

Analysis and interpretation of realworld 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 **PERSPECTIVE** & Therapeutics

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

Peter Arlett^{1,*}, Jesper Kjær², Karl Broich³ and Emer Cooke¹

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." 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 multiannual work plan was published in August 2021.° 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.

PERSPECTIVES

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 sources8 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," 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

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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

⁴European Medicines Agency, Amsterdam, Netherlands; ²Danish Medicines Agency, Copenhagen, Denmark; ³BfArM, Bonn, Germany. *Correspondence: Peter Arlett (Peter.Arlett@ema.europa.eu)



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PERSPECTIVES

"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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... it's a global responsibility for all stakeholders to support



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

... it's a global responsibility for all stakeholders to support



OHDSI community We're all in this journey together...

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

OHDSI Collaborators

• 2,367 collaborators

- 74 countries
- 21 time zones
- 6 continents

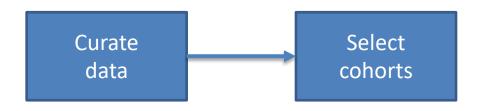
OHDSI Data Network

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



Curate data

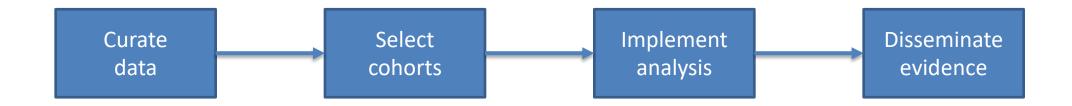






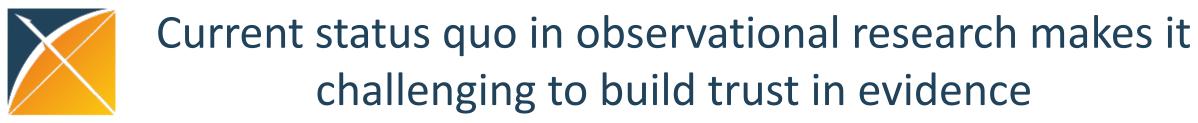


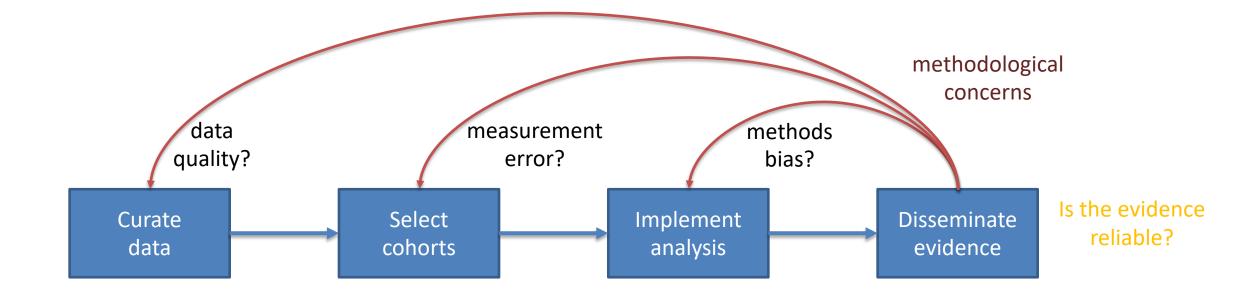










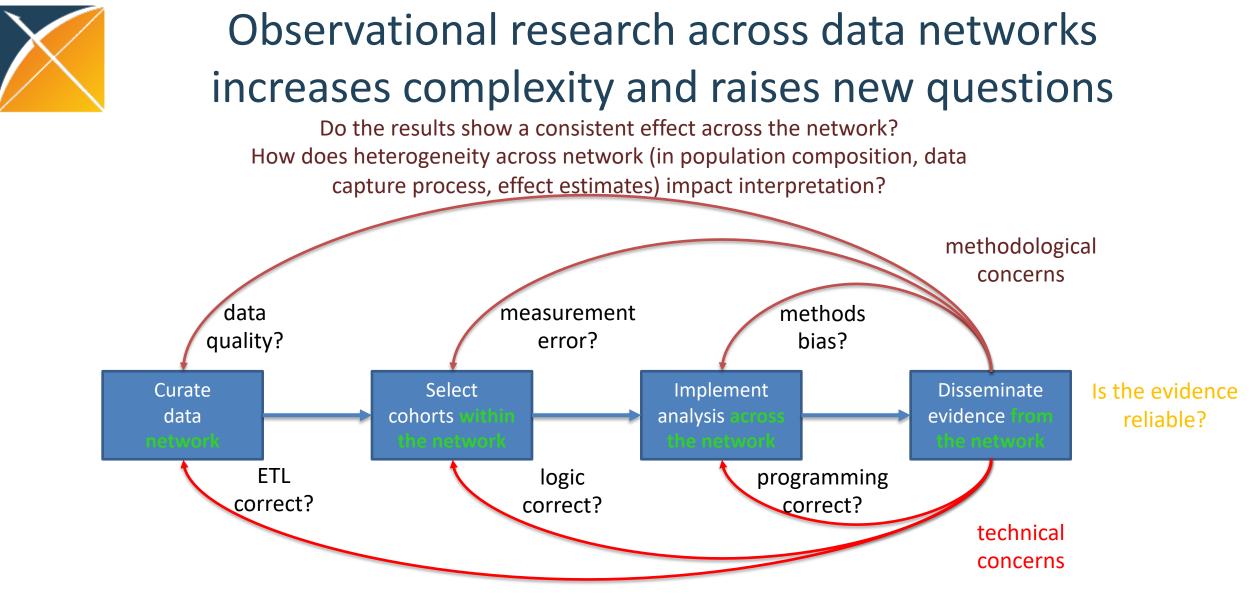


Current status quo in observational research makes it challenging to build trust in evidence Does the study provide an unbiased effect estimate? Are the findings generalizable to the population of interest? methodological concerns data measurement methods quality? error? bias? Is the evidence Select Implement Curate Disseminate reliable? data cohorts analysis evidence

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Can the study be fully reproduced? Does the analysis actually do what the protocol said it would do?



Can the study be fully reproduced across the network?



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



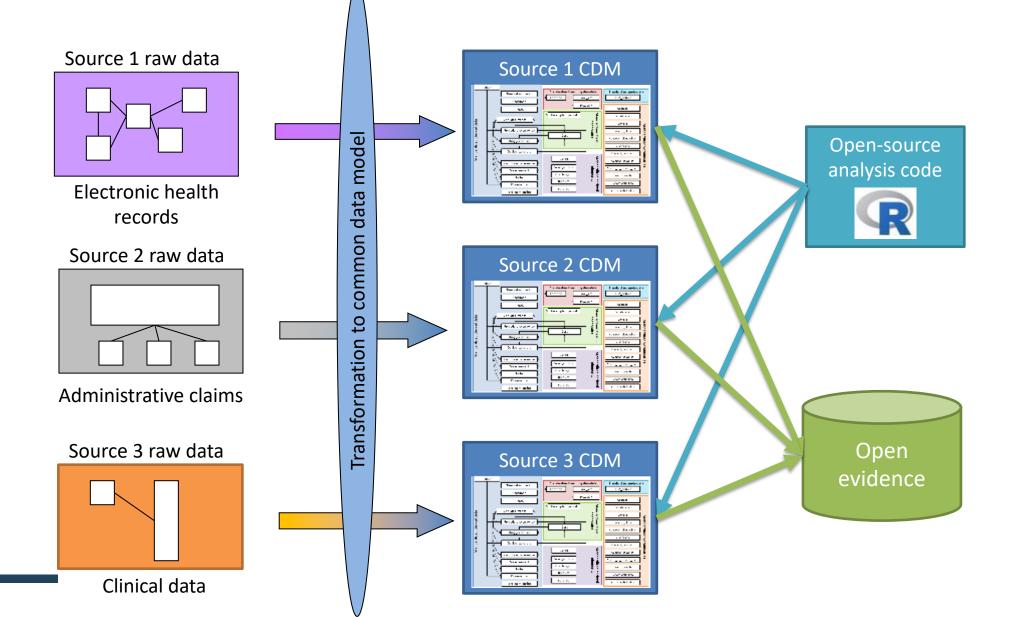
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Calibrated	Similar (controls)	Identical	Identical	Identical	=	Statistically consistent
A system for real-world evidence generation based on consistent application of standardized						

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

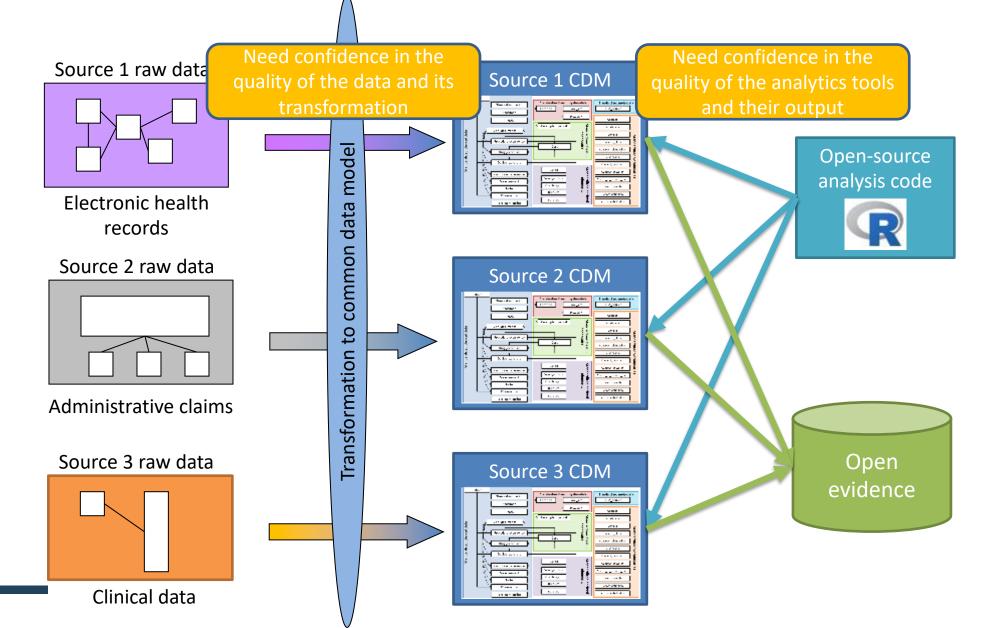


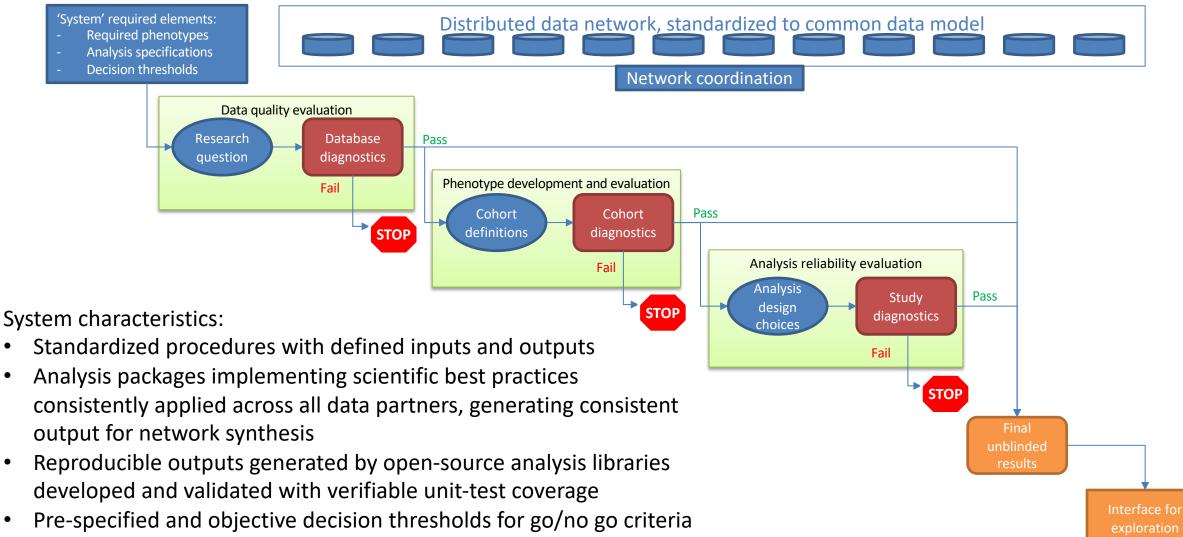
Common data model can enable standardized analytics across a distributed data network



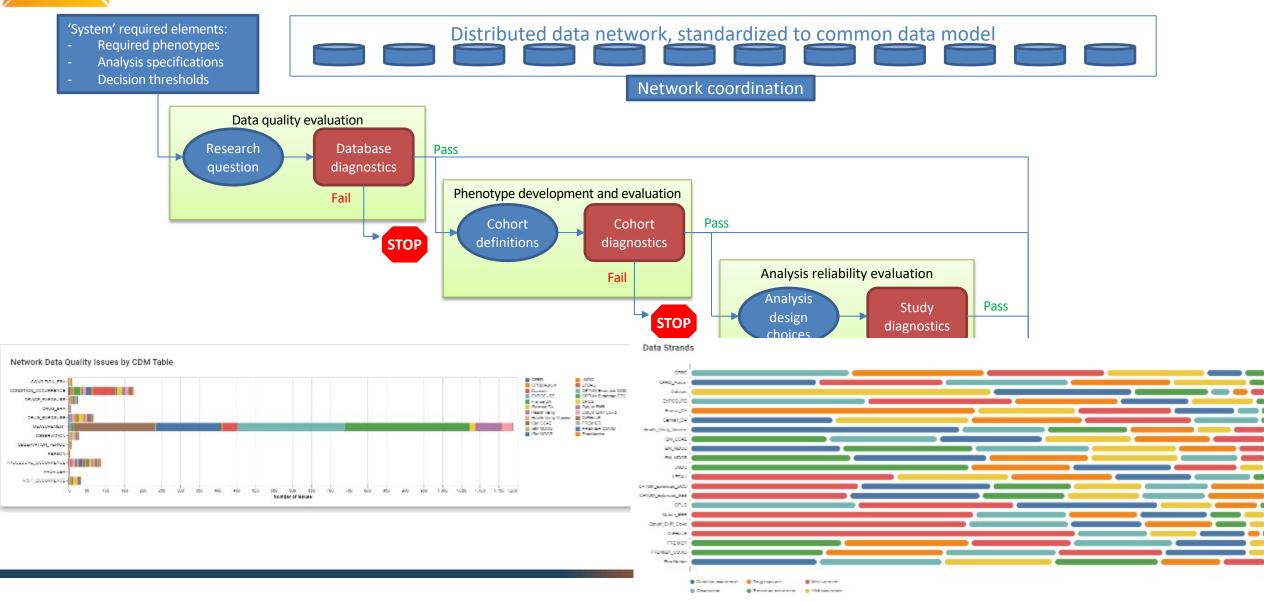


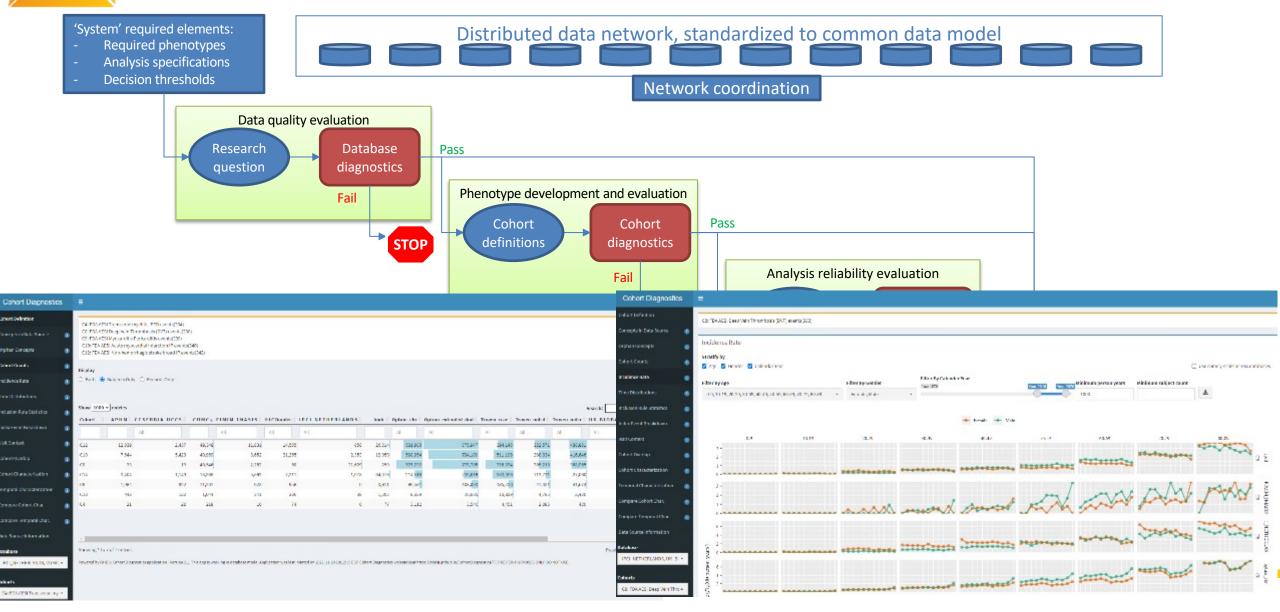
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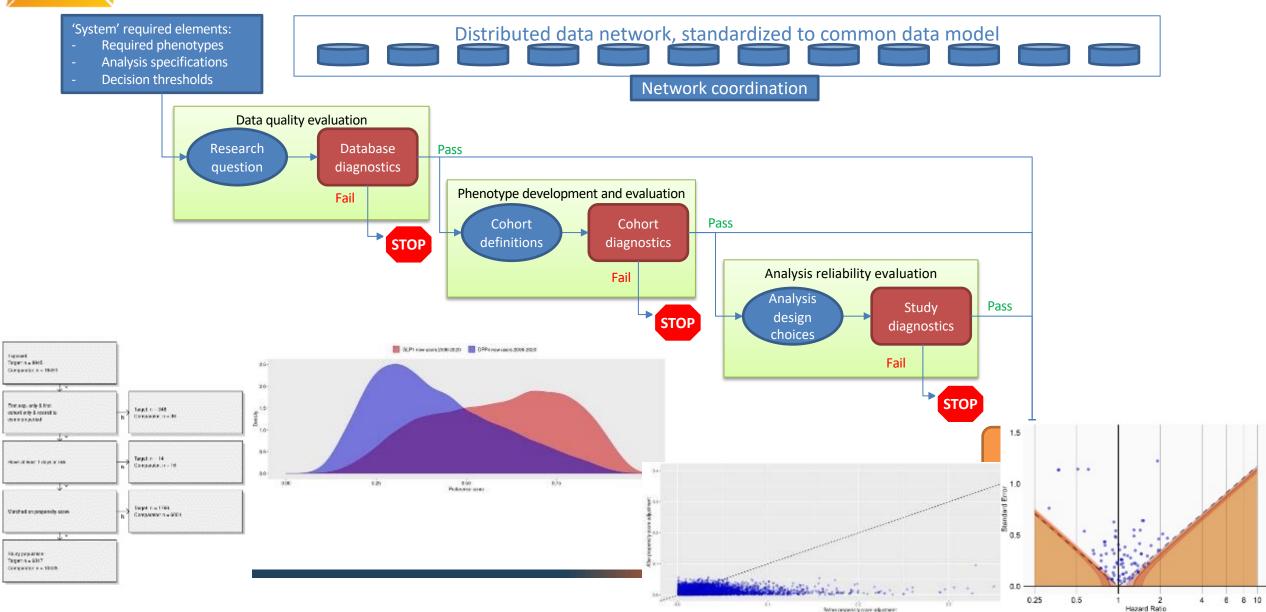


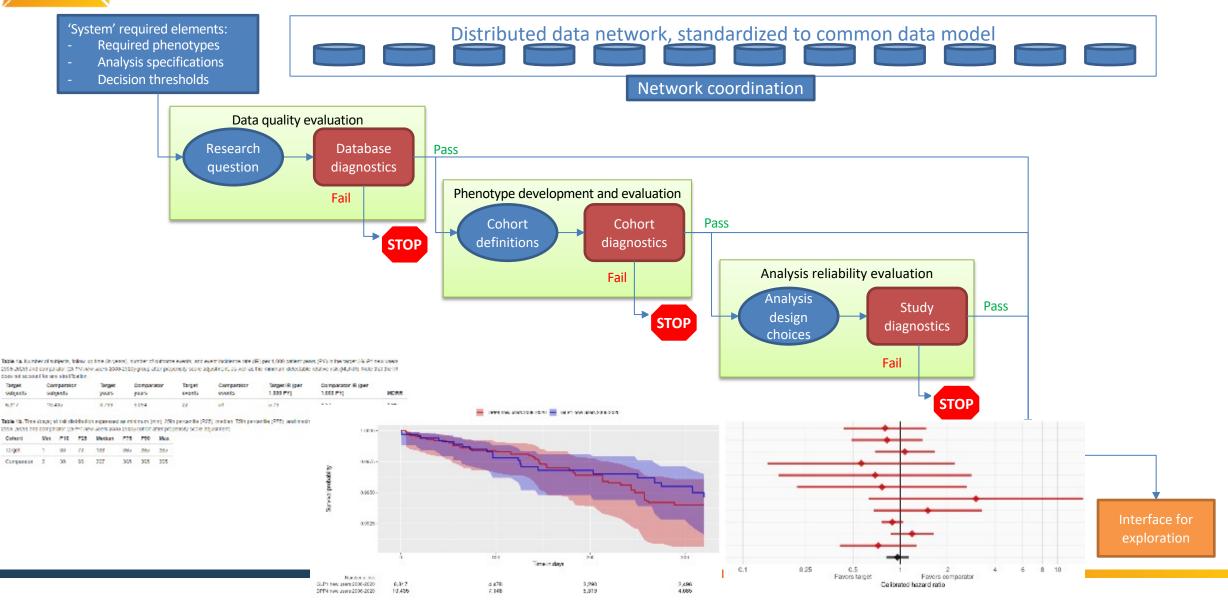


Measurable operating characteristics of system performance



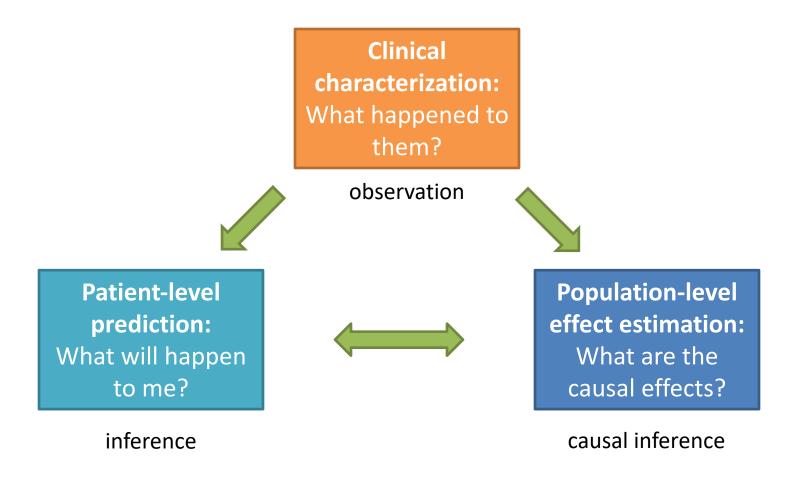








Complementary types of evidence to generate from real-world data







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



Support the planning & validity of applicant studies

Design and feasibility of planned studies

Representativeness and validity of Completed studies

Understand clinical context

Disease epidemiology

Clinical management & drug utilisation

Investigate associations and impact

Effectiveness and safety studies

Impact of regulatory actions

Clinical characterization: What happened to them?

Population-level effect estimation: What are the causal effects?

Patient-level prediction: What will happen to me?



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Patient-level prediction: What will happen to me? Questions that can be informed with real world evidence:

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?

Is the outcome causally related to exposure to treatment? How does the risk compare with alternative treatments?



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Which risks can be actionably predicted with available data? Which patients are at highest risk of adverse events?

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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







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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Level of proactivity in delivering real-world evidence



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



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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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Anticipatory

Prepared

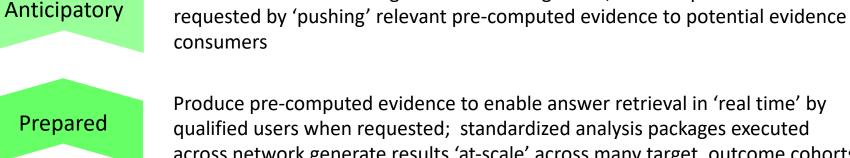
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Service bespoke project requests by convening team to align on problem statement, author protocol/analysis plan documents, implement statistical programming code to custom specification, execute analysis across databases, iteratively review results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

Standardized dissemination

Standardized analysis configurations

Standardized analysis tools

Standardized data, network execution

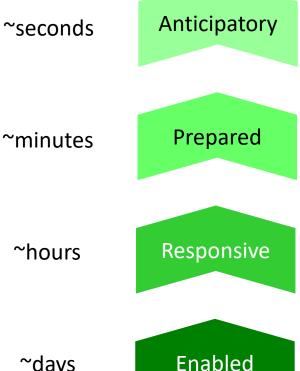
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Time-to-evidence



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across network generate results 'at-scale' across many target, outcome cohorts

~days



consumers

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 dissemination

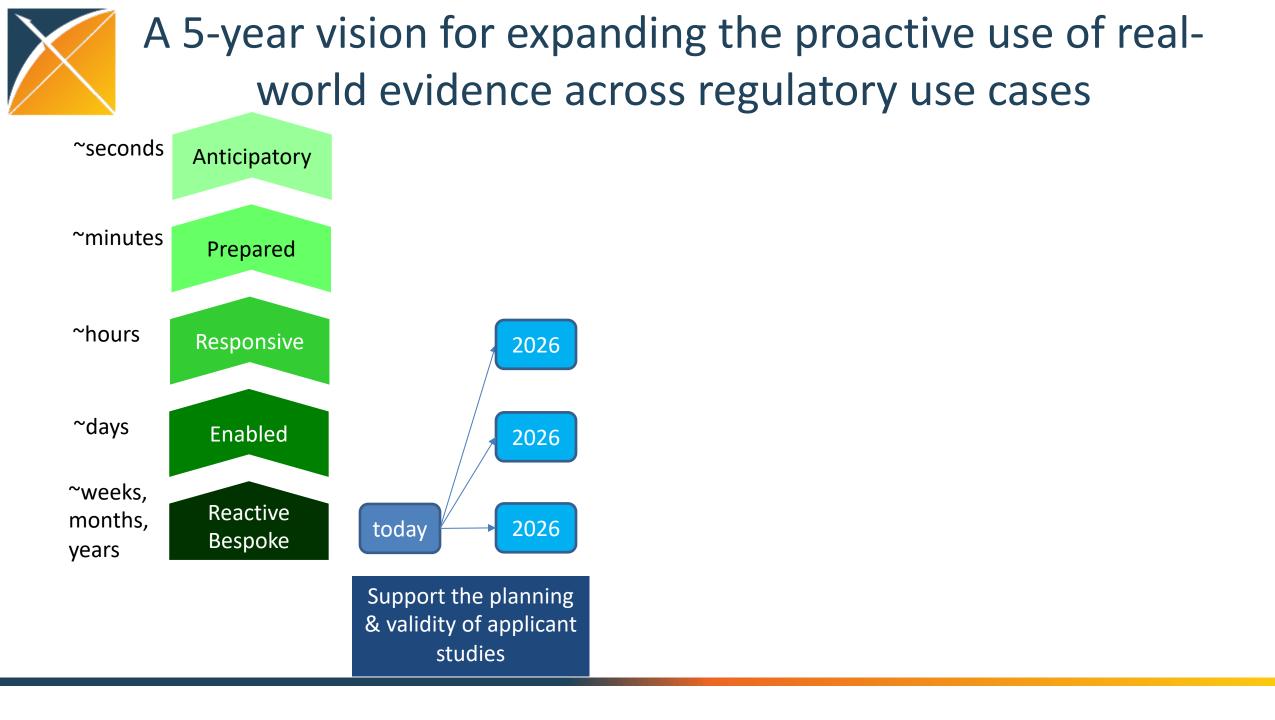
Standardized analysis configurations

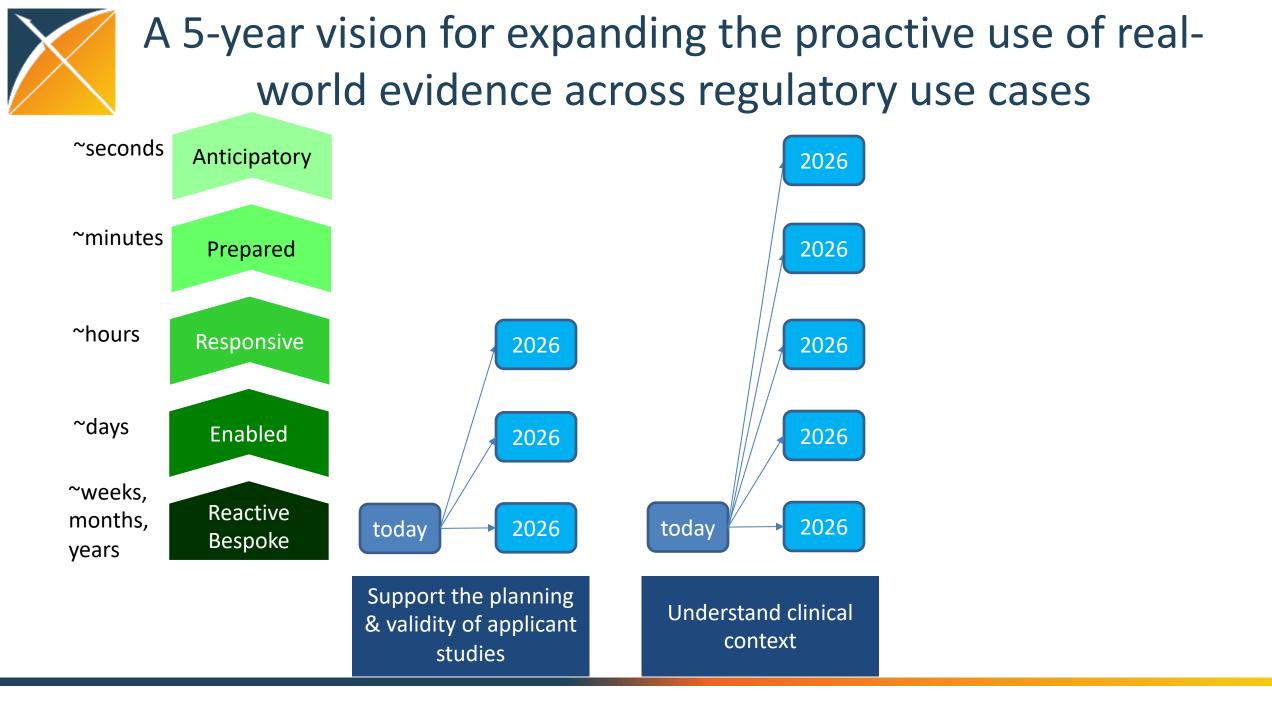
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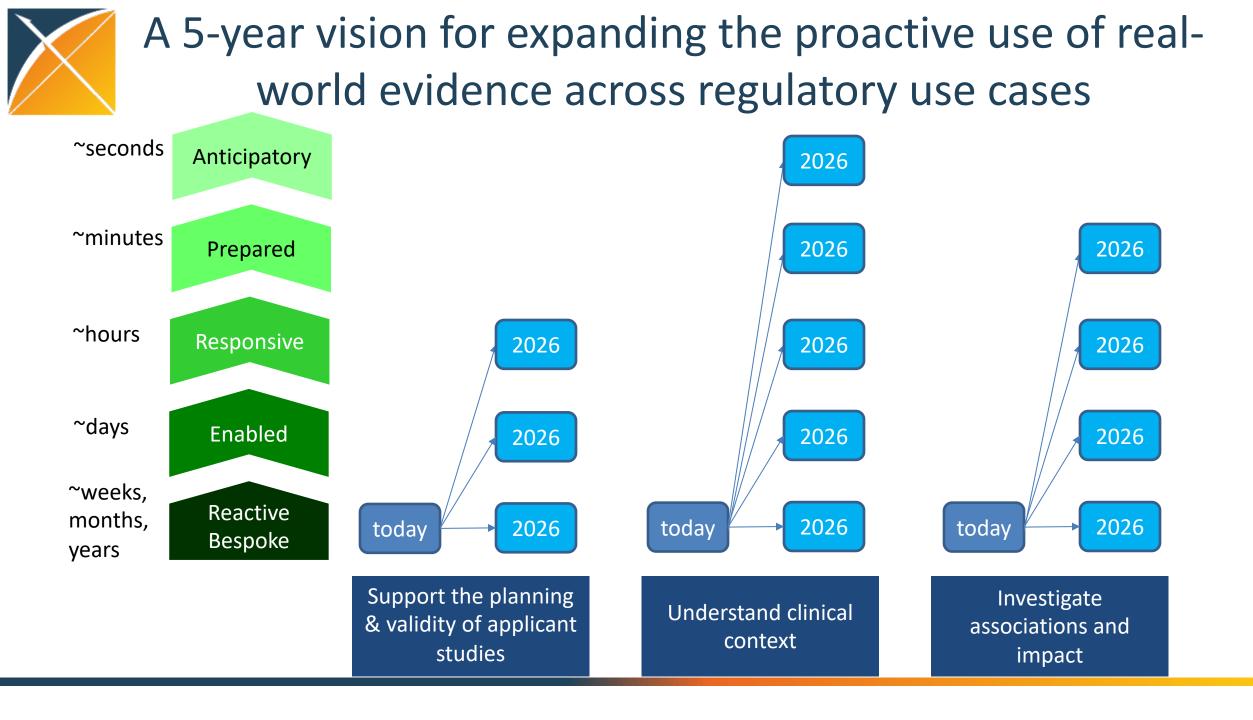
Standardized data, network execution

~weeks, months, years

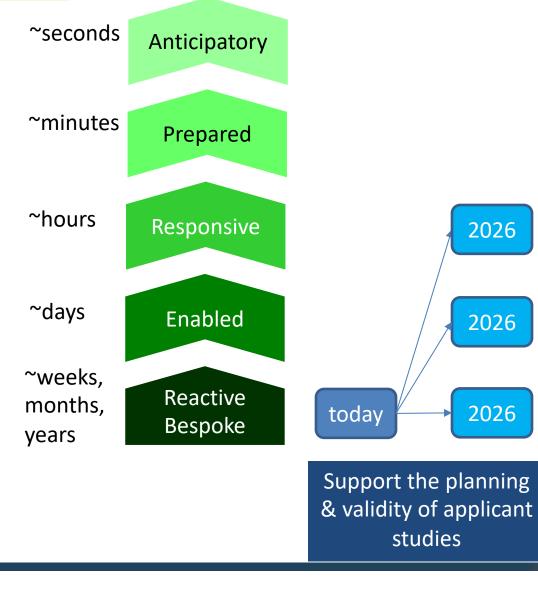








Expanding the proactive use of real-world evidence for study planning and validity



Journal of the American Medical Informatics Association, 28(1), 2021, 144–154

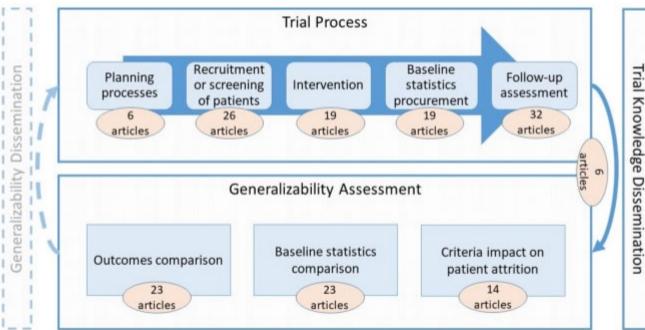
doi: 10.1093/jamia/ocaa224 Advance Access Publication Date: 4 November 2020 Review



Review

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

James R. Rogers 0,¹ Junghwan Lee,¹ Ziheng Zhou,² Ying Kuen Cheung,³ George Hripcsak,^{1,4} and Chunhua Weng¹



Trial Knowledge Dissemination

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

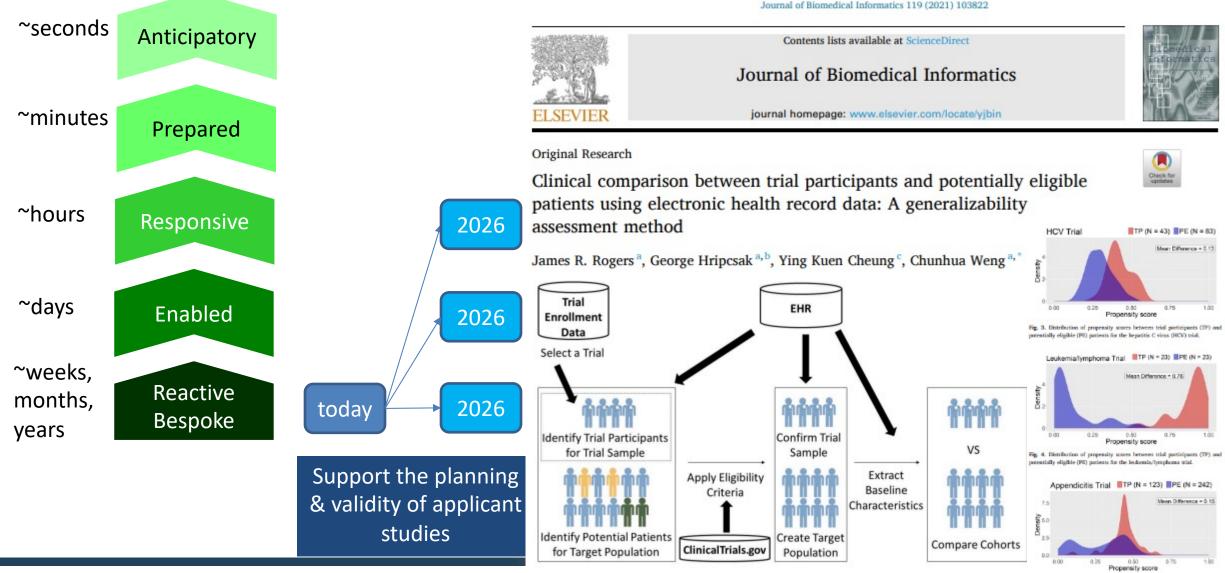
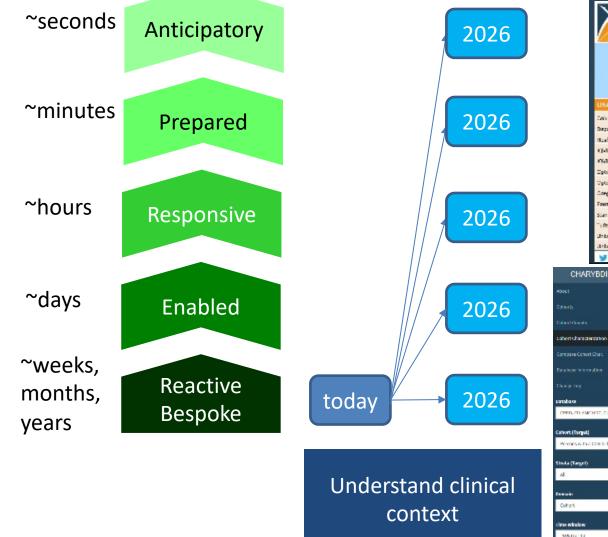


Fig. 1. Overview of study methodology.

Fig. 5. Distribution of propensity scores between trial participants (TP) and potentially eligible (PG) parients for the appendicitis trial.

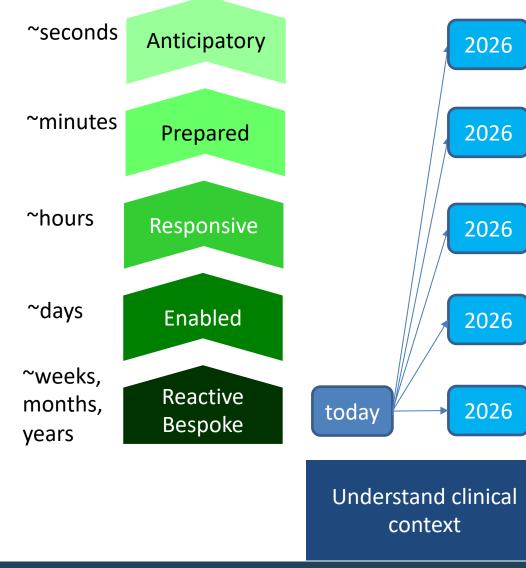
Expanding the proactive use of real-world evidence for understanding clinical context

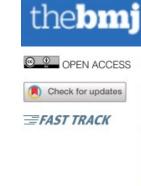


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https://data.ohdsi.org/Covid19CharacterizationCharybdis/

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



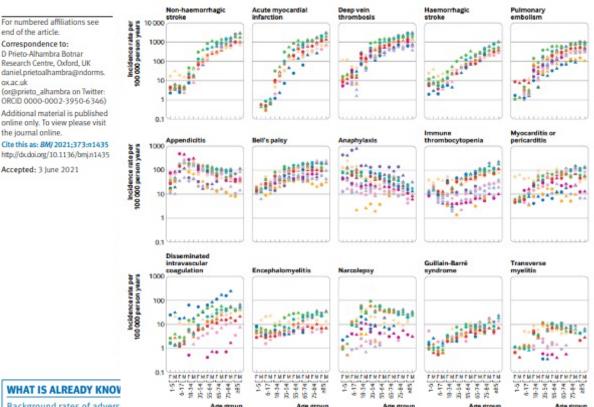


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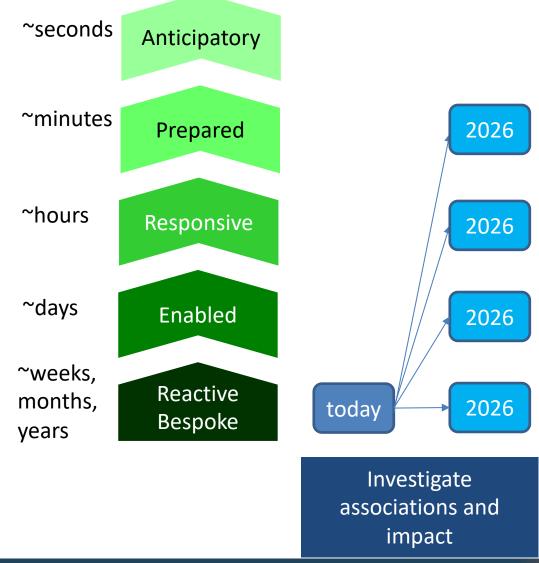
Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries:

RESEARCH: SPECIAL PAPER

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}



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



THE LANCET Rheumatology

Articles

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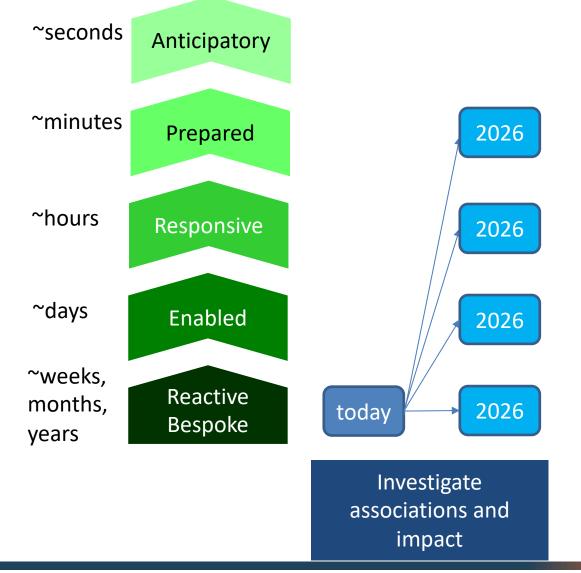
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Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study

Jennifer C E Lane*, James Weaver*, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F Abrahao, Heba Alghoul, Osaid Alser,

hamir M Alshammari, I		HCQ vs SSZ					HCQ plus AZM vs H	ICQ plus AMX			
lexander Davydov, Scot enjamin Skov Kaas-Hai		Calibrated HR (95% CI)	P				Calibrated HR (95% CI)	٢			
upa Makadia, Andrea V	Cardiovascular-related mortality									· · · · ·	
redrik Nyberg, Anna Os	Clinformatics	1497 (1-25-3-12)				-	1.12(0.80-1.58)		-	+	
	CPRD	0.74 (0.23-2.37)		· · ·			Not reported				
elva Muthu Kumaran S	VA	1-69 (1-27-2-25)					122 (0 91-1-65)			++-	
armen O Torre, David Vi	Meta-analysis	1-65 (112-2-44)	0.25				120(0.96-1.50)	-0-01		+	
aniel Prieto-Alhambra.	Chest pain or angina										
umer Pheto-Amumora,	AmbEMR	147(086-135)			-		0.94 (0.72-1.22)			+	
	CCAE	1-00 (0-88-1-14)			+		0.98 (0.90-1.08)			+	
	Clinformatics	0.99(0.82-1.19)			+		101(091-113)			+	
	CPRD	0.92 (0.49-872)			•		Not reported				
	DAGenmany	0-86 (0-51-1-45)			+		Not reported			1	
	IMRD	0-81(0-52-1-38)			+		Not reported			1	
	MDCD	147(085-134)			+		114 (0-85-152)		-	+-	
	MDCR	146 (0.91-1/23)					143 (0-97-1-32)			+	
	Open Claims	1-00 (0-79-1-27)			+		0.96 (0.91-1.02)			+	
	VM	1-02 (0-92-0-14)			+		088(073-145)			+	
	Meta-analysis	1-01 (0-79-1-30)	<0.01	1.0	÷		0.98 (0.94-1.02)	<0.01		4	
	Heart failure										
	AmbEMR	1-04 (0-74-1-85)		-	→		0-99 (0-66-1-50)			÷ .	
	CCAE	0.96 (0.72-1.28)			+		142(079-1-31)		-	+	
	Clinformatics	104(083-130)		1.2	+		093(077-111)			+	
	CPRD	1-40 (0-57-3-43)			+ •	_	Not reported				
	DAGenmany	0-49 (0-22-1-09)		· · · ·	+		Not reported			1	
	IMRD	1-30 (0-56-3-02)			+ •	_	Not reported				
	MDCD	0-85 (055-1-31)		_	+		095(053-148)			÷	
	MDCR	0.94(0.77-1.16)		-	+		112(093-135)			+-	
	Open Claims	1403 (0-81-132)			+		0.98 (0.91-1-05)			+	
	VA	1-04 (0-90-1-20)			+		113(091-140)			+	
	Meta-analysis	1-04 (0-80-1-33)	<0.01	-	-		099(094-105)	<0.01		¢	
			0.3	5 0.5	1 2	4		0.25	0.5	1 2	
				+					-	-	
				Favours HCQ	Favours SSZ				Favours HCQ plus AZM	Favours H plus AMOX	

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



RHEUMATOLOGY

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

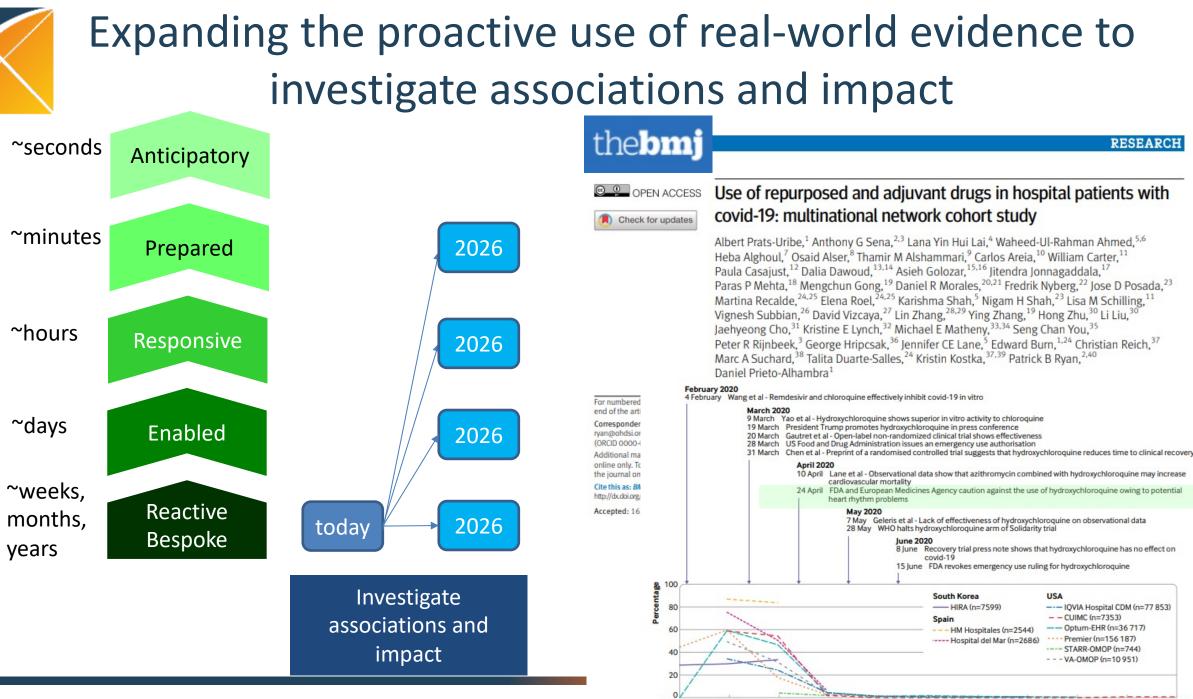
Original article

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

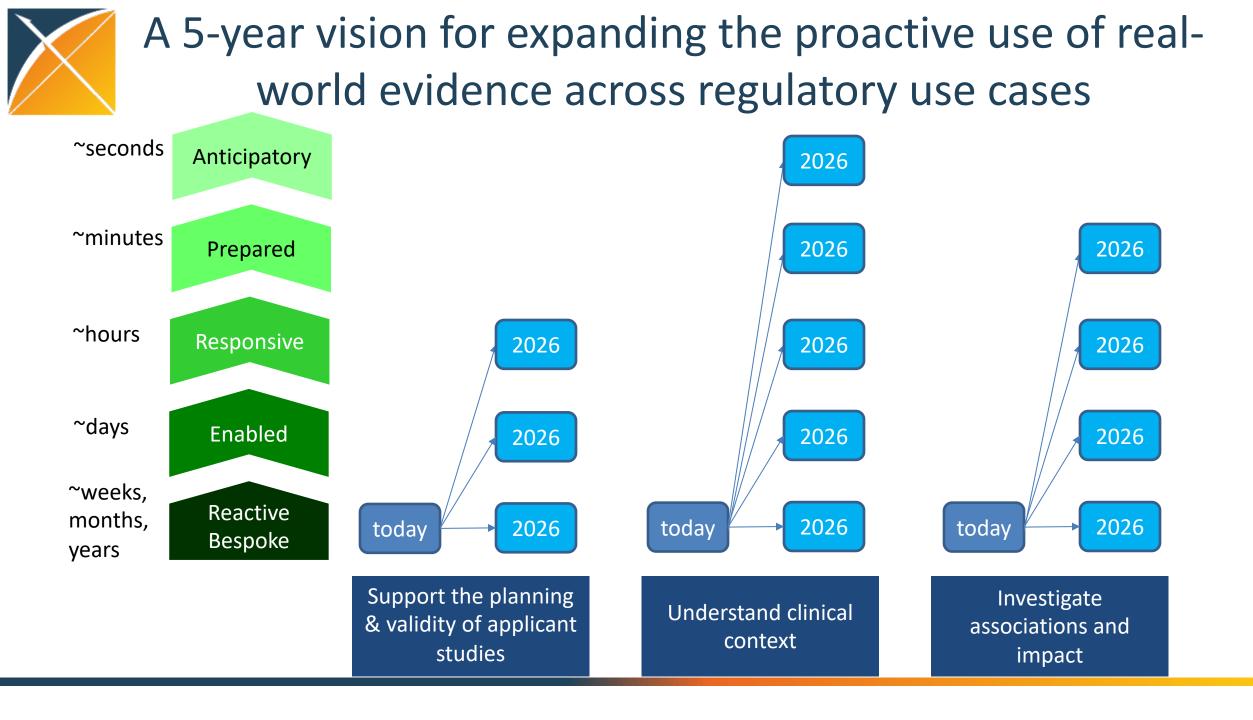
Jennifer C. E. Lane (1,*, James Weaver^{2,*}, Kristin Kostka³, Talita Duarte-

Salles⁴, Maria Fig. 1 Forest plot of the association between short- (top) and long-term (bottom) use of HCQ (vs SSZ) and risk of de-Thamir M. Als pression, by database and in the meta-analysis

uan M. Band	Time-at-risk	Database	cHR (95%)	
ill Hardin ² , La	30-day	AmbEMR	1.28 (0.85, 1.95)	
Benjamin Sko		CCAE	0.86 (0.54, 1.38)	
		Clinformatics	0.72 (0.48, 1.09)	
ristine E. Lyr		CPRD	0.21 (0.03, 1.25) ++-	
enry Morgan		DAGermany	0.38 (0.11, 1.40)	• •
		MDCD	0.66 (0.22, 1.93) -	
edrik Nyber		MDCR	0.83 (0.30, 2.30)	
bert Prats-U		OpenClaims	1.03 (0.86, 1.25)	+
thony G. Se		OptumEHR	1.12 (0.85, 1.48)	-+
		Summary (12=0.23)	0.96 (0.79, 1.16)	-4-
arc A. Sucha	On-treatment	AmbEMR	0.99 (0.76, 1.30)	-
nging Xie ¹ ,		CCAE	0.97 (0.74, 1.28)	-
		Clinformatics	0.89 (0.68, 1.17)	-+-
trick Ryan ²		CPRD	0.70 (0.31, 1.59)	
consortium		DAGermany	0.62 (0.40, 0.97)	
		IMRD	0.85 (0.40, 1.84)	
		MDCD	1.29 (0.69, 2.39)	
		MDCR	0.65 (0.44, 0.97)	
		OpenClaims	1.00 (0.76, 1.32)	-
		Summary (I2=0.21)	0.94 (0.71, 1.26)	



February March April May June July August September October November December





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