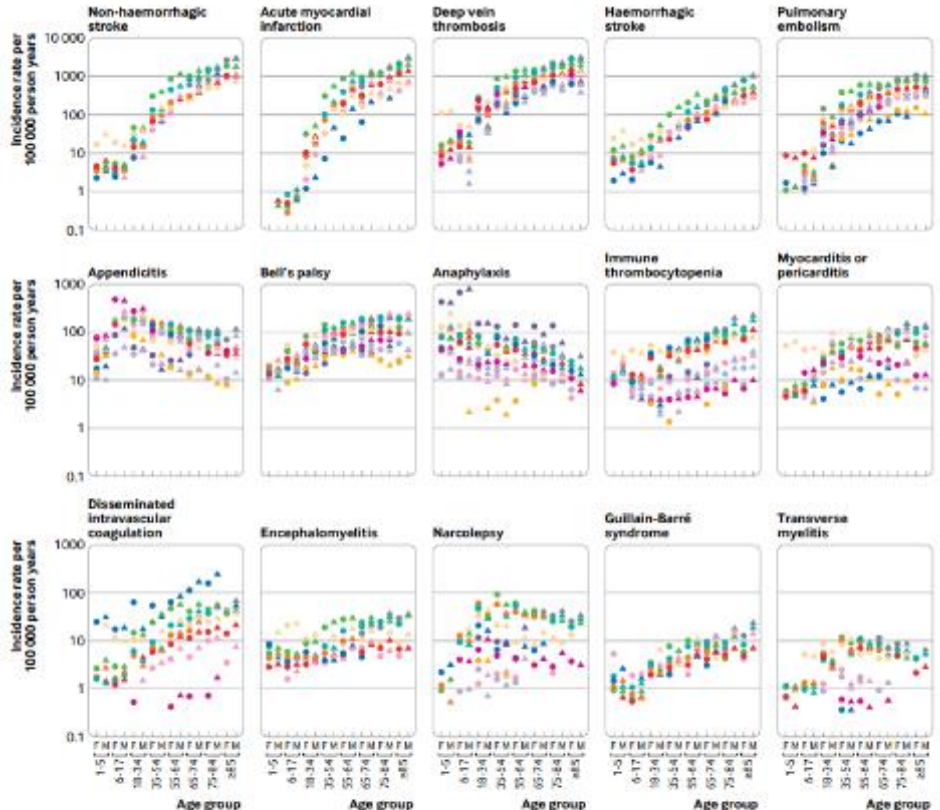
ORCID 0000-0002-3950-6346)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;373:n1435
http://dx.doi.org/10.1136/bmj.n1435

Accepted: 3 June 2021



WHAT IS ALREADY KNOW

Expanding the proactive use of real-world evidence to investigate associations and impact

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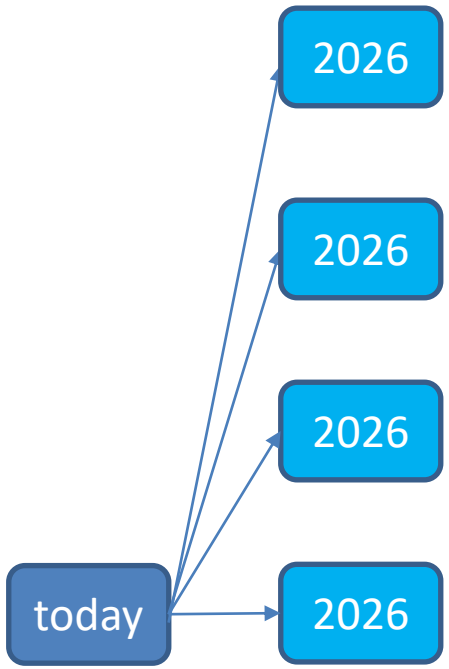


Investigate associations and impact

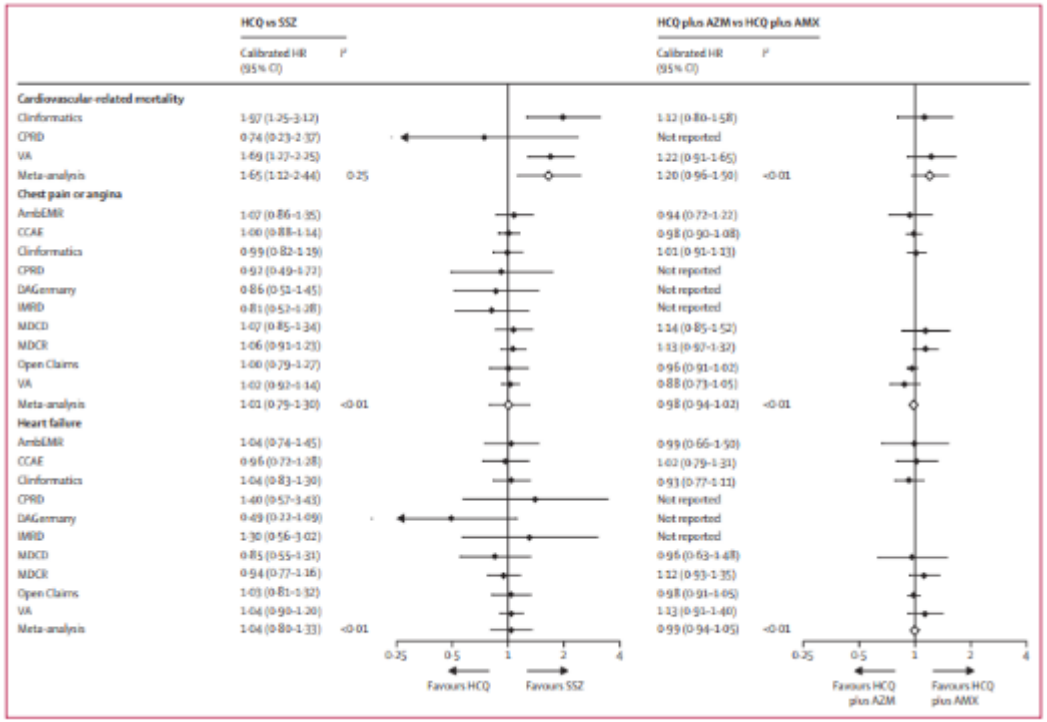
THE LANCET Rheumatology

Articles

Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study

Jennifer C E Lane*, James Weaver*, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F Abrahao, Heba Alghoul, Osaid Alser, Thamir M Alshammari, I Alexander Davydov, Scot Benjamin Skov Kaas-Ha Rupa Makadia, Andrea V Fredrik Nyberg, Anna Os Selva Muthu Kumaran S Carmen O Torre, David V Daniel Prieto-Alhambra,

oa



Expanding the proactive use of real-world evidence to investigate associations and impact

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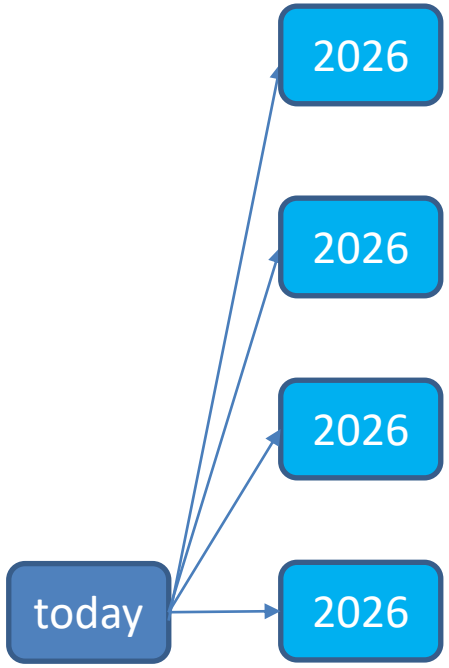


Investigate associations and impact

RHEUMATOLOGY

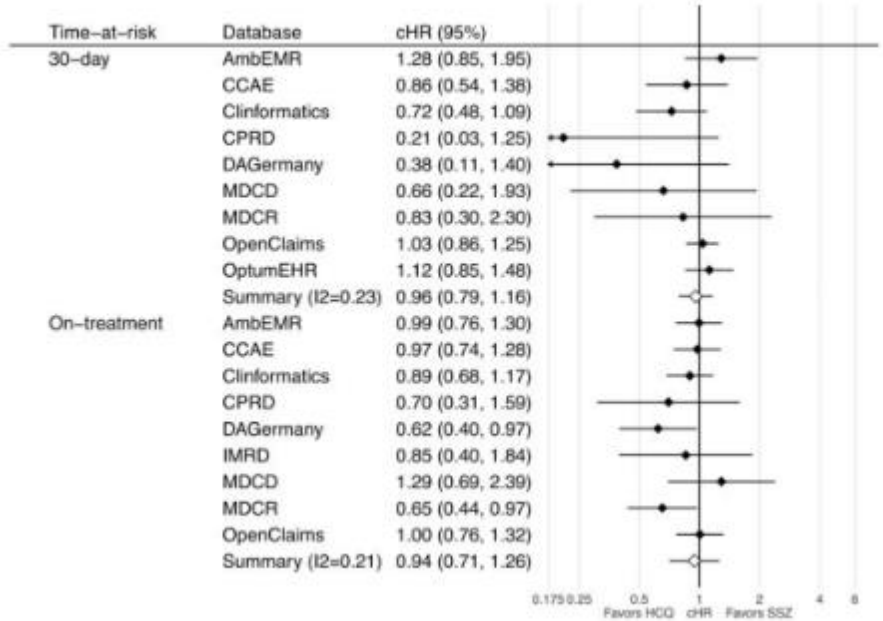
Rheumatology 2021;60:3222–3234
doi:10.1093/rheumatology/keaa771
Advance Access publication 25 December 2020

Original article

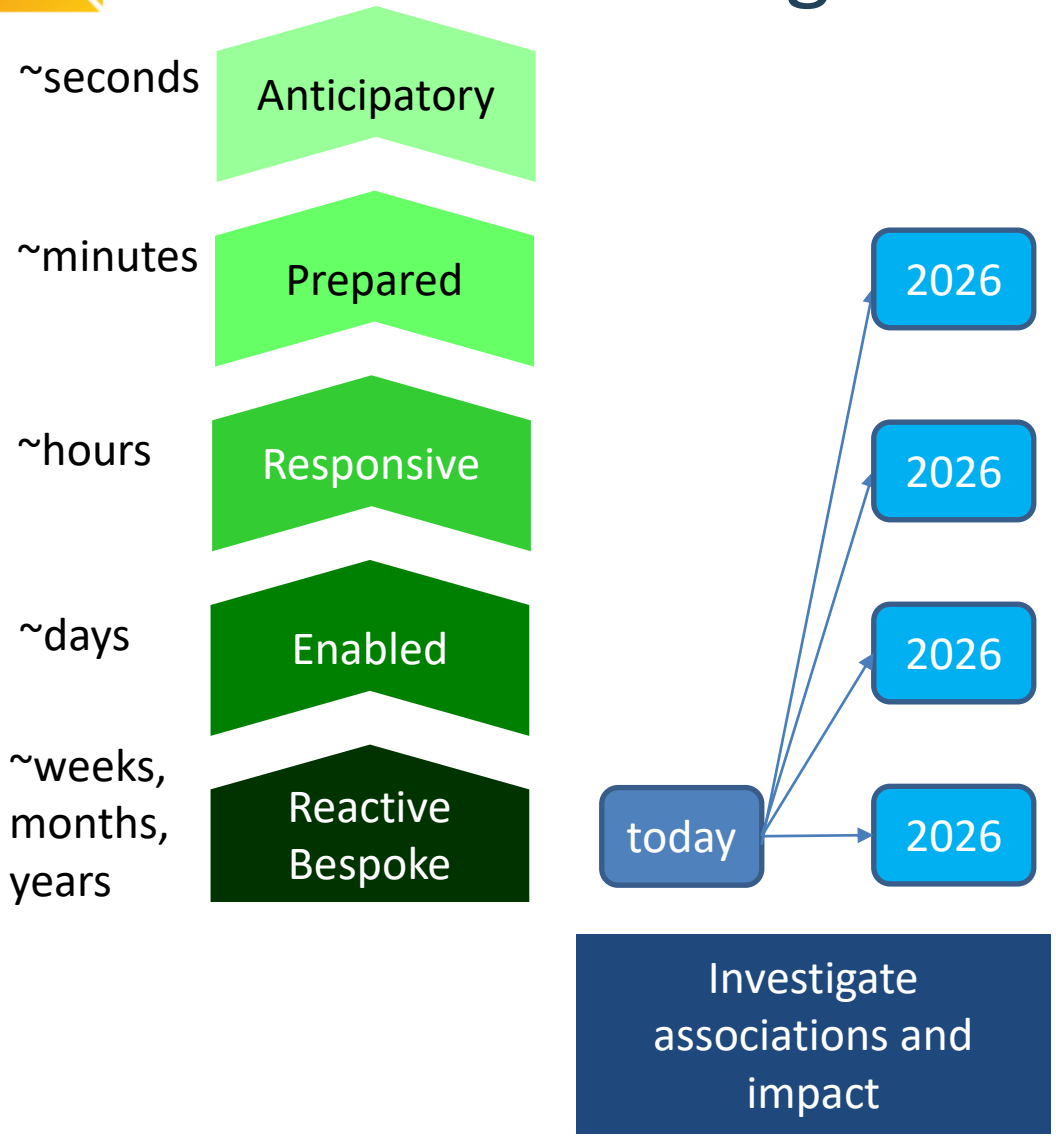
Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multinational network cohort study

Jennifer C. E. Lane [1,*], James Weaver[2,*], Kristin Kostka[3], Talita Duarte-Salles[4], Maria
Thamir M. Als
Juan M. Band
Jill Hardin[2], La
Benjamin Sko
Kristine E. Lyn
Henry Morgan
Fredrik Nyberg
Albert Prats-U
Anthony G. Se
Marc A. Sucha
Junqing Xie[1],
Patrick Ryan[2],
consortium

FIG. 1 Forest plot of the association between short- (top) and long-term (bottom) use of HCQ (*vs* SSZ) and risk of depression, by database and in the meta-analysis



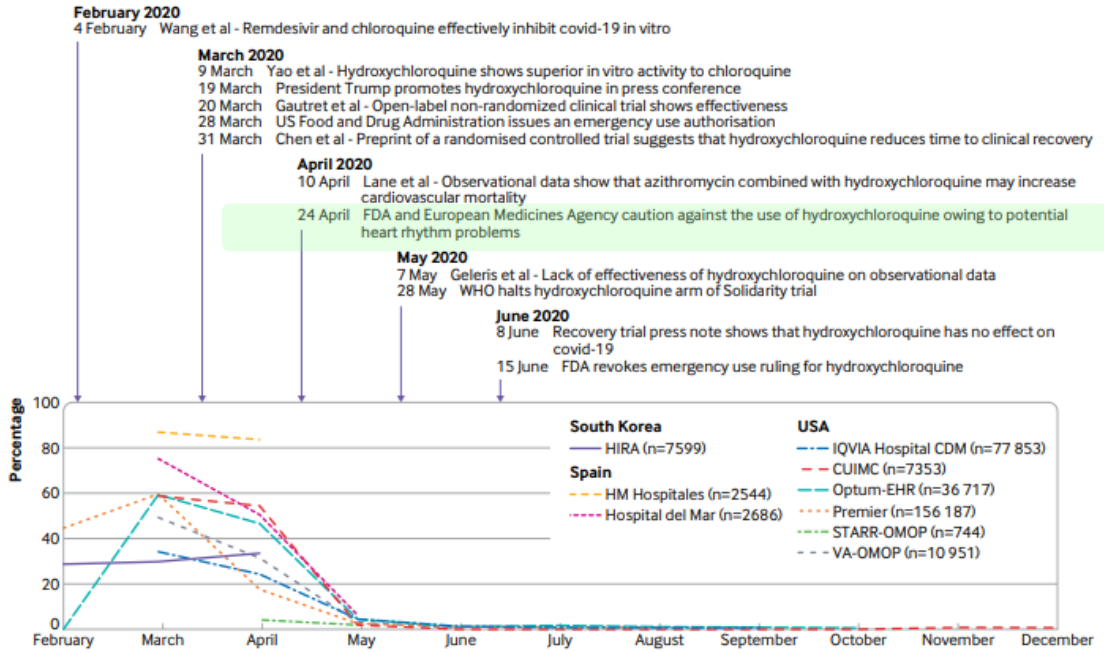
Expanding the proactive use of real-world evidence to investigate associations and impact



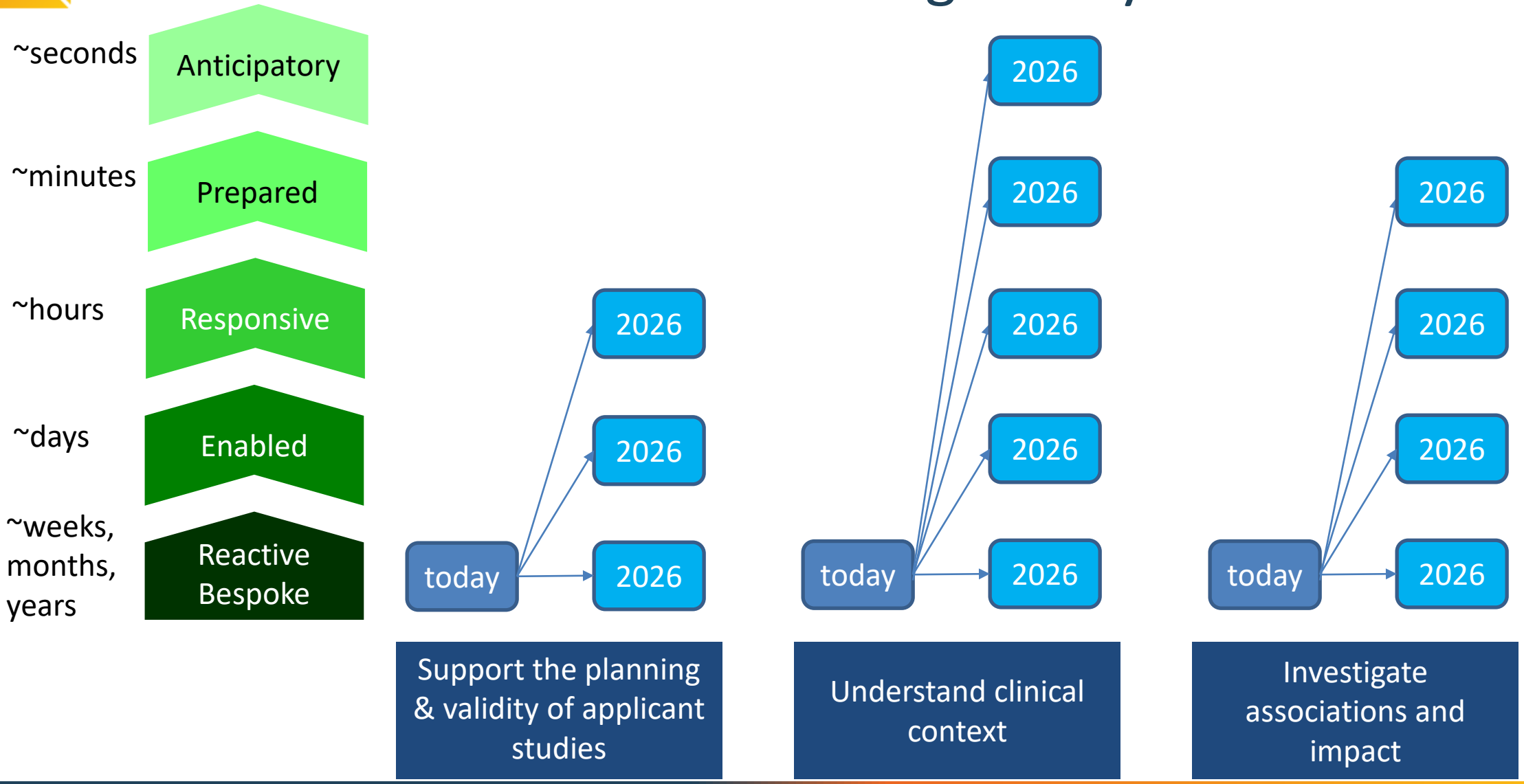
thebmj
RESEARCH
OPEN ACCESS
Check for updates

Use of repurposed and adjuvant drugs in hospital patients with covid-19: multinational network cohort study

Albert Prats-Uribe,[1] Anthony G Sena,[2,3] Lana Yin Hui Lai,[4] Waheed-Ul-Rahman Ahmed,[5,6] Heba Alghoul,[7] Osaid Alser,[8] Thamir M Alshammari,[9] Carlos Areia,[10] William Carter,[11] Paula Casajust,[12] Dalia Dawoud,[13,14] Asieh Golozar,[15,16] Jitendra Jonnagaddala,[17] Paras P Mehta,[18] Mengchun Gong,[19] Daniel R Morales,[20,21] Fredrik Nyberg,[22] Jose D Posada,[23] Martina Recalde,[24,25] Elena Roel,[24,25] Karishma Shah,[5] Nigam H Shah,[23] Lisa M Schilling,[11] Vignesh Subbian,[26] David Vizcaya,[27] Lin Zhang,[28,29] Ying Zhang,[19] Hong Zhu,[30] Li Liu,[30] Jaehyeong Cho,[31] Kristine E Lynch,[32] Michael E Matheny,[33,34] Seng Chan You,[35] Peter R Rijnbeek,[3] George Hripcsak,[36] Jennifer CE Lane,[5] Edward Burn,[1,24] Christian Reich,[37] Marc A Suchard,[38] Talita Duarte-Salles,[24] Kristin Kostka,[37,39] Patrick B Ryan,[2,40] Daniel Prieto-Alhambra[1]



A 5-year vision for expanding the proactive use of real-world evidence across regulatory use cases



Concluding thoughts

- Enabling use and establishing value of real-world evidence is a reasonable vision, which requires building trust across evidence generators and consumers
- People and processes need to be augmented with science, technology and engineering
- Community efforts today can enable a more proactive future tomorrow
  - Data network standardization and quality assessment
  - Design of standardized outputs for regulatory use cases
  - Standardized analytic tool development
  - Phenotype development and evaluation
- Open science systems that promote transparency and reproducibility can increase reliability and efficiency
- Regulatory use cases largely involve characterization analyses, have been demonstrated to be feasible, and are ready-to-scale