



Applications of Real World Data and Real World Evidence in Drug Discovery and Development

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Session Outline

- Introductions, Outline, Learning Objectives (5 min)
- What are Real World Data (RWD) and what is its use in Pharma? (10 min)
- Use of RWD in Early Research/New Target Discovery (30 min)
- RWD Development and Use in the Drug Approval Process (30 min, break – 10 min)
- Application of RWE for Safety and Late Phase Lifecycle Management (30 min)
- Breakout groups for Deeper Dives: (45 min)
 - › 1) New Target Discovery
 - › 2) Regulatory Submission of a Synthetic Control Arm
 - › 3) Characterizing Real World Effectiveness Post-Authorization
- Wrap up (10 min)

Learning Objectives

- Defining Real World Data (RWD) and Real World Evidence
- Describing the utility of RWD for pharmaceutical and biotech companies
- Detailing the use of RWD in early research/target discovery
- Demonstrating development and application of RWD in regulatory submissions
- Describing the use of RWD to inform pharmacovigilance, market access, and commercial strategies





Poll 1



Poll 2

What is Real World Evidence & Real World Data and Where is it Used in Pharma?

Real World Data and Real World Evidence

What is Real World Data (RWD)?

RWD is an overarching term for data on the effects of health interventions (such as benefits, risks or resource use) that are not collected in the context of conventional randomized controlled trials (RCTs). Instead, RWD is collected both prospectively and retrospectively from observations of routine clinical practice. It may include clinical and economic outcomes, patient-reported outcomes and health-related quality of life.

What is Real World Evidence (RWE)?

Real-world evidence (RWE) is the evidence derived from the analysis and/or synthesis of real-world data (RWD).



The FDA Guidance on the Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics: Guidance for Industry

Real World Data are data relating to patient health status and/or the delivery of health care that are routinely collected from a variety of sources.

- Data derived from electronic health records (EHRs)
- Medical claims and billing data
- Data from product and disease registries
- Patient-generated data, including in-home use and/or other decentralized settings
- Data gathered from other sources that can inform on health status, such as mobile devices

Real World Evidence is the clinical evidence regarding the usage and potential benefits, or risks of a medical product derived from analysis of RWD.

- RWE can be generated, for example, by collecting information about effectiveness or safety outcomes from an RWD source in randomized clinical trials or in observational studies.



Primary Use and Secondary Use

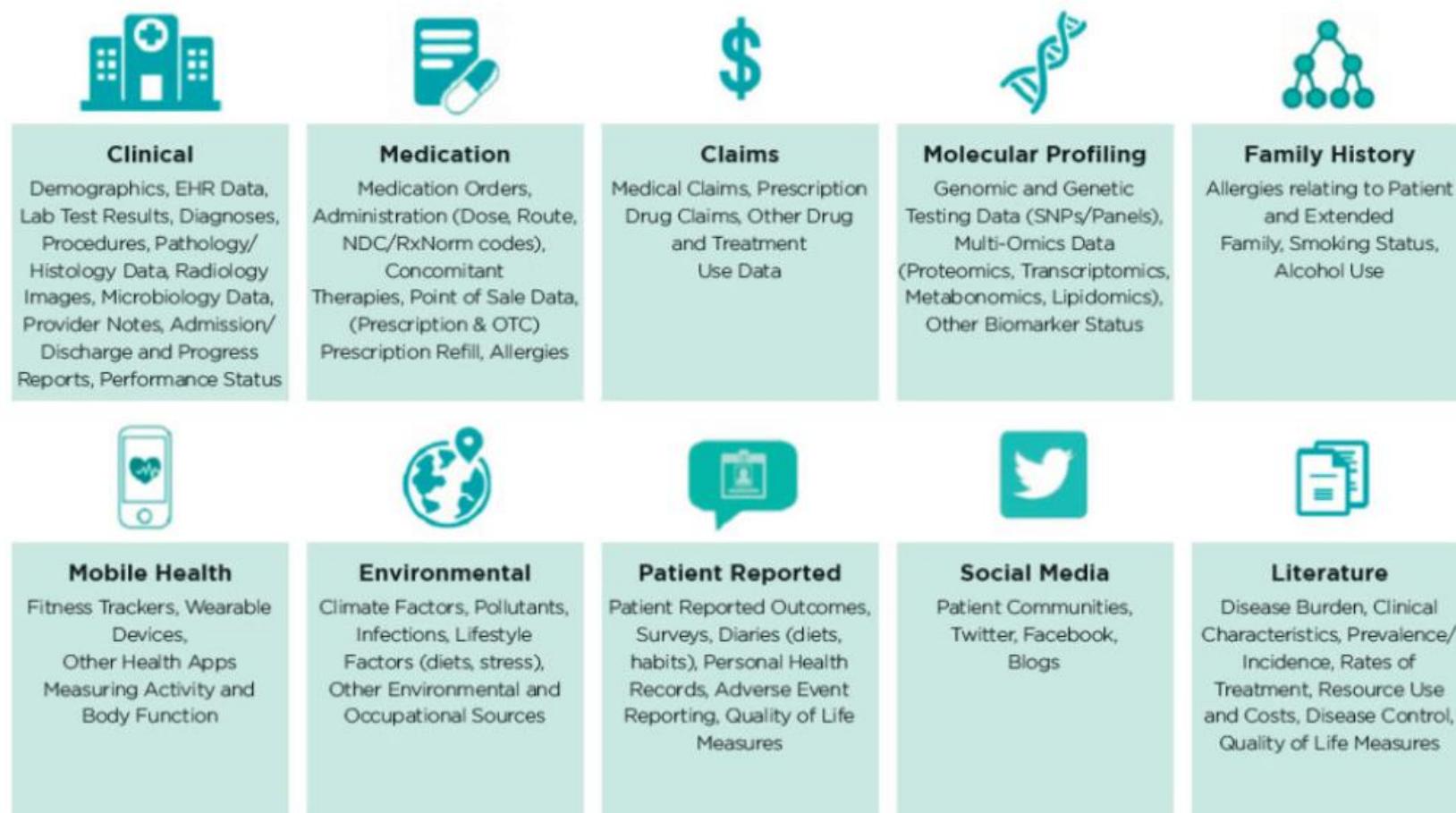
Primary Use: The use of healthcare data for the purpose for which it was originally collected

Secondary Use: The use of healthcare data for a different purpose than the one for which it was originally collected

Dataset	Primary Use	Example Secondary Use
Clinical Trial Data	Address the trial hypotheses	A natural history of disease study using the control arm of a trial
Claims Data	Medical Billing	Understanding treatment pathways in specific cancers
EHR Data	Inform the patient's care	Creating a comparator cohort to estimate the efficacy of standard-of-care for comparison to a clinical trial



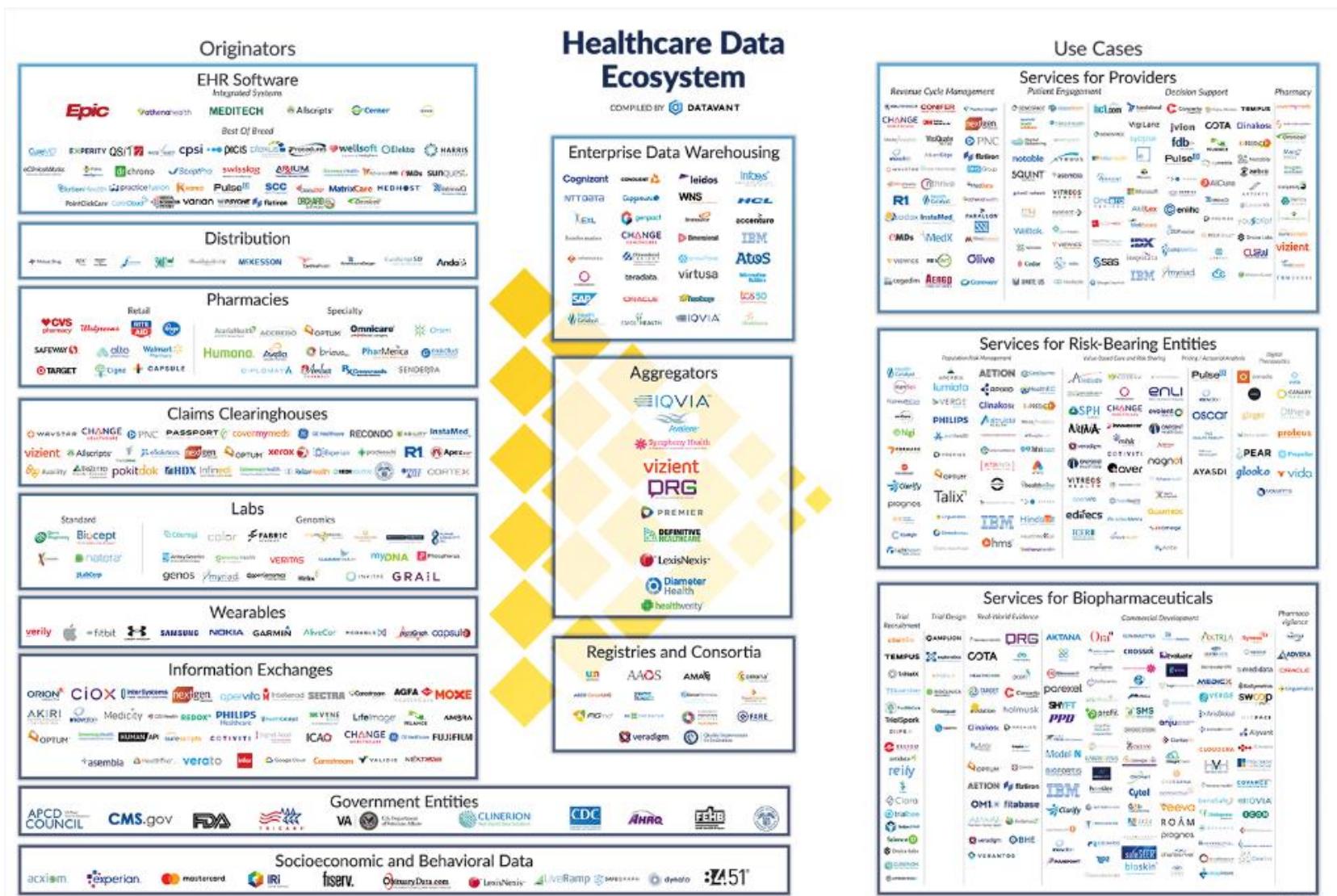
Real-world sources of secondary health data



Reynolds, MW. Leveraging Real-World Data for COVID-19 Research: Challenges and Opportunities, 2023

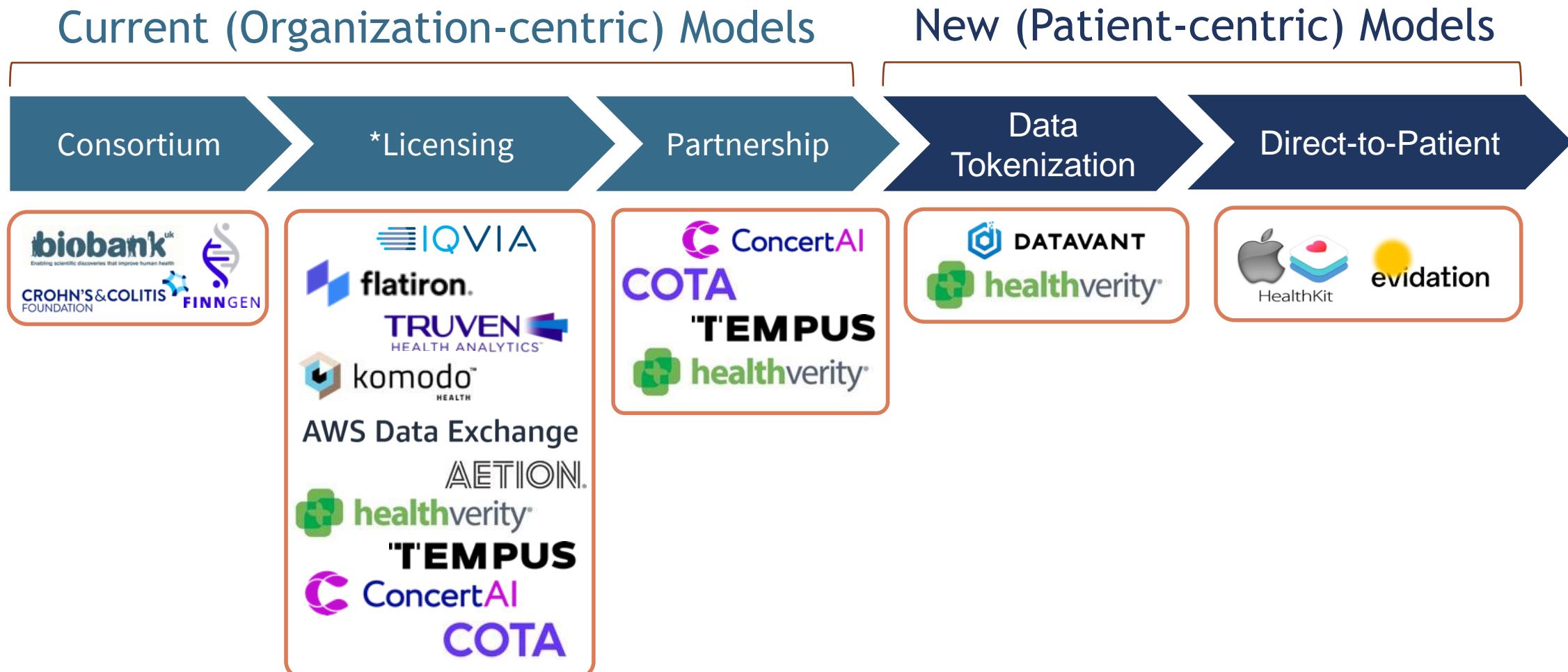
<https://www.thejournalofprecisionmedicine.com/the-journal-of-precision-medicine/leveraging-real-world-data-for-covid-19-research-challenges-and-opportunities/>

Growing, but Fragmented RWD Ecosystem

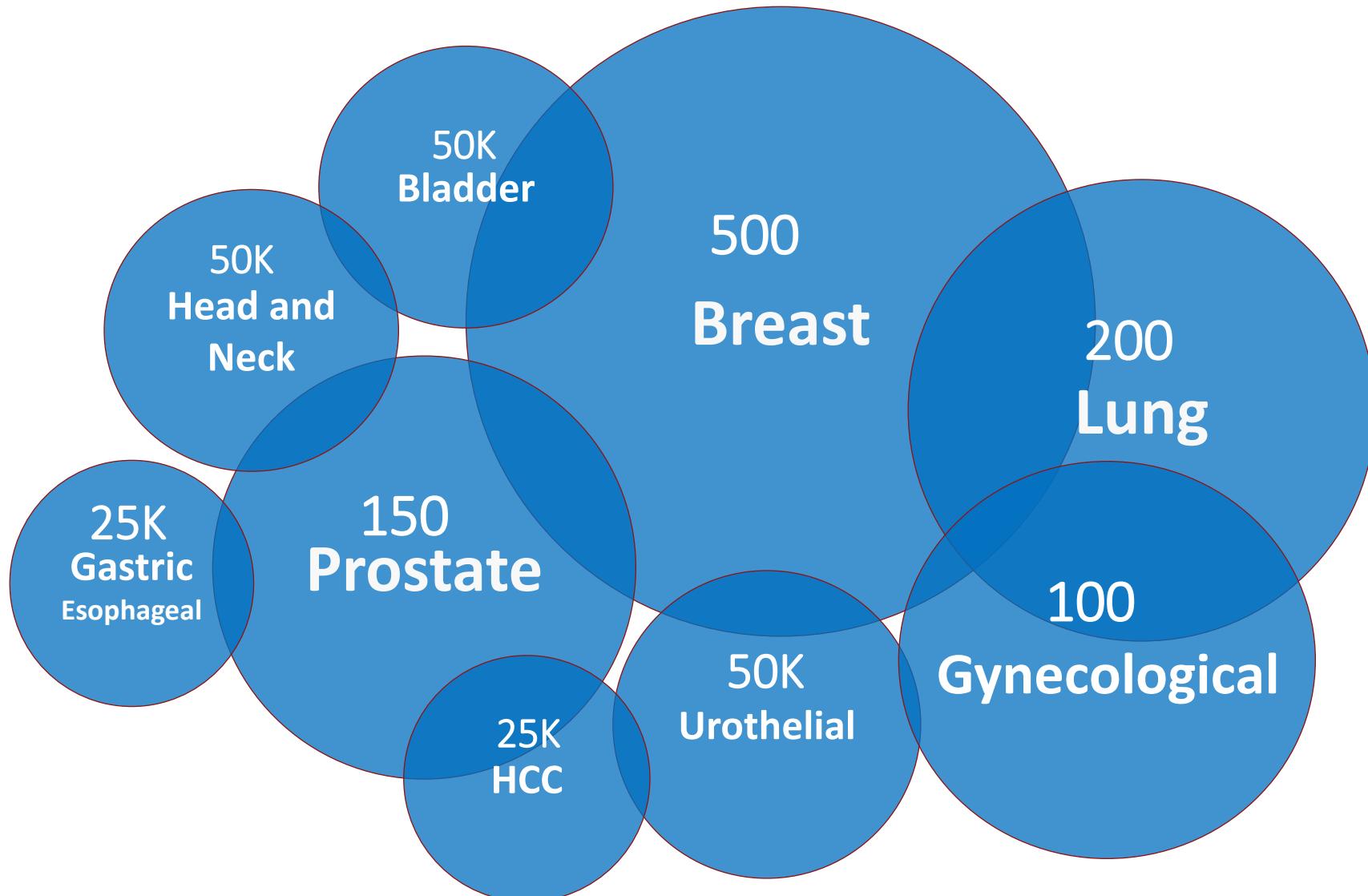


Major Real-World Data Types: <https://datavant.com/resources/blog/how-americas-health-data-infrastructure-is-being-used-to-fight-covid-19/>

RWD Acquisition Business Models are Evolving



Ensuring Coverage of Key Indications (ex Oncology)



Leading Guidance: ISPOR & ISPE Real World Data Task Force

Original Report

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

Marc L. Berger^{1,*}, Harold Sox², Richard J. Willke³, Diana L. Brixner⁴, Hans-Georg Eichler⁵, Wim Goettsch⁶, David Madigan⁷, Amr Makady⁶, Sebastian Schneeweiss⁸, Rosanna Tarricone⁹, Shirley V. Wang⁸, John Watkins¹⁰, C. Daniel Mullins¹¹

VALUE IN HEALTH 20 (2017) 1003–1008

Original Report

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang^{1,2,*}, Sebastian Schneeweiss^{1,2}, Marc L. Berger³, Jeffrey Brown⁴, Frank de Vries⁵, Ian Douglas⁶, Joshua J. Gagne^{1,2}, Rosa Gini⁷, Olaf Klungel⁸, C. Daniel Mullins⁹, Michael D. Nguyen¹⁰, Jeremy A. Rassen¹¹, Liam Smeeth⁶, Miriam Sturkenboom¹², on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making

VALUE IN HEALTH 20 (2017) 1009–1022

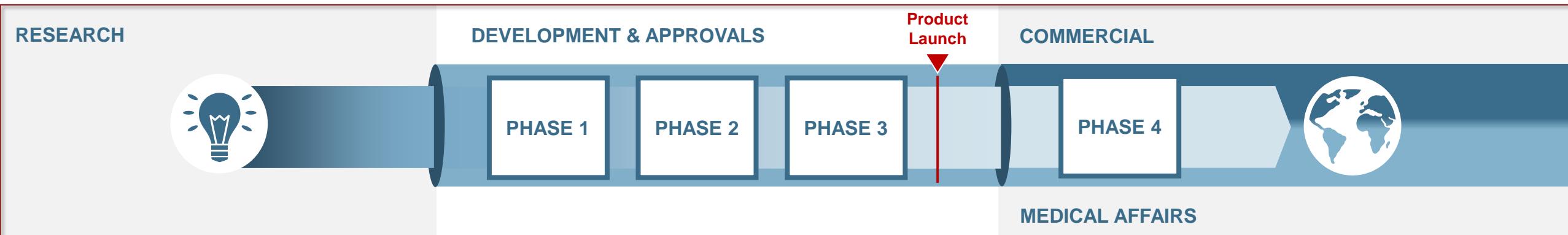


Leading Guidance: Regulatory Agencies

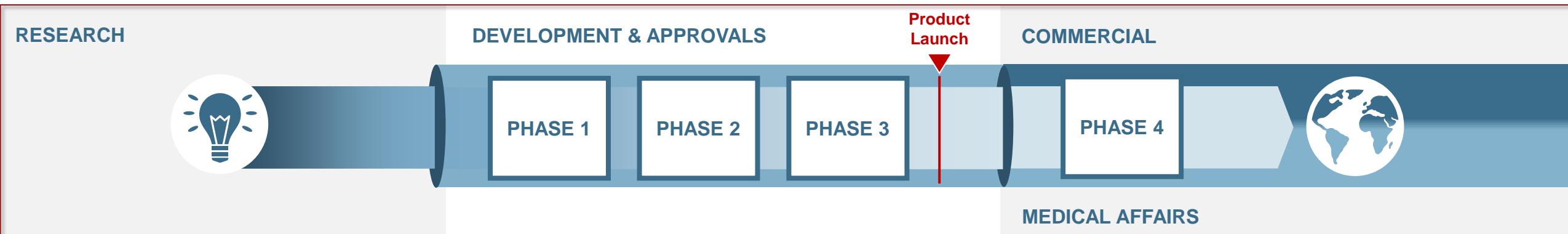
FDA	EMA	PMDA	Rest of World
 FDA 2016: 21st Century Cures Act 2017: PDUFA VI 2018: FDA RWE Framework 2019: Draft Guidance on Submissions Containing RWE 2021: <ul style="list-style-type: none">Draft Guidance on EHR/Claims DataDraft Guidance on Registry DataDraft Guidance on RWD StandardsDraft Guidance on Considerations for RWD/E 2022: <ul style="list-style-type: none">Final Guidance on Submissions Containing RWEPDUFA VIIAdvancing RWE Pilot Program 2023: <ul style="list-style-type: none">Draft Guidance on RW External ControlsFinal Guidance on Considerations for RWD/EDraft Guidance on RCTs leveraging RWD Elements (forthcoming)Draft Guidance on Non-Interventional Studies (forthcoming)	 EMA 2017: EMA/HMA Big Data TF Initiated 2018: EMA Regulatory Science to 2025 Initiated 2020: EC Pharmaceutical Strategy for Europe Adopted 2021: Multiple Big Data Workshops 2021: Registry-Based Studies Final Guideline 2022: <ul style="list-style-type: none">DARWIN EU LaunchedDraft Data Quality FrameworkDraft Good Practices Guide for the Use of the Metadata Catalogue for RWD Sources	 PMDA 2018: PMDA Reliability of Postmarketing Database for Drugs 2020: PMDA Reliability of Postmarketing Database for Regenerative Medicines 2021: PMDA Final Guidance on Basic Principles on the Use of Registries 2022: Q&A Reliability of Postmarketing Databases for Drugs 2023: Q&A Reliability of Postmarketing Databases for Regenerative Medicines	 Rest of World Taiwan <ul style="list-style-type: none">2020: Final TFDA Guidance on Basic Consideration for RWE2021: Final TFDA Guidance on Relevance and Reliability of RWD; Final Guidance on Submitting RWE Canada <ul style="list-style-type: none">2019: HC Notice Optimizing RWE2023: Joint CADTH/HC Final Guidance on Reporting RWE Australia <ul style="list-style-type: none">2023: RWD/RWE Clarifications for AU Brazil <ul style="list-style-type: none">2023: Draft Guideline for RW Studies Switzerland <ul style="list-style-type: none">2022: Swissmedic RWE Position Paper
 MHRA 2021: MHRA Final Guideline on RWD to Support Regulatory Decisions 2021: MHRA Final Guideline on RCTs Generating RWE	 NMPA 2020: Final Guideline on Using RWE in Drug Evaluation; Final Guideline Pediatric RWE 2021: Final Guideline on Data Considerations with RWD 2023: <ul style="list-style-type: none">Final Guideline for Study Design & Protocol Framework for RWEFinal Guideline for Communication of RWE for Registration	 International ICH - 2022 Concept Paper for ICH M14: General Principles for pharmacoepi studies that utilize RWD for Safety ICRMA - 2022 ICRMA Joint Statement on International Collaboration to Enable RWE for Regulatory Decision-Making CIOMS - 2023 Draft Report for RWD & RWE in Regulatory Decision-Making ICH - 2023 Draft Reflection Paper on RWE for Effectiveness	 CERSI UCSF-Stanford

Slide attributed to Rob Kalesnik-Orszulak, Global Regulatory Sciences, Bristol Myers Squibb

Real World Data – Real World Evidence Across the Pharma Lifecycle



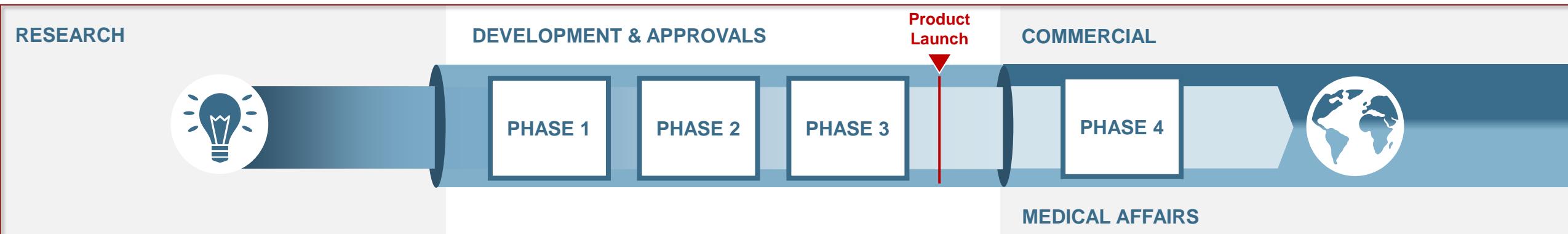
Real World Data – Real World Evidence Across the Pharma Lifecycle



- ▶ Biomarker discovery for resistance mechanisms
- ▶ Inform portfolio decisions with target selection
- ▶ Identify patient segments for targeted therapeutics



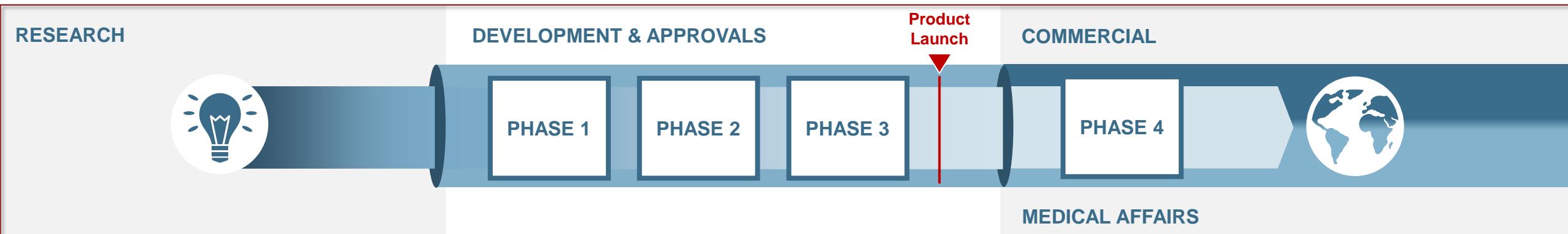
Real World Data – Real World Evidence Across the Pharma Lifecycle



- ▶ Inform study design, patient cohort criteria
- ▶ Clinical trial site selection
- ▶ Support development of companion diagnostics
- ▶ Creation of comparator cohort/synthetic arms
- ▶ Create patient disease registries



Real World Data – Real World Evidence Across the Pharma Lifecycle



- ▶ Demonstrate health economics, reimbursement model
- ▶ Improve patient targeting, inform study design
- ▶ Monitor pharmacovigilance and drug safety
- ▶ Identify areas for label expansion



Poll 3

Use of RWD in early target identification and drug development research



How do we create new molecules
that reverse or cure disease?



Each shot on goal
can cost
hundreds of
millions of
dollars.

How do we make
drug discovery
more efficient?

Multi-modal data in early target identification increases the probability of success to market



10% of new molecular entities (NME's) succeed after they enter early-stage clinical trials.



Combining clinical data (EHR, imaging, labs) with DNA and RNA provide foundational data to discover and test mechanism of action hypotheses.



NME's with causal human genetic evidence are twice as likely to succeed (Nelson 2015, King 2019).



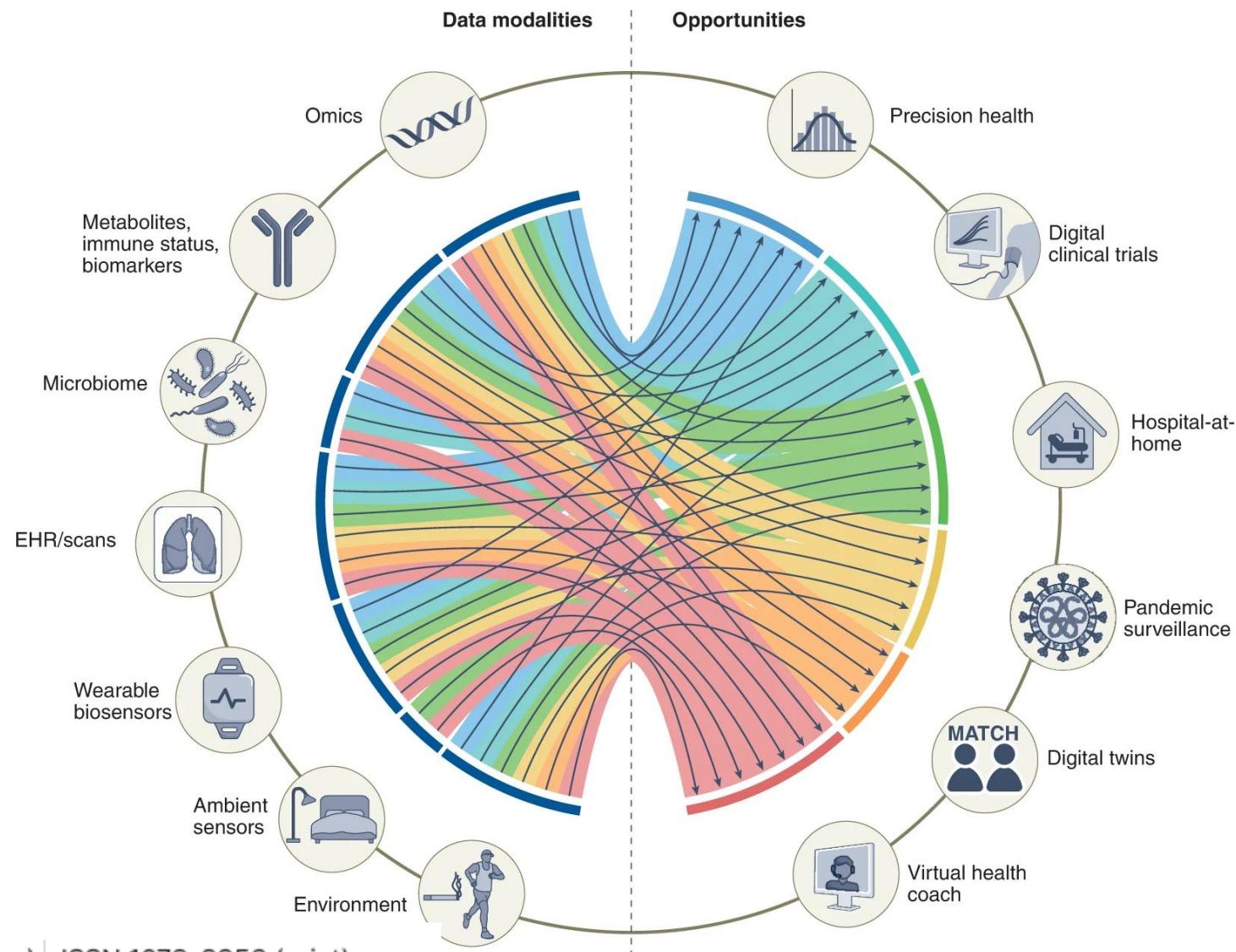
Given the high failure rate in drug development, multi-modal data in research and early development is crucial.

Multi-modal data

Arises from a wide range of clinical and non-clinical sources.

Depends on disease of interest.

Can lend insights into molecular mechanisms of severity, resistance to standard of care, or subtypes.



Focus on how multi-modal data is used in early target identification

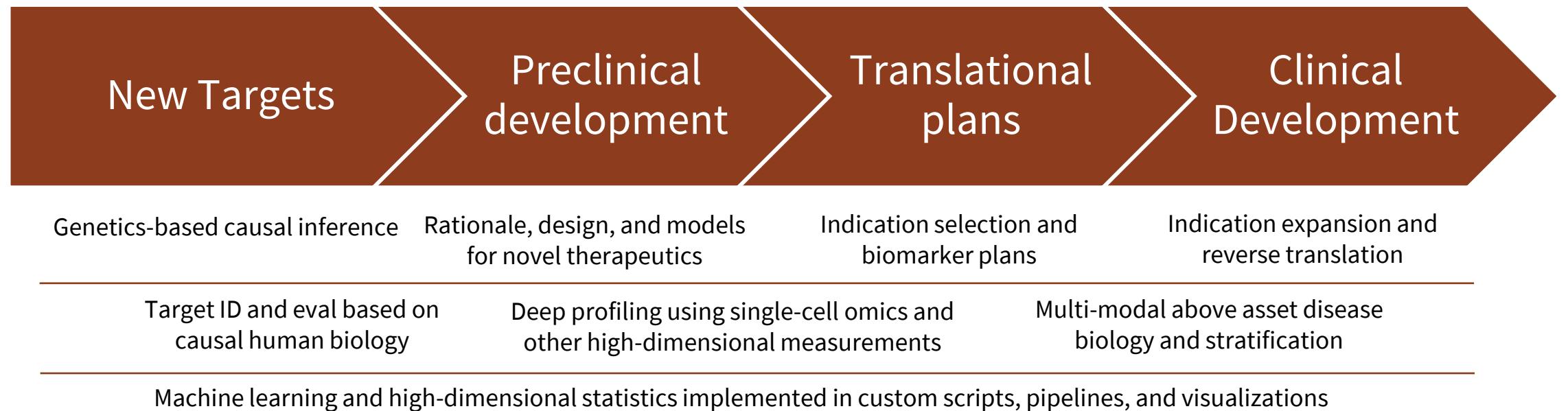
What is early target identification?

Our goal is to understand **causal human biology** in the pathogenesis of human disease. To do that, we need to identify key components that govern that disease process and interrupt them while minimizing off target effects.

Some common early research questions.

- What are the underlying susceptibilities to disease?
- Why do some people have more severe disease than others?
- Why are some people non-responsive or intolerant to available treatments?

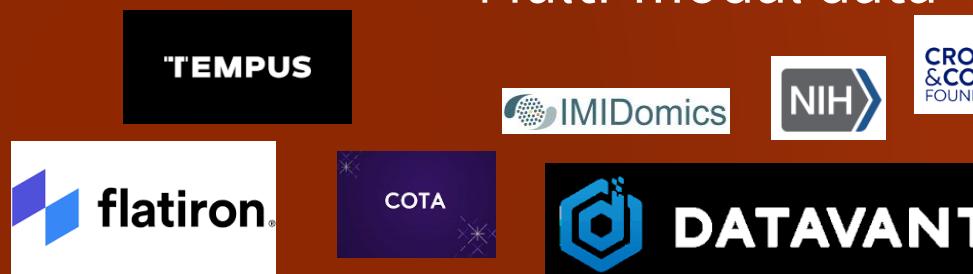
Multi-modal data informs the full pipeline of drug discovery



Genetic biobanks

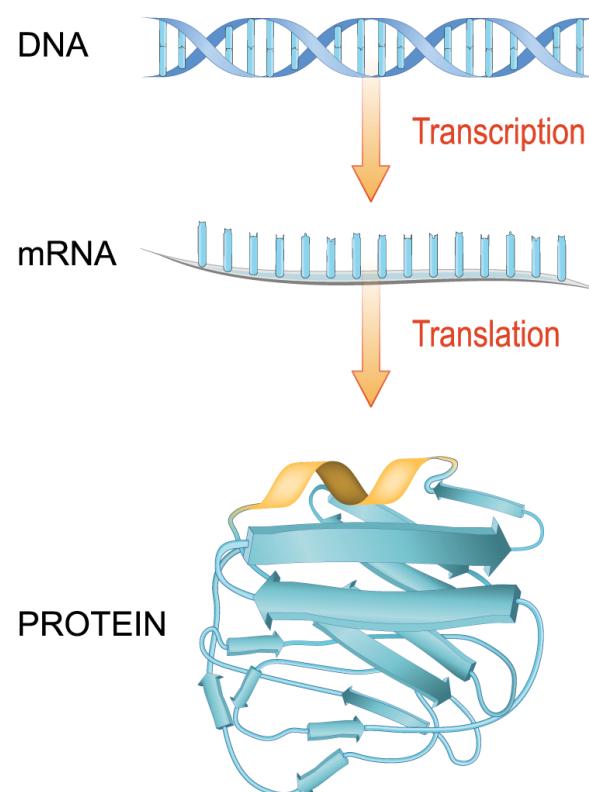


Multi-modal data



Key biological concepts that underpin target identification

Transcription and Translation



Variation in the human genome

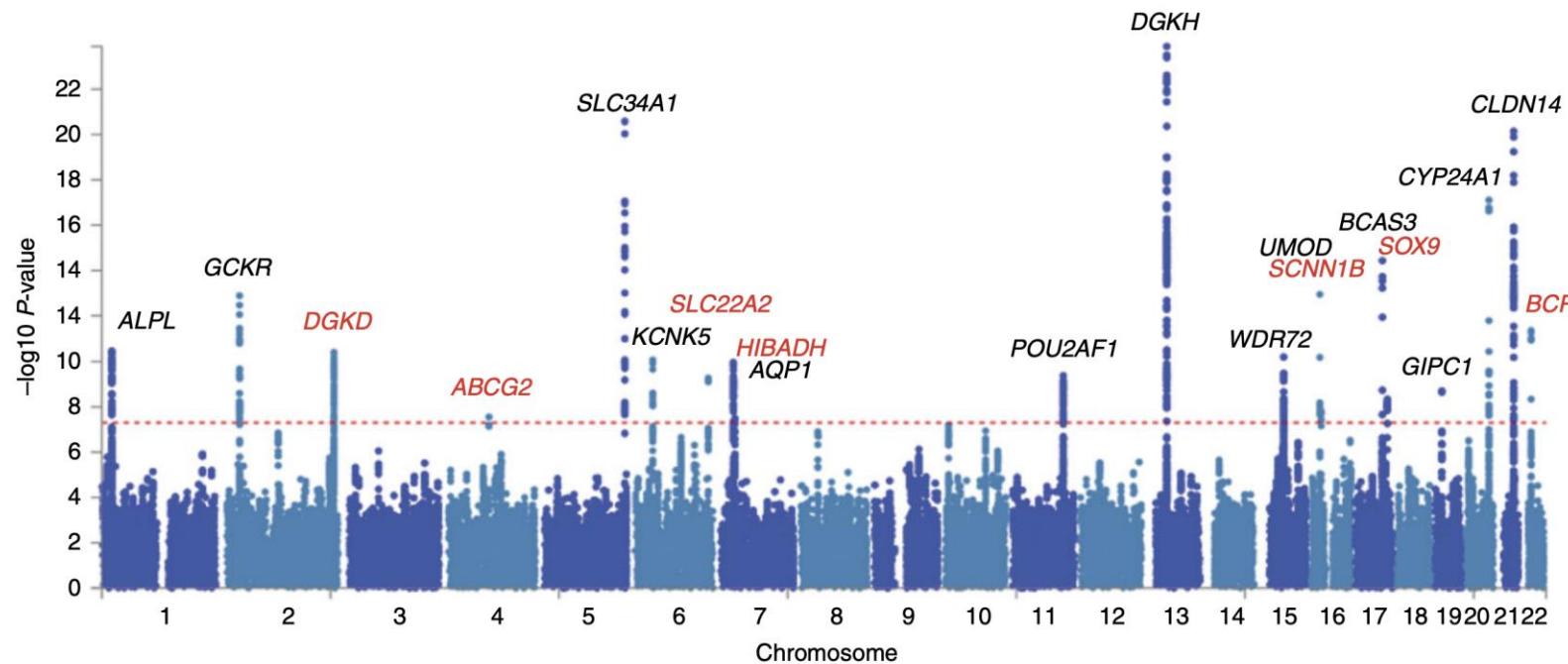
Differential gene expression

Consequences to protein structure or amount



Human genetic variation lends clues to underlying disease biology

Genome wide association studies comparing disease cases to controls can reveal a wide range of genetic differences. Understanding the causal gene and functional effect requires far more in-depth analyses.



Manhattan plot of kidney stone disease. [Source](#): Wikimedia commons

Tying genetic associations to causal biology is non-trivial

- Genetic associations (GWAS "hits") imply variation at the locus of a single nucleotide
- For example, you could have a AT, TT, or AA at a particular point in your double stranded DNA
- Occasionally it will be in a protein coding region, but not always
- Determining how genetic variation relates to function can be informed by a host of other data types paired with clinical or outcomes information

RNA expression in relevant tissue

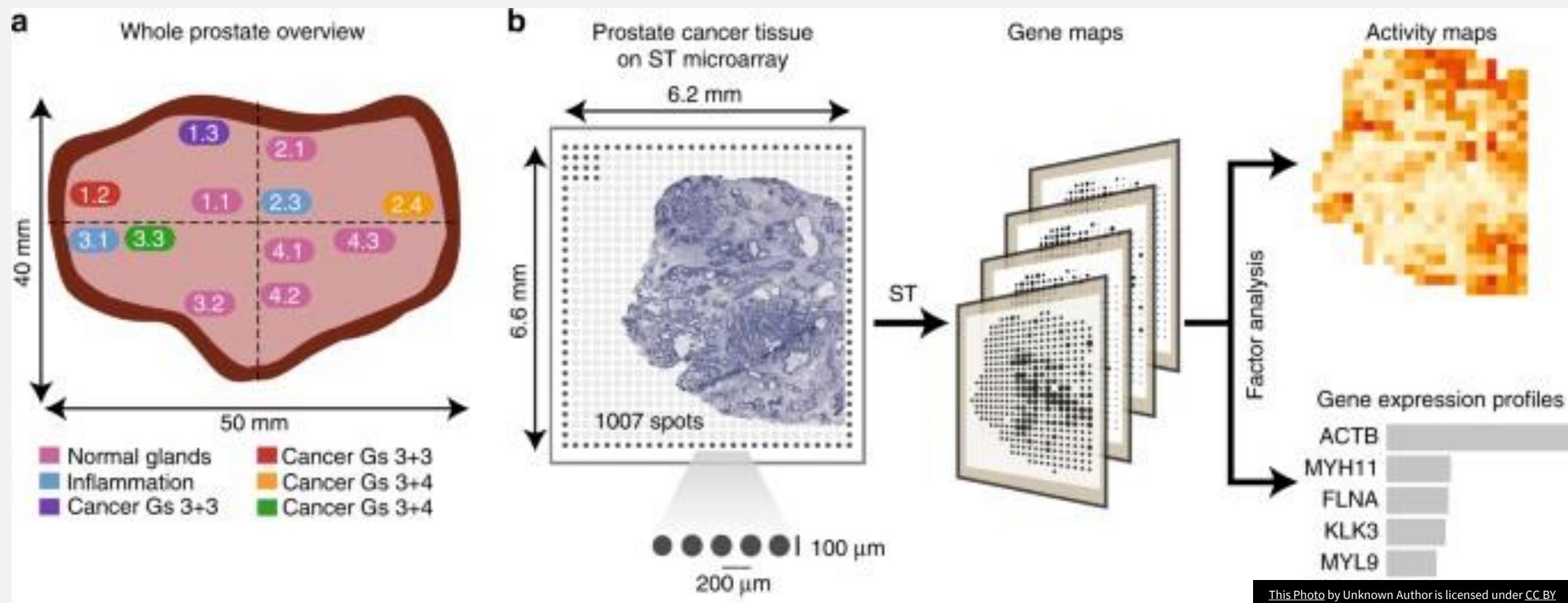
Protein quantification

Phenotyping of knockouts in cells, animals

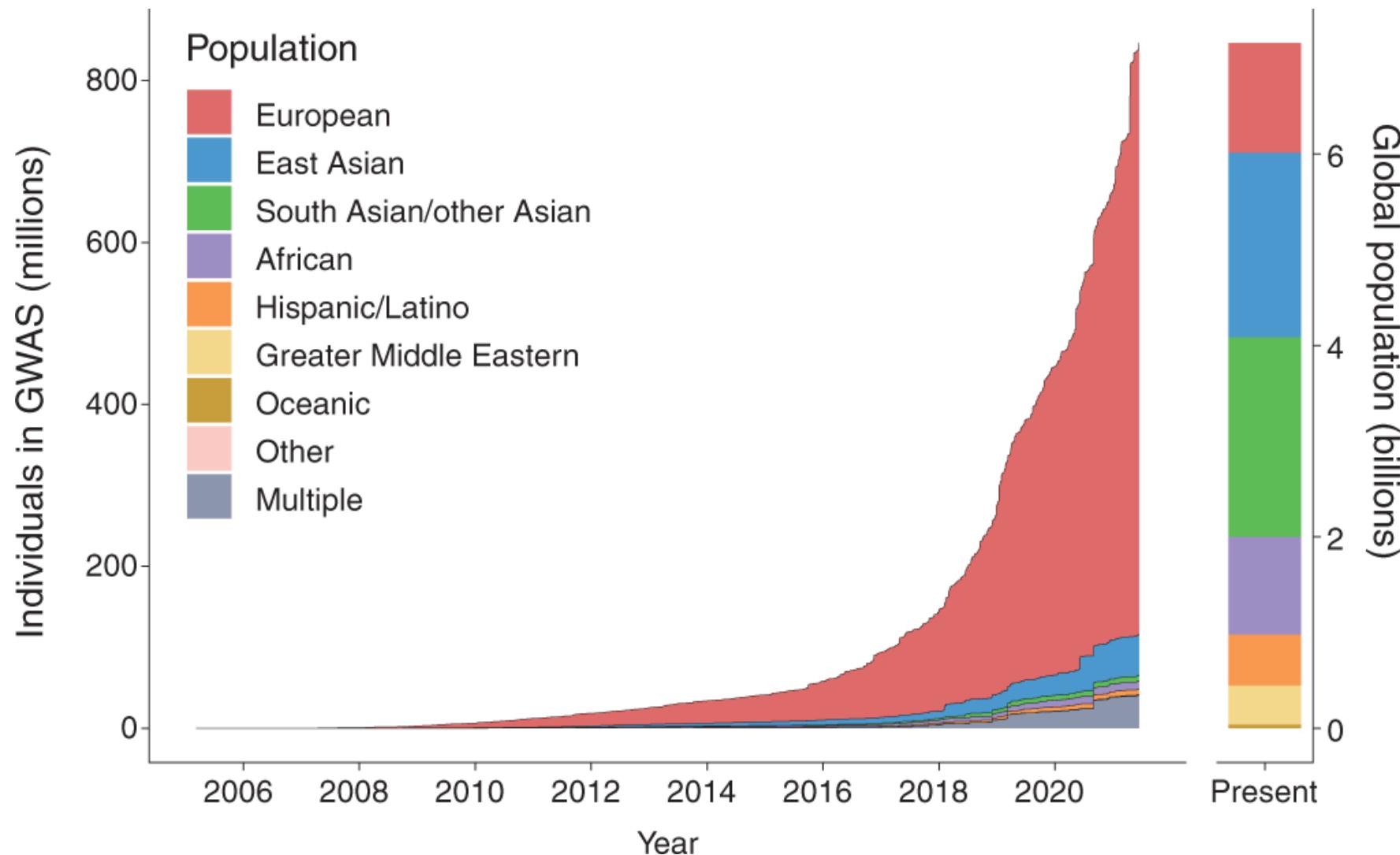
Types of genetic variation

- Polymorphism
- Deletion
- Insertion
- Translocation
- Inversion
- Mutation
- Copy number variation

Spatial Transcriptomics: Drug discovery biologists need to understand mechanisms at the cellular level



Much of what we know of the human genome is limited to European populations



Source: Fatumo, S., Chikowore, T., Choudhury, A. et al. A roadmap to increase diversity in genomic studies. *Nat Med* **28**, 243–250 (2022). <https://doi.org/10.1038/s41591-021-01672-4>

Two famous drug discovery vignettes relied on non-European genetic variation

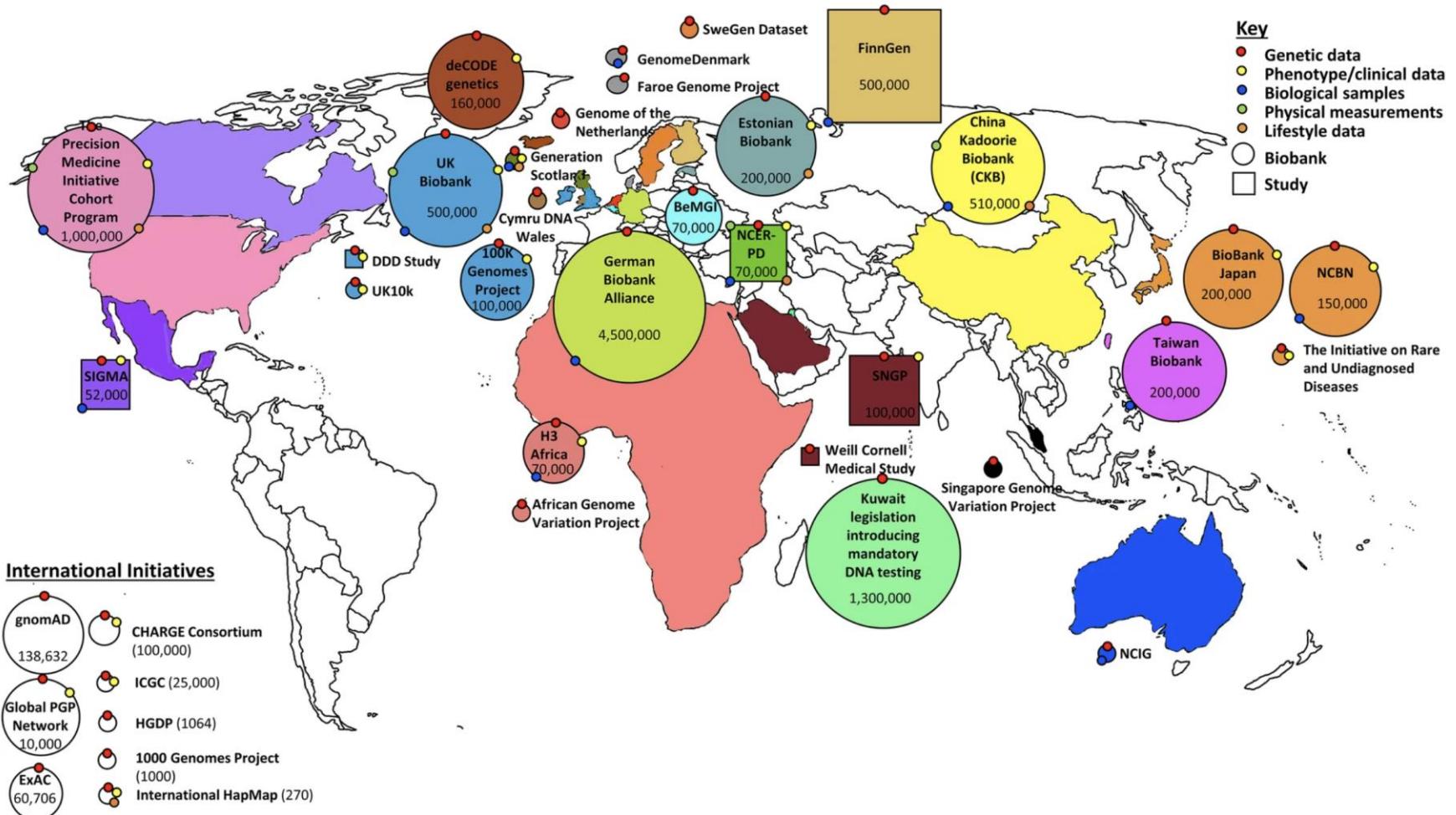
APOL1

- African ancestry is associated with an elevated risk of chronic kidney disease.
- Genetic variants under positive selection due to protection against African Sleeping Sickness were associated with damage to kidneys.
- Inhibition of APOL1 is now in clinical trials with positive phase 2b result.

PCSK9

- Loss of function led to exceptionally low LDL cholesterol in an otherwise healthy African American woman, whereas gain of function mutations led to hypercholesterolemia.
- Today, there are two effective PCSK9 inhibitors on the market for statin intolerant patients.

Global expansion of genetic biobanks facilitates discovery



Source: Carress, H., Lawson, D.J. & Elhaik, E. Population genetic considerations for using biobanks as international resources in the pandemic era and beyond. *BMC Genomics*

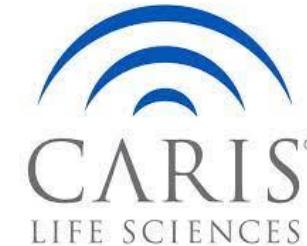
Multi-modal data includes tumor sample characteristics for oncology



Whole transcriptome RNA of tumors can reveal molecular adaptations to cancer treatments.



Some people respond to the most effective cancer therapies on the market and others don't, why?



Limitations and opportunities of multi-modal data in early R&D

Health data lives in silos

Linkage solutions are expensive and imprecise

Research participation is low, particularly over time

Privacy concerns for genomic data, health records being accessed for research



Merging multi-modal data with epidemiology principles to inform early discovery efforts



Identification of unmet medical need



Analytical methods to leverage complex data types



Identification or cultivation of data to understand causal human biology



Understanding limitations such as bias or threats to generalizability

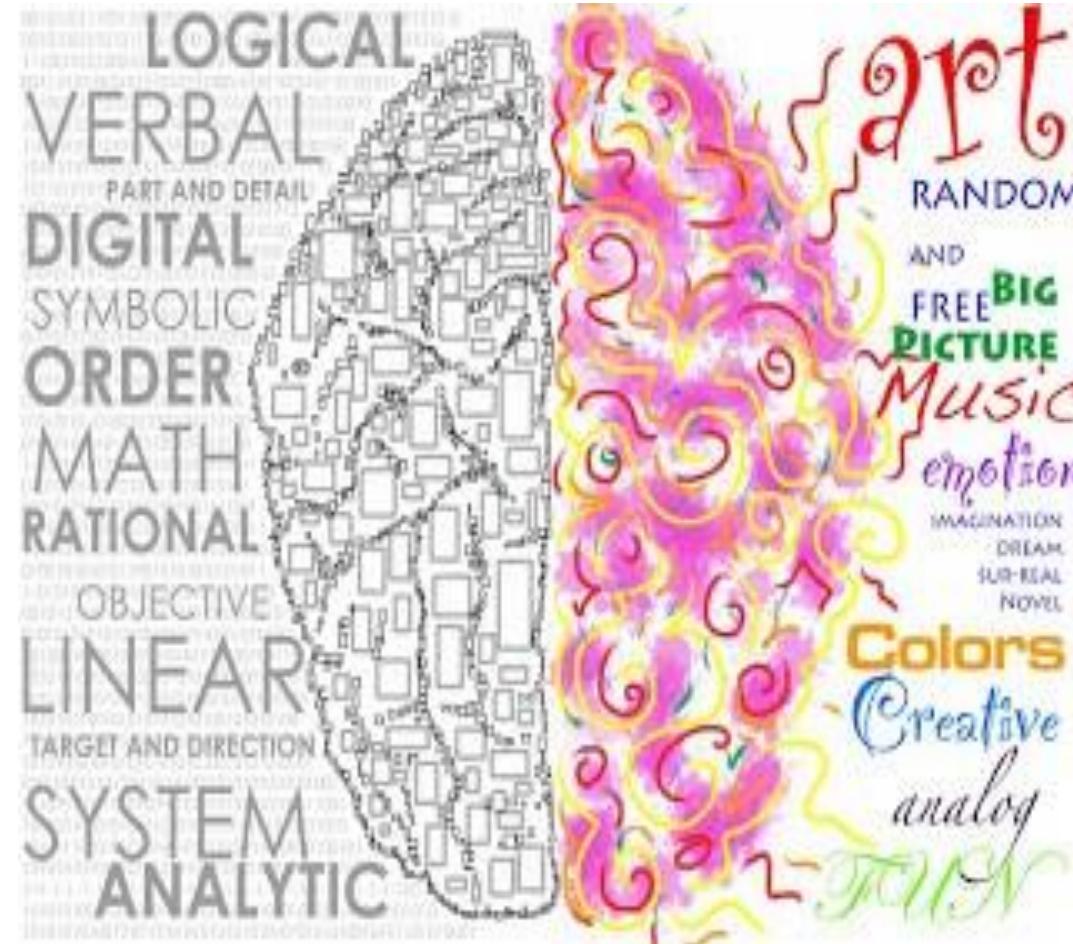
Question & Answer

RWD Development and Use in the Drug Approval Process

Translating Research Questions into Analytic Problems

The Data

- Highly structured
- Ontologies (e.g., ICD-9, CDISC)
- Multi-variable algorithm

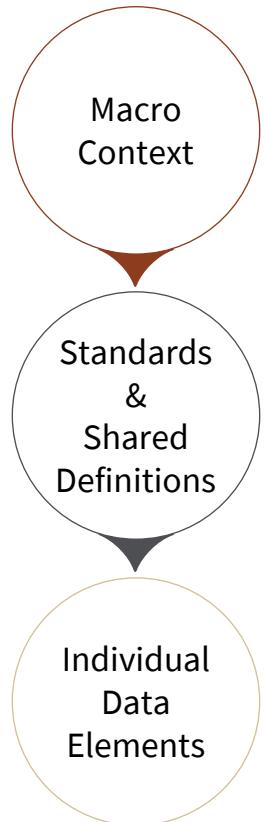


The Business Question

- Language-based
- Domain jargon
- Same word – different meanings

Inventory and Assessment of Available Data

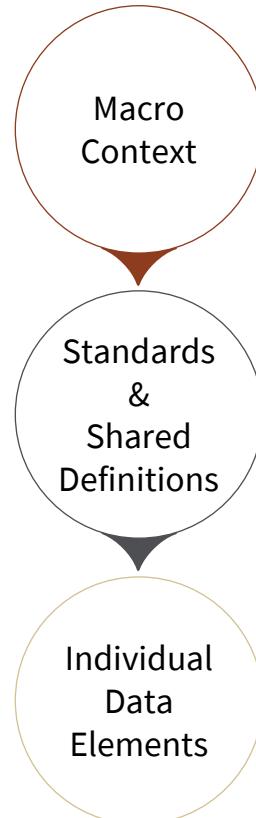
Data assessment across various levels of detail is necessary



- Did the data originate from a context that is appropriate for the question at hand?
- Is the data standardized?
- Can the data be mapped to a common data model?
- Is the available data operationally defined in a manner consistent with the question?
- Structured, unstructured, derived

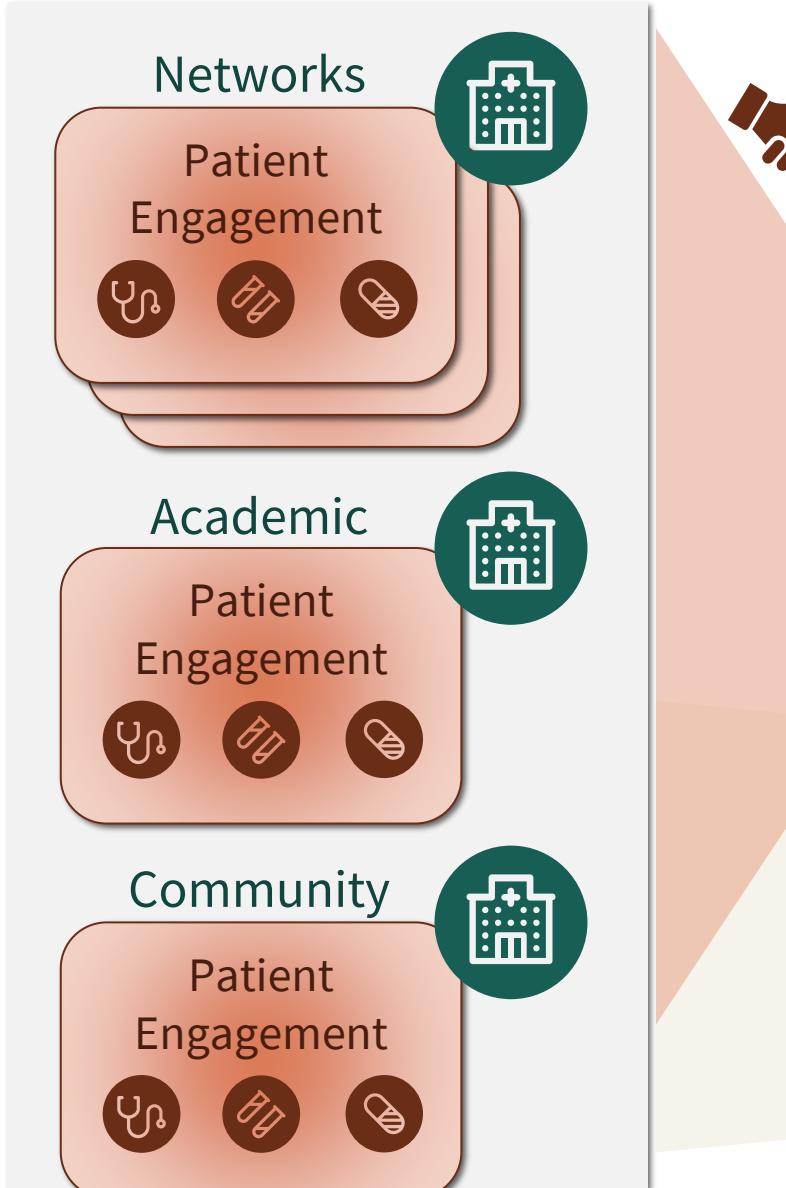
**Absence of Evidence
Is Not Evidence of Absence**

Evaluate the Gap Between the Question and Available Data

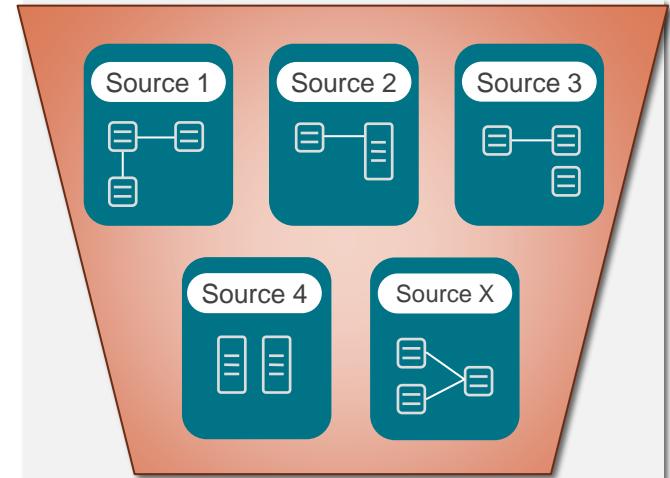


What proportion of cancer patients metastasize on first line therapy?	Which drug compounds are good repurposing candidates?	Do patients on immuno-oncology drugs have a higher rate of immune-related adverse events?
Claims, EMR, Tumor Registry, Biobank, Clinical Trial	Compound Library, High-throughput Screening, In Silico, Safety, Bioactivity, Target, Patent	Claims, EMR, Registry, REMS, Clinical Trial, FAERS, Spontaneous Case Reports, Publications
ICD-9 / ICD-10, ICD-O-3, Histology, Biomarkers, Cytogenetics, Genomics, Therapies, CDISC	Chemical Structures, SMILES, Chemical Markup Language	ICD-9 / ICD-10, Therapies, Comorbid Conditions, Unstructured Text of Case Narratives
Example: ICD-9 174.x AND (HER2+ biomarker positive OR Herceptin (trastuzumab) therapy)	Example: “Good candidate” Bioactive, Safe in Human, No Patent Infringement, No Legal Constraints	Example: Adverse Event Temporal Indicators, Correct Diagnosis and Coding of Event

Sourcing Quality Data



Data Partnerships
(Reduced Time and
Operational Complexity)



Internal Data Processing



Harmonized Analysis File



Refresh Data



Traditional Chart Abstraction
(High Site Burden and Time)

Challenges of the Secondary Use of Real World Data

1 Bias

2 Missing Data

3 Generalizability

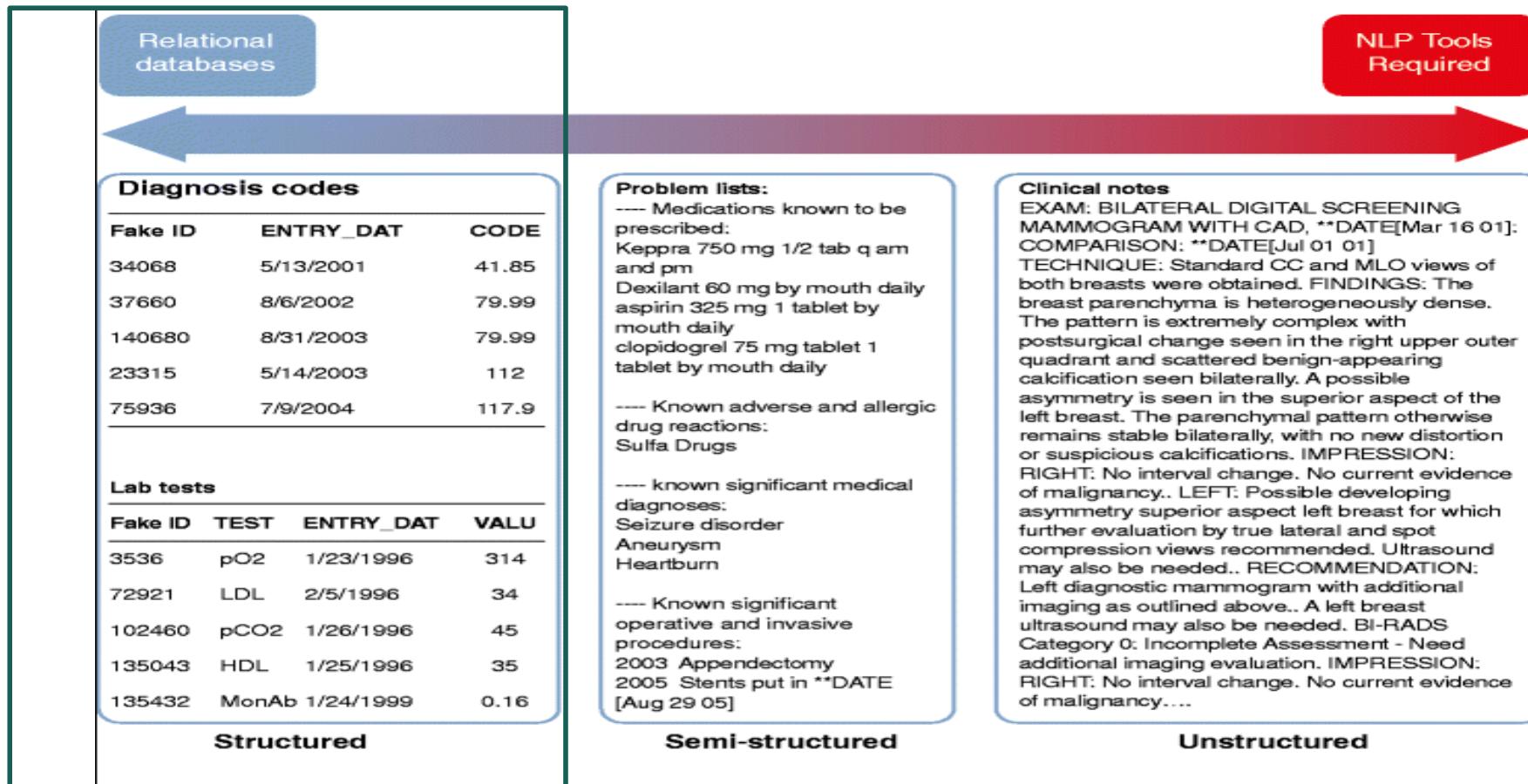


The extent and impact of each will differ based on the question(s) you are asking

Before using any dataset in your analysis, you should consider its weaknesses relative to your question(s)

Structured and Unstructured Data

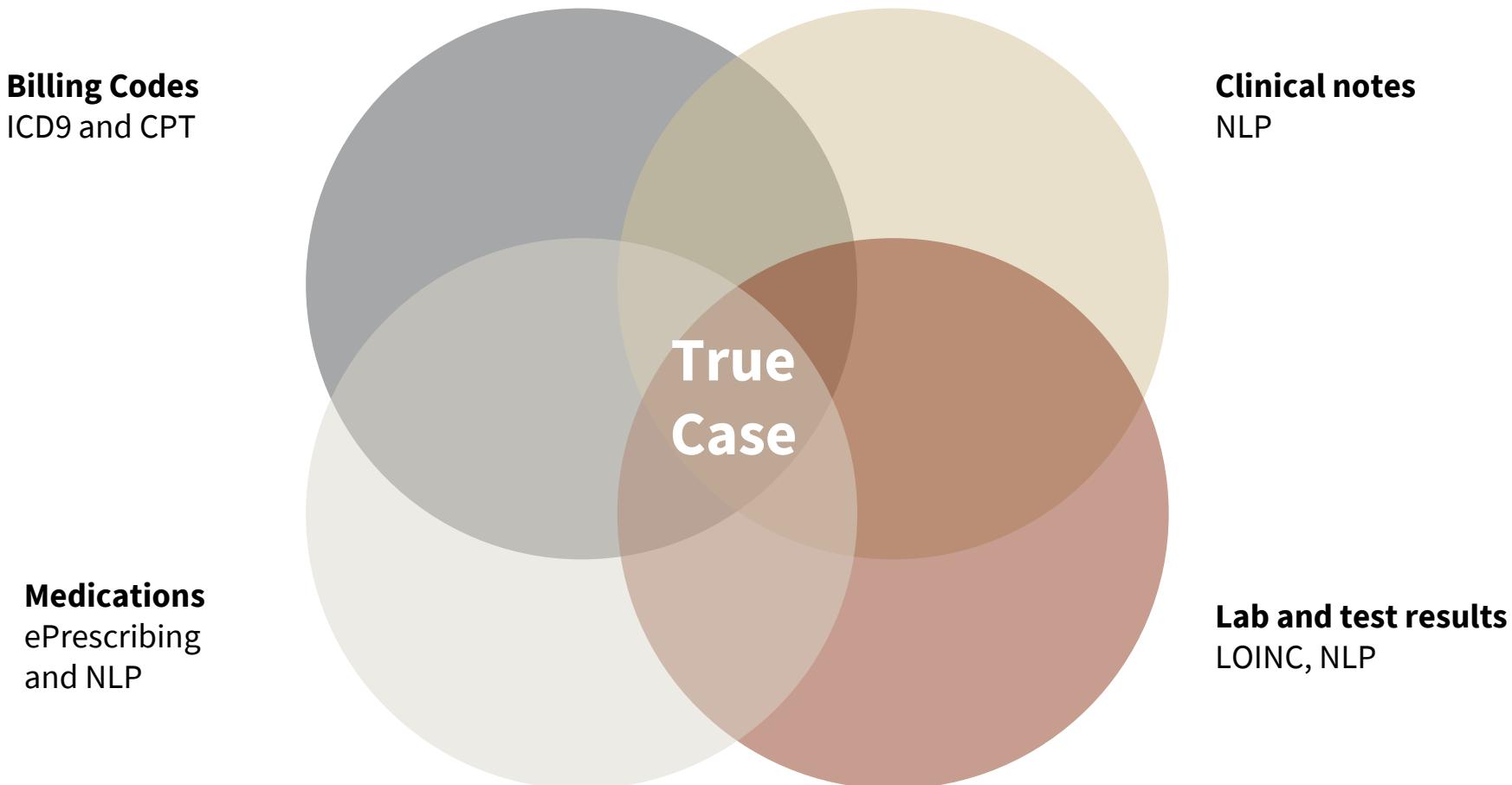
Data exists in a variety of forms including structured, semi structured, and unstructured. Each have key advantages as we look to improve the basis of patient care. For Ontologies, we will largely focus on structured data



Source: <https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-015-0166-y>

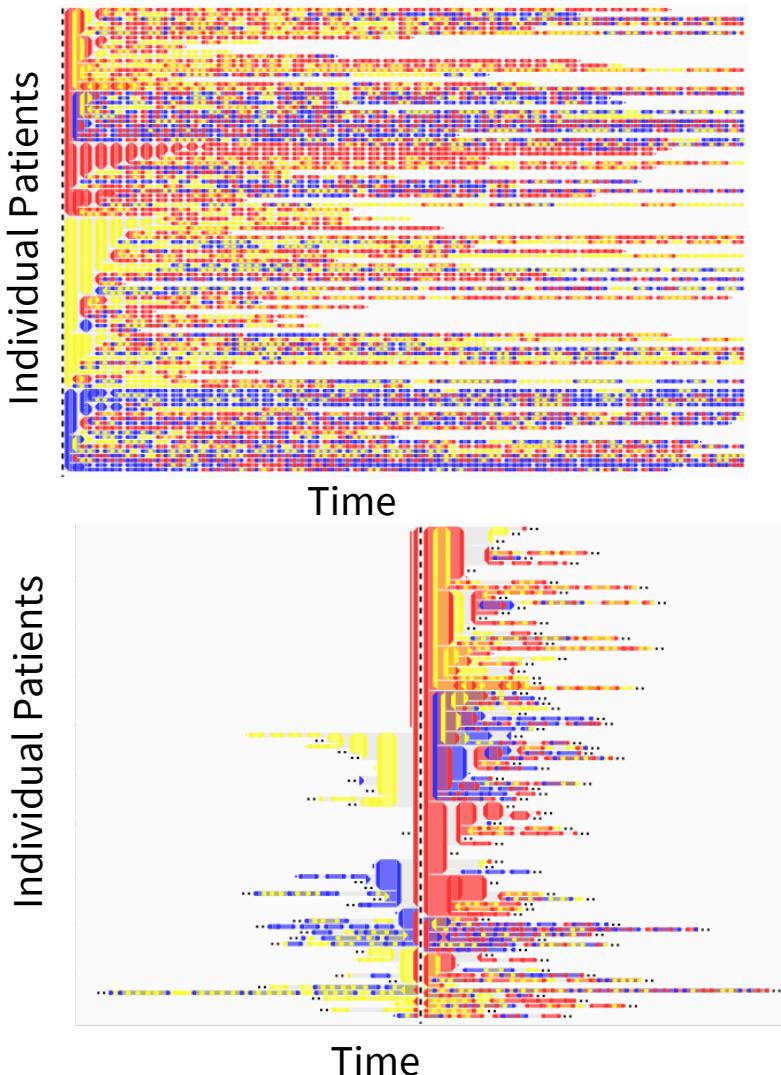
Structured and Unstructured Data

Creating accurate phenotypes requires the use of many different types of data sources that are both structured and unstructured in nature



Source: <https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-015-0166-y>

Importance of Data Quality and Completeness



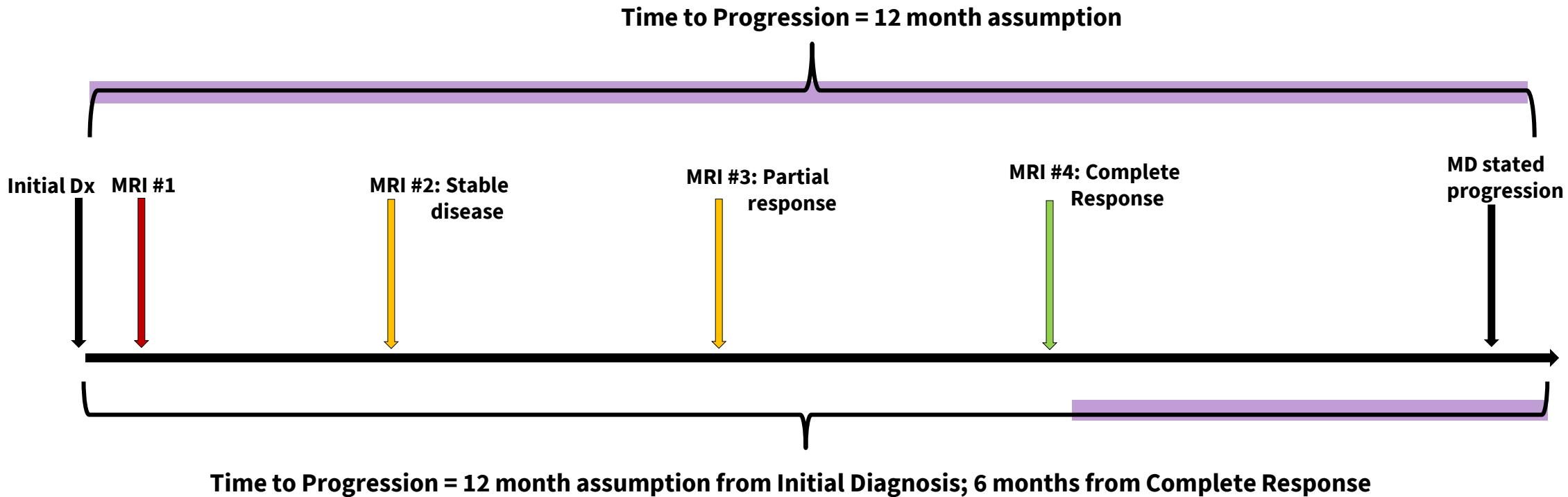
Category	Data Element	Check
Category	Data Element	Check
Duplication	ID	No duplicated patient id from different data sources
	Test result	If there are multiple results from the same day, identify the cause and apply rules to convert them into a single observation.
Completeness	ID	Not allowed
	Diagnosis date	Not allowed
	Treatment start date	Not allowed
	Treatment end date	Allowed, impute if possible
	Test date	Not allowed
	Staging	Not allowed (If missing check reason)
	Transplant date	Not allowed
	Death date	Allowed
Values	Test result	Check lab value outlier after normalizing the unit. The value of outliers is not important but the pattern is. If all values come from a single site, it may suggest that the site used the wrong unit.
	Test result	Check if there are string value in the numeric field. If so, 1) ask clarification from data vendor and 2) convert to numeric value is possible (may need clinical input)
	Test result	No negative allowed for most of the test results
Frequency	Test result (only selected tests)	Check the frequency of the test results especially the key labs that are related to outcome. In standard of care lab tests are usually done in the fix frequency, e.g. SPEP is usually performed every 3 to 6 months. [For MM the key labs are Serum M, Urine M and FLC.]
Logic	death date	Ensure all activity happened on or before the date of death
	Latest Possible Date	Ensure all activity happened on or before the data cut
	Treatment Start Date	Medication start date needs to be earlier than the end date.
	Treatment Start Date	Ensure treatment start dates are after initial diagnosis or within 14 days before initial diagnosis.
	Treatment Start Date	Check if the first diagnosis is > 1 year after that the start date of the first DLBCL therapy.
	Treatment Start Date	Ensure treatment start dates are after DOB
	Treatment Start Date	Ensure treatment start dates are before last known follow-up or visit
	Treatment Start Date	Ensure treatment end dates are before last known follow-up or visit
	Treatment End Date	Treatment end date of later line should be at/after treatment start date of former line. (X days tolerance)
	Abstraction Date	Abstraction date is after all activity dates
	Test Result	Ensure all tests results are after DOB and date of initial diagnosis

Exploring Point and Interval Event Patterns: Display Methods and Interactive Visual Query

Monroe, M., Wongsuphasawat, K., Plaisant, C., Shneiderman, B., Millstein, J., Gold, S. April 2012

Importance of Data Density

'Absence of evidence is not evidence of absence' - Martin Rees, Carl Sagan



What can we measure well?

Construct validity

- Frequency of measurement in standard of care
- Types of assessments

Pilot project data: Correlation of real-world endpoints to overall survival among immune checkpoint inhibitor-treated aNSCLC patients

Real-world Overall Survival (OS), Time to Discontinuation (TTD) & Time to Next Treatment (TTNT)

Table 2

Data Set	rwOS	rwTTD	rwTTNT
Data Set A	13.50 [12.80, 14.50] #	7.03 [6.27, 9.97]	22.50 [NA]
Data Set B	15.78 [12.2, 24.59]; 8.58 [7.56, 10.26] *	3.25 [2.76, 3.75]	
Data Set C	8.67 [6.83, 10.02]	4.70 [3.68, 5.52]	11.60 [8.80, 16.10]
Data Set D	9.15 [8.82, 9.51]	3.21 [3.21, 3.44]	14.03 [12.89, 15.15]
Data Set E	12.69 [11.7, 13.87]	3.63 [3.40, 3.87]	12.07 [11.24, 13.48]
Data Set F	12.30 [9.61, 16.94]	4.60 [3.71, 6.32]	12.50 [9.29, NA]

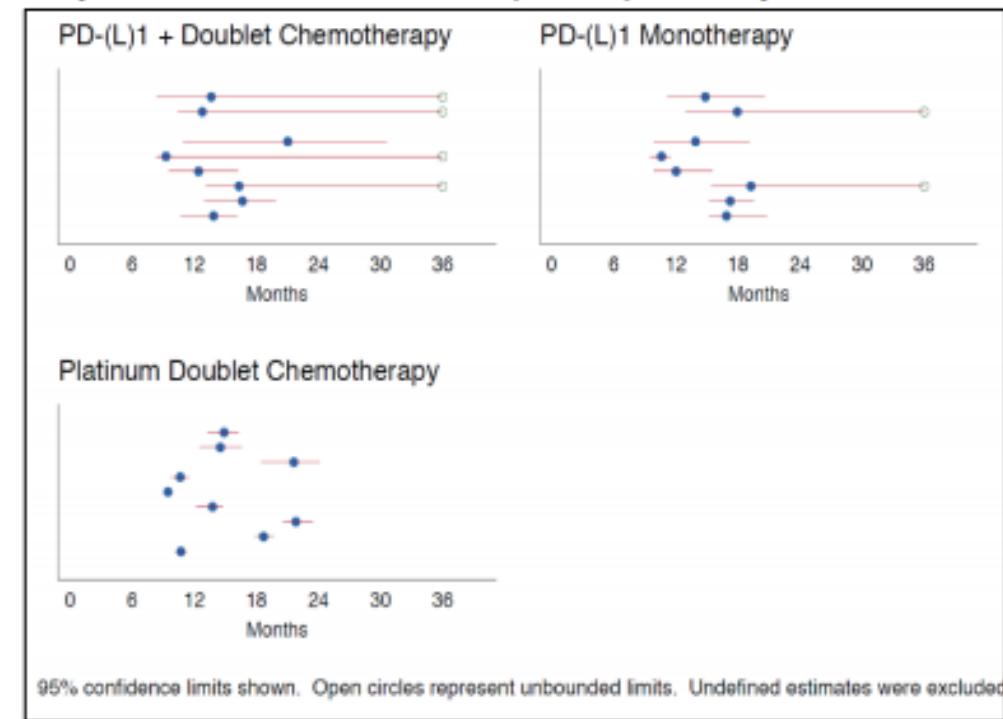
OS was calculated as days between I/O initiation and disenrollment.

* Sites with social security or state death data, censored at estimated earliest date such data should be available if no death was observed



8th Annual Blueprint for Breakthrough Forum
Validating Real-World Endpoints for an Evolving Regulatory Landscape
September 18, 2019
Washington, DC

Graph 18. Estimates of Median (95% CI) rwOS by Treatment Category

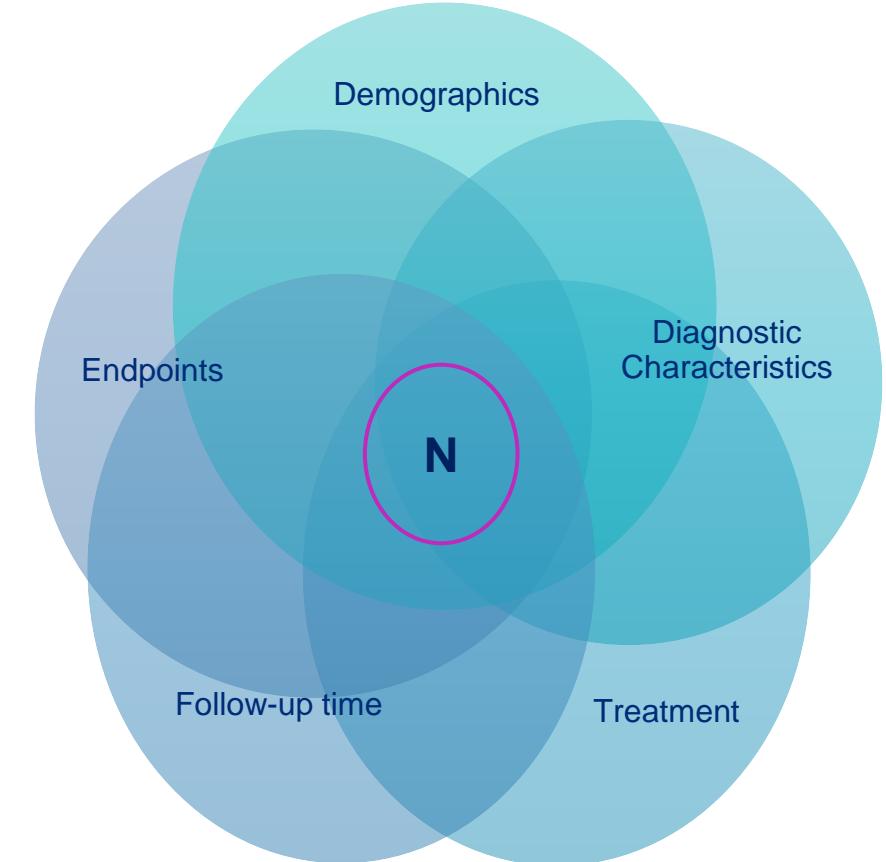


Translating the Data Strategy into a Data Model



Discrete &
Verifiable

Robust &
Reusable



What is a Common Data Model (CDM)?

A **Common Data Model (CDM)** is used to standardize multiple data sources and content (terminologies) to support a systematic approach of assessing and analyzing multiple data sources

- The structure and design of CDMs are driven by both the type of activity and the data sources available
- There have been a number of projects that utilize CDMs:
 - *Sentinel Common Data Model*
 - *Healthcare Systems Research Network (HCSRN) / PCORnet*
 - *Meningococcal Vaccine Study*
 - *Observational Medical Outcomes Partnership (OMOP)*
 - *Post-Licensure Rapid Immunization Safety Monitoring (PRISM)*
 - *Informatics for Integrating Biology and the Bedside (i2b2)*
 - *Vaccine Safety Datalink Project*

Why Use Common Data Models?

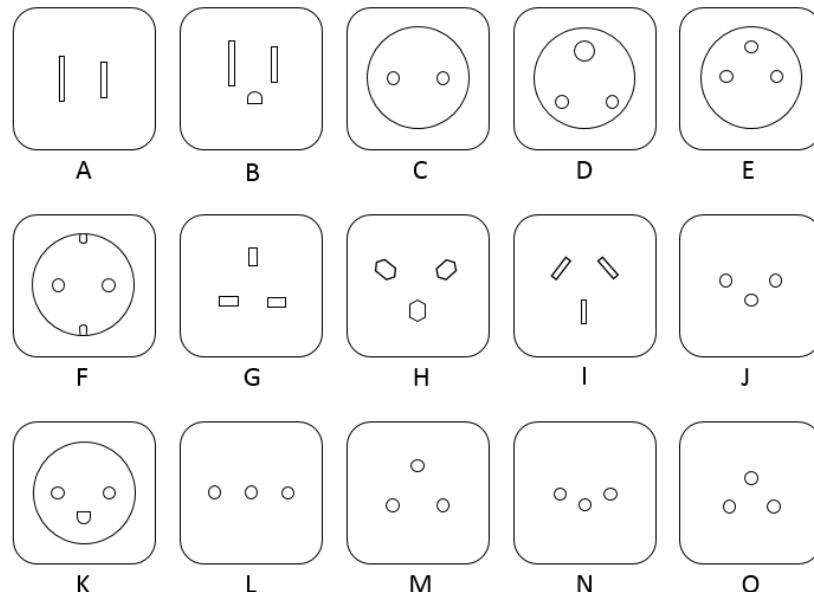
When you let the data speak, it is not always in a common language. Even if data are designed for the same purpose, outputs may not be comparable across data sets

Use Case



"I want to blow dry my hair"

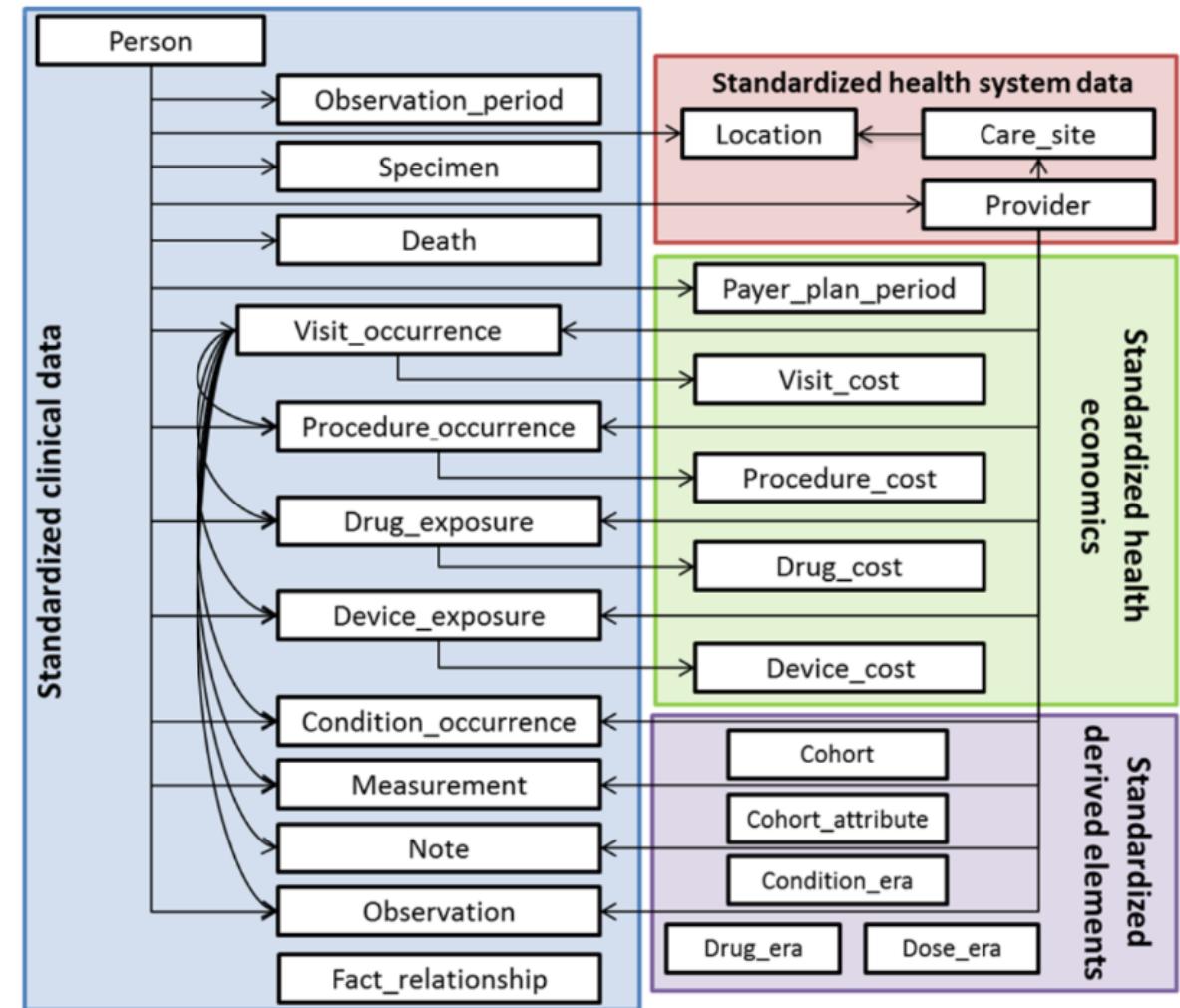
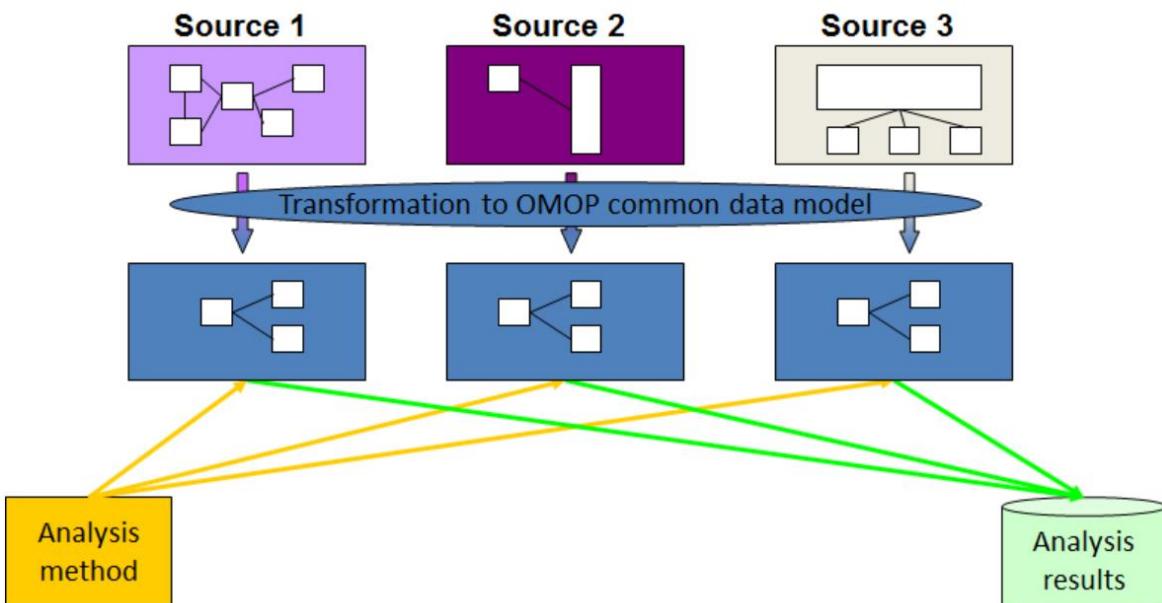
Native Data Models



Benefits

- Data standardization
- Common research methods
- Concurrent access to multiple data sources
- To ensure that research methods can be systematically applied to produce meaningful comparable and reproducible results

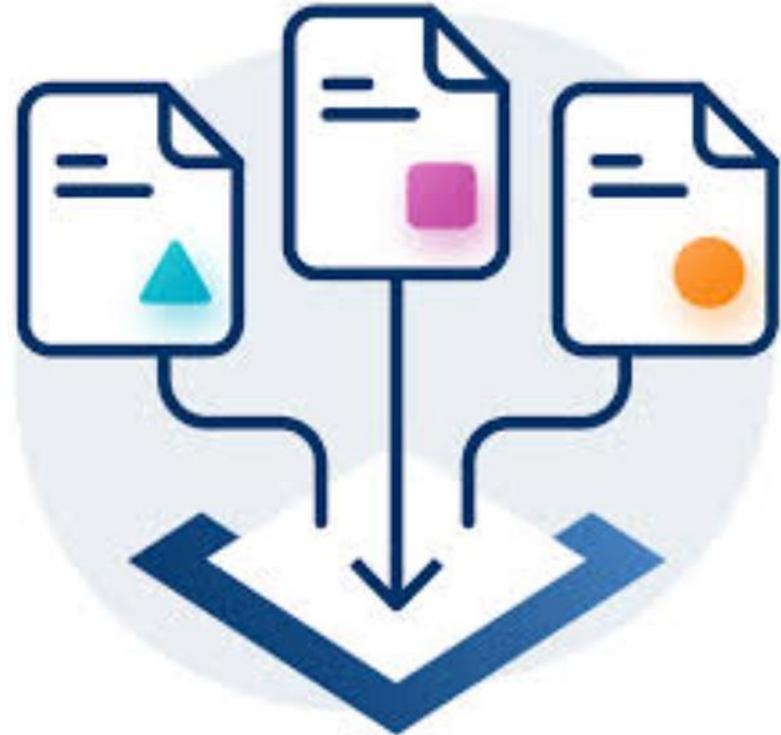
Observational Medical Outcomes Partnership (OMOP) Schema



<https://www.ohdsi.org/data-standardization/the-common-data-model/>

Data Integration: Challenges

- Conform unstructured data
- Handling of dates
 - › Variability across data partners for de-identification
 - › Imputation rules
- Unit conversions
- Drug standardization
- Ontology mapping and standardization

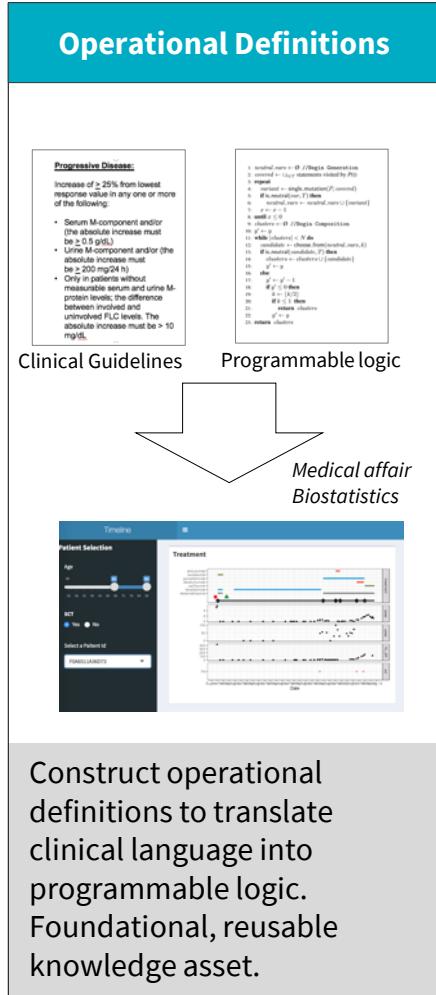


Data Harmonization: Challenges

- Evaluation of appropriateness of data elements for harmonization
- Duplication of patients across disparate data sources
- Common operational definitions (line of therapy, index date, response/endpoint)



Standardizing Operational Definitions



Start with the Clinical Concept

Consider the Source Data

- Macro context – where does the data come from?
- Standards & Shared Definitions – what ontologies are used?
- Individual Data Elements – do they cover the complete concept?

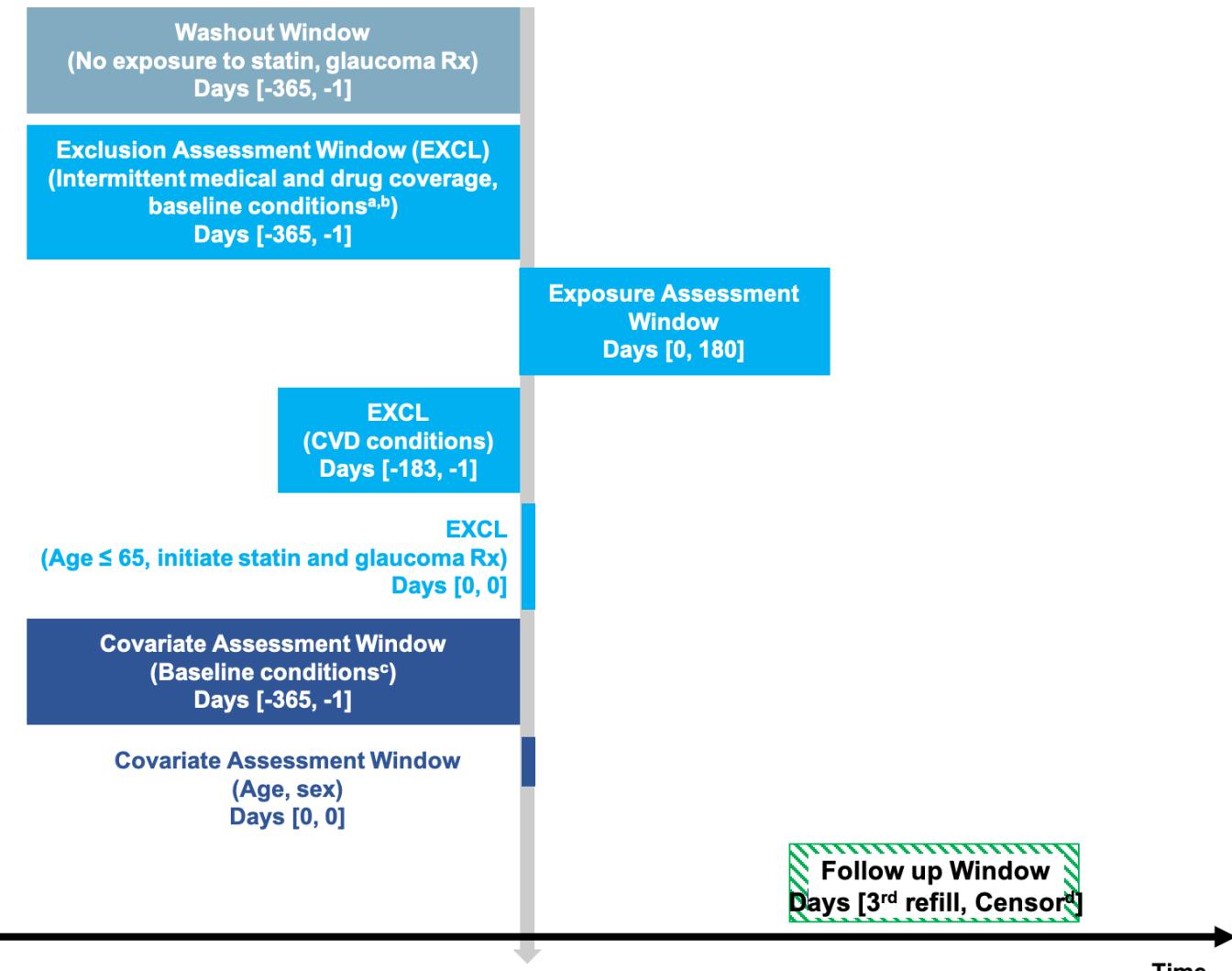
Code and Validate Code



Transparency Facilitates Validity Assessment

Document details to remove assumptions

- Study design
- Quality control protocols
- Analytic derivations
- Pre-specified analyses
- Sensitivity analyses to address potential bias



Graphical depiction of longitudinal study design in health care databases

Schneeweiss S, Rassen JA, Brown JS et al.. Ann Intern Med. 2019.

Strengths and Challenges of RWE Study Designs for Regulatory Use

	Observational Study	Single Arm Trial with RW Comparator Arm	Pragmatic Clinical Trials
Description	Non-interventional clinical study: prospective, retrospective, cross- sectional	<ul style="list-style-type: none">Interventional clinical trial is compared to external non-interventional RW data as the control arm (non-randomized)	<ul style="list-style-type: none">Randomized interventional/ clinical trial focusing on correlation between treatments and outcomes in RW settings rather than strictly controlled RCT.
Strengths	<ul style="list-style-type: none">Relatively quick and inexpensiveLarge scale and long follow-up	<ul style="list-style-type: none">Provides contextualization to single arm clinical trial resultsReduces trial timeProvides comparator when RCT not feasible	<ul style="list-style-type: none">Randomization, if desired and applicable to RW settingsPotential to streamline RCT
Challenges	<ul style="list-style-type: none">Likelihood of unmeasured confounders and bias potentially limit ability to draw causal inference	<ul style="list-style-type: none">Likelihood of unmeasured confounders and bias potentially limit ability to draw causal inference	<ul style="list-style-type: none">Operational challenges: special informed consent concepts, blindingRWD more heterogeneous than normal RCT
Typical Regulatory Use	<ul style="list-style-type: none">Post-marketing Requirements (Safety / Longterm Efficacy)Supportive, Background Evidence.Indirect comparisons (MAIC)	<ul style="list-style-type: none">New Indications and New Product Approvals	<ul style="list-style-type: none">Comparative Effectiveness

Uses in Regulatory Approval Settings

- Advances in the availability and analysis of RWD have increased the potential for generating robust RWE to support regulatory decisions.
- RWD needs to be fit-for-purpose to generate RWE with the goal of advancing the development of therapeutics.
- RWD is most commonly used as supportive evidence to complement clinical trial data with handful of exceptions of primary evidence.
- RWD source representativeness, validity, and reliability/quality are key acceptance factors.

Question & Answer



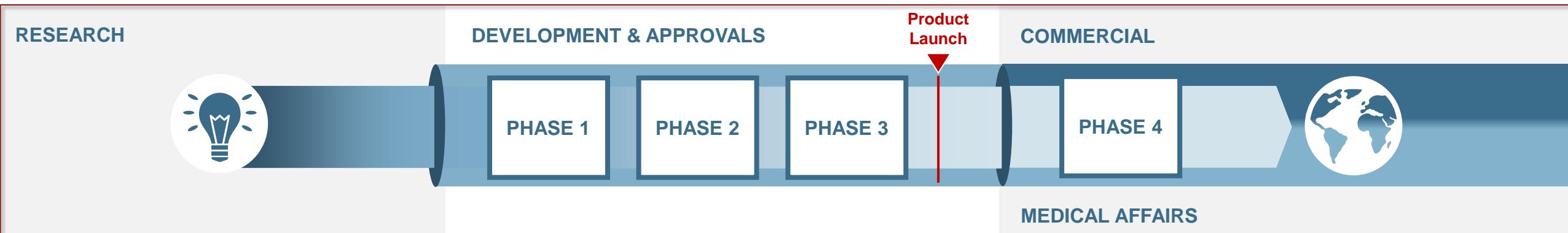
10 Minute Break



Poll 4

Application of RWE for Safety and Late Phase Lifecycle Management

Real World Data – Real World Evidence Across the Pharma Lifecycle



- ▶ Demonstrate health economics, reimbursement model
- ▶ Improve patient targeting, inform study design
- ▶ Monitor pharmacovigilance and drug safety
- ▶ Identify areas for label expansion

A few key biases

Confounding

Channeling bias

Immortal time bias

Confounding

When the effect of an exposure on outcome is distorted by one or more other factors

In RCTs, random assignment ensures balance in confounding variables between treated and controls

Including both known and unknown confounding factors

In non-randomized comparisons, including in RWD, balance is typically achieved by

1. multivariate adjustment
2. propensity score methods

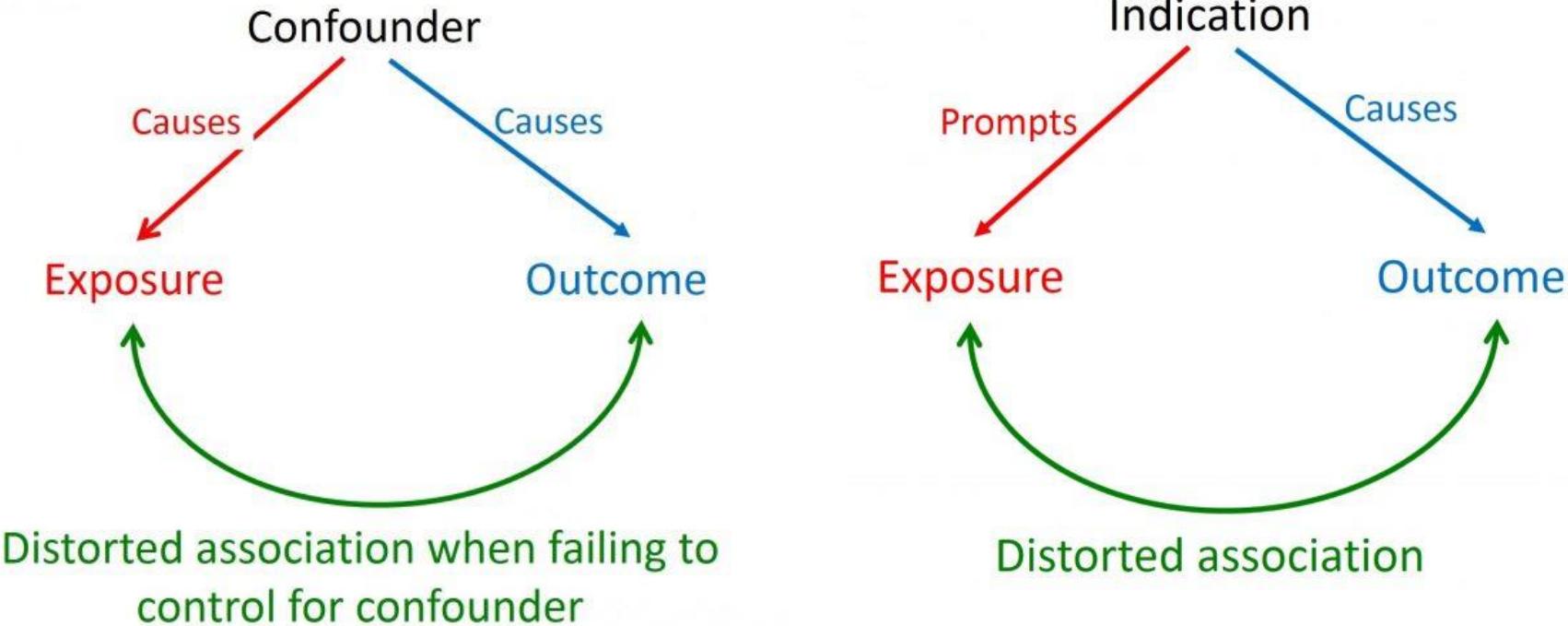
Note: these approaches all require that we know a lot about potential confounders



Is observed association causal?

Dales and Ury, Int J Epidemiol, 1978

Confounding vs Channeling Bias



1. Multivariate adjustment

Allows adjustment of potential confounding variables in a final outcome model

Commonly used in epidemiology, but declining use in Comparative Effectiveness Research (CER)

Easy to implement



Key shortcomings in the context of CER

- ✓ 1. Makes assumptions about the relationships between each confounding variable and the outcome
- ✗ 2. Assumes that each of those relationships is the same regardless of Treatment or Control group
- ✗ 3. Increase in degrees of freedom, yielding less statistical power

2. Propensity Score Methods

Balance Treated and Control patients on propensity to receive treatment

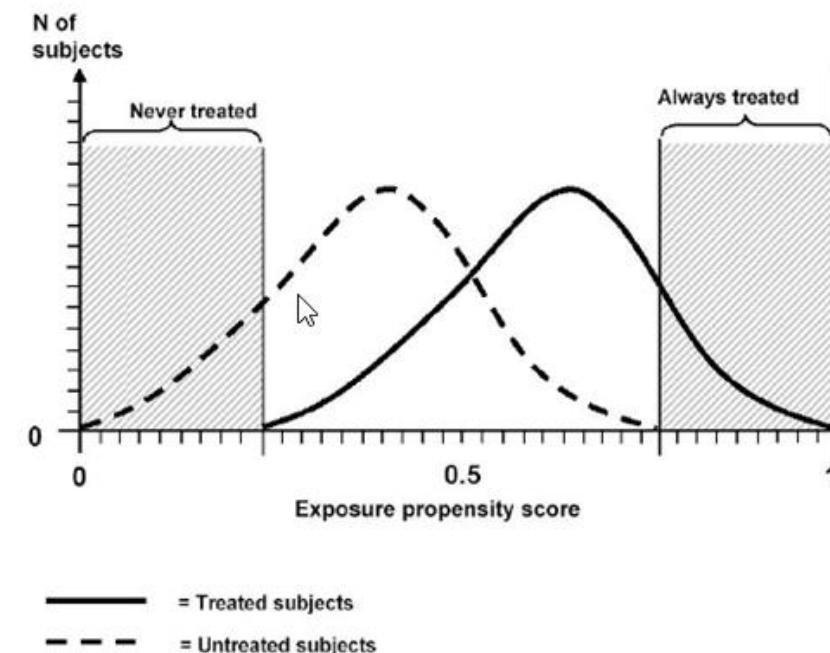
2-step approach:

1. Estimate propensity scores: the conditional probability that a patient receives treatment given the distribution of covariates at/prior to baseline
2. Adopt either a **matching** approach or a **weighting** approach to balance propensity scores between Treated and Control groups

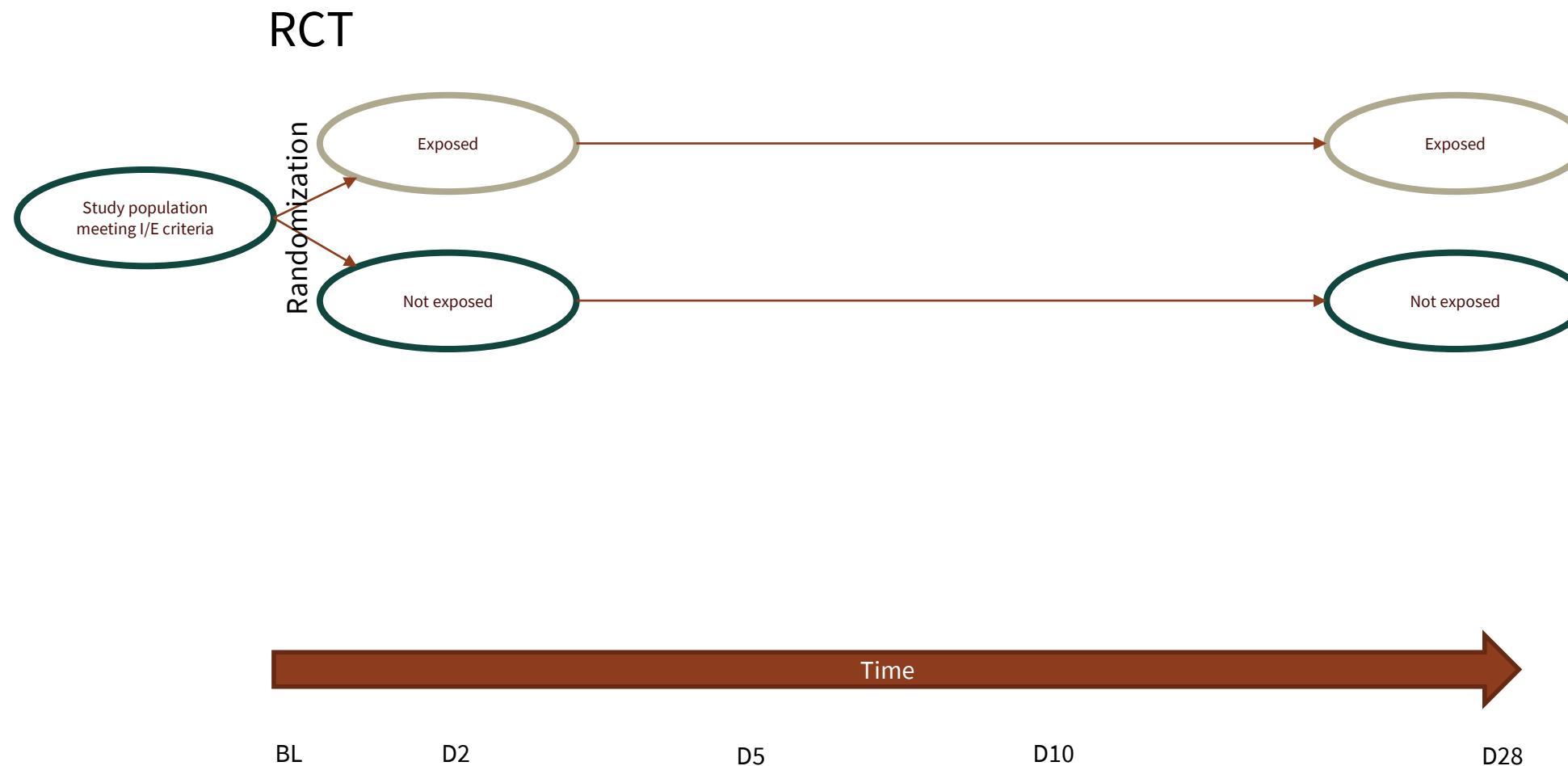
Goal of this process is to balance Treated and Control populations in aggregate across all covariates – simulate “randomization”

Assessment of balance comes from assessing differences in distributions of covariates after application of matching/weighting

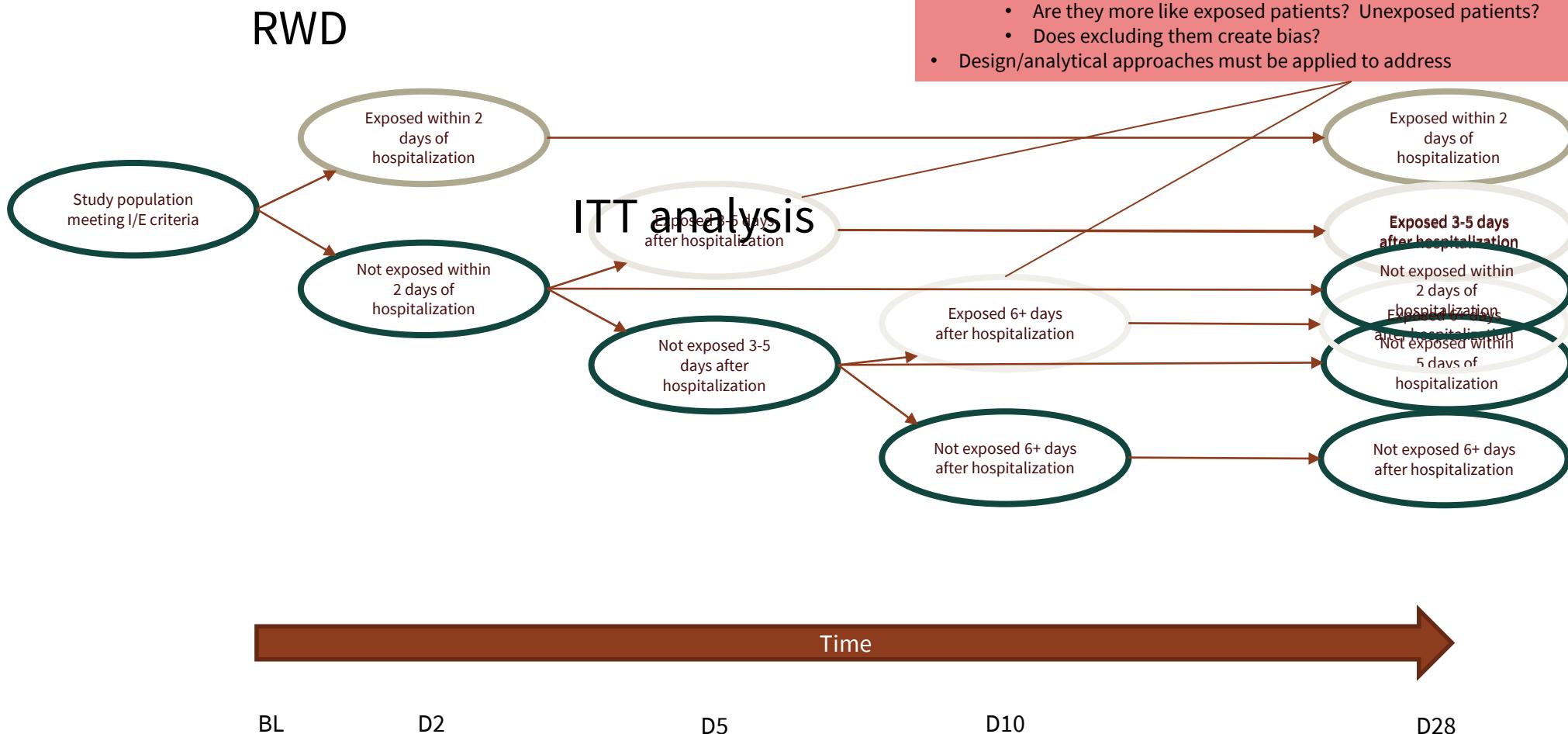
- Standardized Mean Differences of <0.10 are considered good



Immortal Time Bias – Defining Exposure

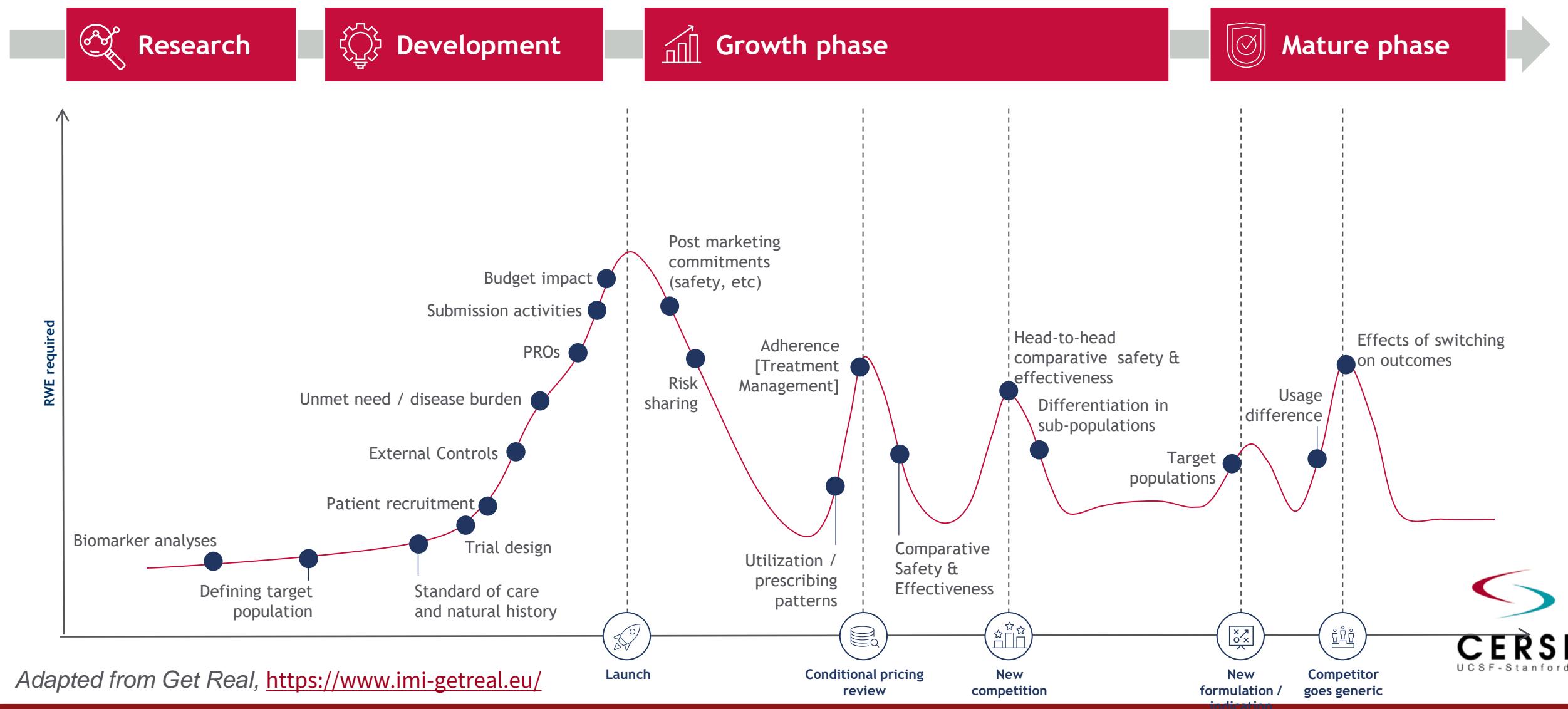


Immortal Time Bias – Defining Exposure

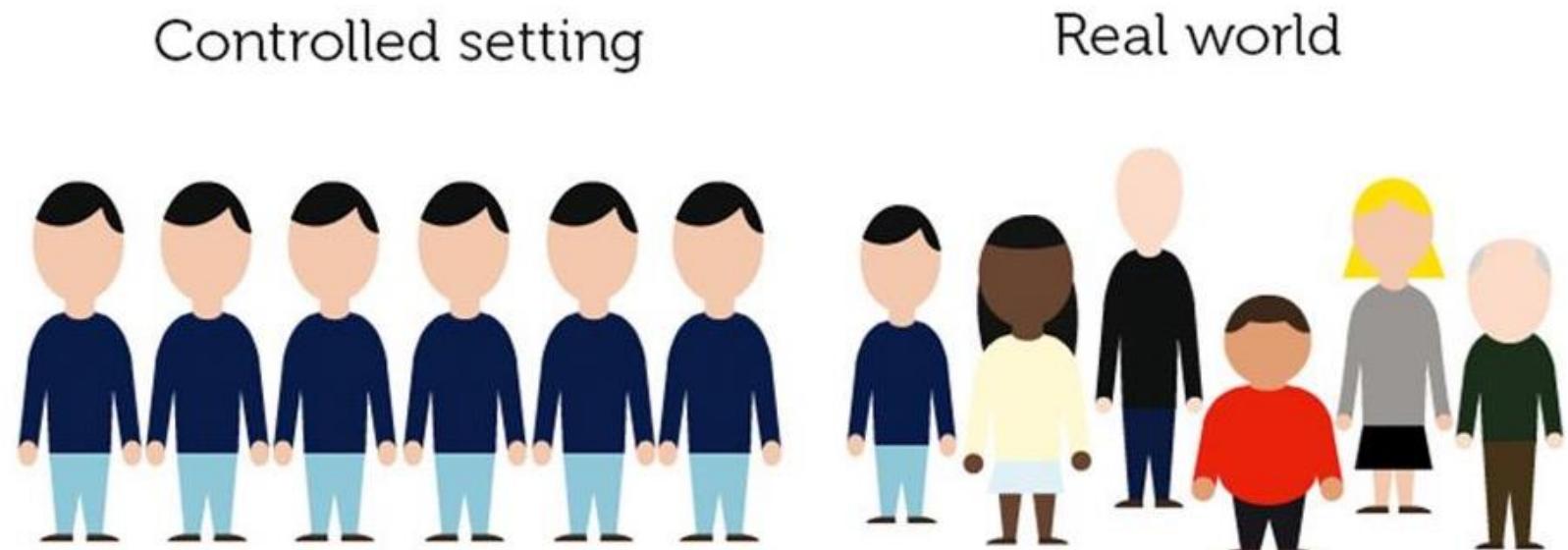


- What to do with these patients?
- Are they different from patients who are not treated within 2 days?
 - Are they more like exposed patients? Unexposed patients?
 - Does excluding them create bias?
- Design/analytical approaches must be applied to address

RWE and the product lifecycle



Clinical Trial Data vs Real World Data



Drugs in the Wild
Larger denominators
New subpopulations



Implications!



Get Real, <https://www.imi-getreal.eu/>

RWE for Safety vs Effectiveness

Safety

- Typically post-approval
 - Exception: Known/expected safety issues may be examined prior
- Almost always reactive (DPA, literature, agency, etc) and therefore hypothesis driven
 - Exception: background event rates, natural history

Effectiveness

- Pre-approval
 - Supplemental or Substantial evidence to support application
- Post-approval
 - Typically destined for literature
 - Confirmatory evidence
 - New populations/subgroups
 - Potential label expansion
 - Stakeholder engagement
 - Payers
 - Providers



Market Access

Key External Stakeholder: Payers

Continuous evaluation

Evidence sought for:

- Effectiveness, safety, ease of use
- For currently labeled indication
- Against current and future comparators

Health Care Resource Utilization

Examples

- Inpatient stays, duration
- Outpatient visits
- ED visits
- Prescription fills
- Skilled nursing facility visits
- Re-admissions
- Costs

Patient Reported Outcomes

-  Health-related quality of life (HRQOL)
-  Symptoms
-  Function
-  Satisfaction with care or symptoms
-  Adherence to prescribed medications or other therapy
-  Perceived value of treatment

NIH Pragmatic Trials Collaboratory
<http://rethinkingclinicaltrials.org>



Post-marketing commitments

Conditions of approval/market authorization

- Obligatory
- Negotiated with regulatory authorities in advance

Major types

- Targeted safety (*hypothesis driven*)
 - Identified or potential risks
 - Missing information (e.g., key populations, long-term exposures)
- Active safety surveillance (*hypothesis free*)
 - Typical in certain countries/regions, esp. APAC
- Special case
 - Establishing clinical benefit



Poll 5

Deep Dive Breakouts

- 1) New Target Discovery
- 2) Regulatory Submission of a Synthetic Control Arm
- 3) Characterizing Real World Effectiveness Post-Authorization

Deep Dive Breakout 1:

Multi-modal data for target discovery

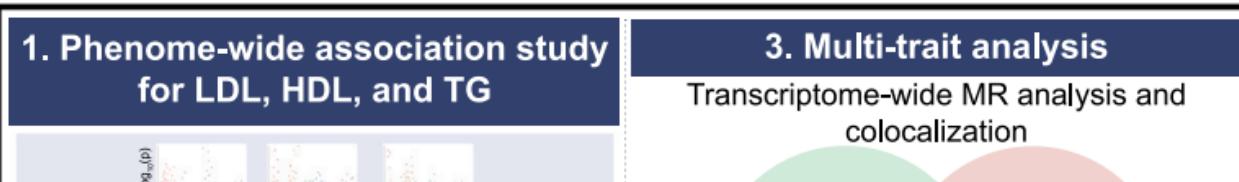
Deep dive into leveraging multi-omics for discovery

Cell Reports
Medicine

Article

Prioritization of therapeutic targets for dyslipidemia using integrative multi-omics and multi-trait analysis

Graphical abstract



Authors

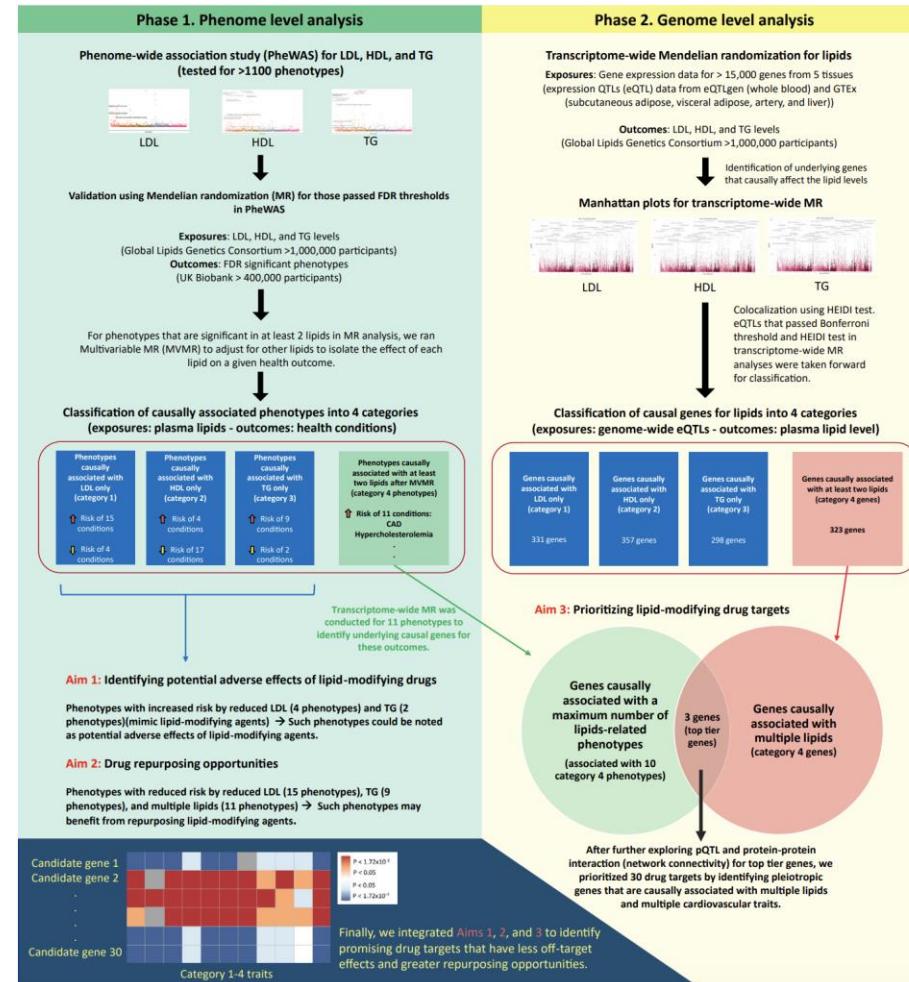
Min Seo Kim, Minku Song,
Beomsu Kim, ..., Pradeep Natarajan,
Ron Do, Hong-Hee Won



Overview of Kim et. al., 2023

Background

- Dyslipidemia is the eighth leading cause of death and a major risk factor for cardiovascular disease
- Less than 4% of drugs for these outcomes reach approval after entering Phase 1 vs. 9% for anti-cancer drugs
- Half of RCT's fail due to lack of efficacy but ¼ fail due to adverse events.
- Leveraging a purely computational approach, Kim et al. use multi-trait multi-modal data to prioritize therapeutic targets.
- Targets identified this way were 22-fold more likely to be approved or under investigation for approval.



Phase 1: Phenome level analysis

1. Multi-trait database (UK Biobank) to find diseases associated with HDL, LDL, and Triglycerides
2. Mendelian randomization (MR) to identify causal associations, only progress diseases associated with 2 or more lipid concentrations
3. Multi-variable MR adjusting for other lipids to isolate the effect of the lipid ~ disease specific relationship
4. Defined 4 categories
 1. Only LDL
 2. Only HDL
 3. Only TG
 4. 2 or more lipids
5. Transcriptome-wide MR to identify genes causally associated with the outcomes

AIM 1: Adverse events | These lipid-modifying agents will increase the risk of the outcome
AIM 2: Drug repurposing | These lipid modifying agents may decrease the risk of the disease outcome

Phase 2: Genome level analysis

1. Transcriptome-wide Mendelian randomization for lipids (lipids ~ gene expression (15k genes)
2. Fine mapping to ensure signals detected are not tagging other genes (colocalization)
3. Classification of causal genes for lipids into 4 categories
4. Venn diagram of genes associates with maximal number of lipid-related phenotypes & genes associated with multiple lipids
5. pQTL network connectivity for top tier genes
6. 30 drug targets prioritized

AIM 3: Prioritizing lipid modifying drug targets

Results

SORT1, PSRC1, CELSR2, PCSK9, HMGCR, APOB, GRN, HFE2, FJX1, C1QTNF1, and SLC5A8
20% (6/30) prioritized targets are already approved or under investigation for dyslipidemia.

This computational approach used the following data types on a large cohort:

Lab based measurements of HDL, LDL, and TG

SNP's from genotyped biospecimens

Quantified messenger RNA (transcriptomics)

Full medical history of disease diagnoses ("traits")

Separate data obtained to translate the genetic loci into suspected causal genes (eQTL, pQTL)

Concluding the targets identified here are 22x more likely to be approved or under investigation compared to GWAS-only curation (e.g. triaging hits from a dyslipidemia GWAS without the additional analytical contributions).

Deep Dive Breakout 2: Regulatory Submission of a Synthetic Control Arm

RWD as synthetic controls for regulatory submissions



Orphan Disease & Oncology Therapeutics

- Medical urgency / inadequate standard of care
- Expected large effect size
- Small patient population
- Rapidly changing treatment landscape
- Endpoints measurable with Real-World Data

applications (above not exhaustive list).

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics; Guidance for Industry; Draft Guidance

FDA issues policy to facilitate the use of electronic health record data in clinical investigations

July 18, 2018
Today, the U.S. Food and Drug Administration published a guidance for industry entitled, "Use of Electronic Health Record Data in Clinical Investigations: Guidance for Industry." The guidance provides recommendations for the use of electronic health record data in clinical investigations, including how boards (IRBs), and clinical investigations.

May 2019

FDA In Brief: FDA issues new guidance to facilitate expanded use of real-world evidence in medical device development

Aug 31, 2017
The FDA has issued a new guidance for industry, "Use of Real-World Evidence to Support Medical Device Development," which provides recommendations for the use of real-world evidence in medical device development, including how to collect, analyze, and interpret real-world evidence to support device safety and effectiveness.

July 2018

21st Century Cures Act: Making Progress on Shared Goals for Patients

Posted on December 13, 2016 by FDA Voice

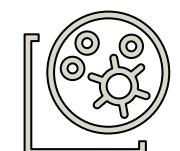
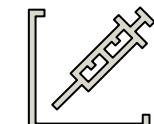
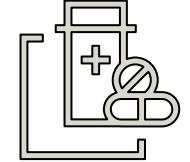
Publication of a Regulatory Decision- and Drug

Aug 2017

Dec 2016

Criteria for RWD Synthetic Controls/ Comparator Cohorts

- Medical urgency / inadequate standard of care
- Expected large effect size
- Small patient population
- Rapid entry of new therapies / Standard-of-Care changes often
- Endpoints measurable with Real-World Data

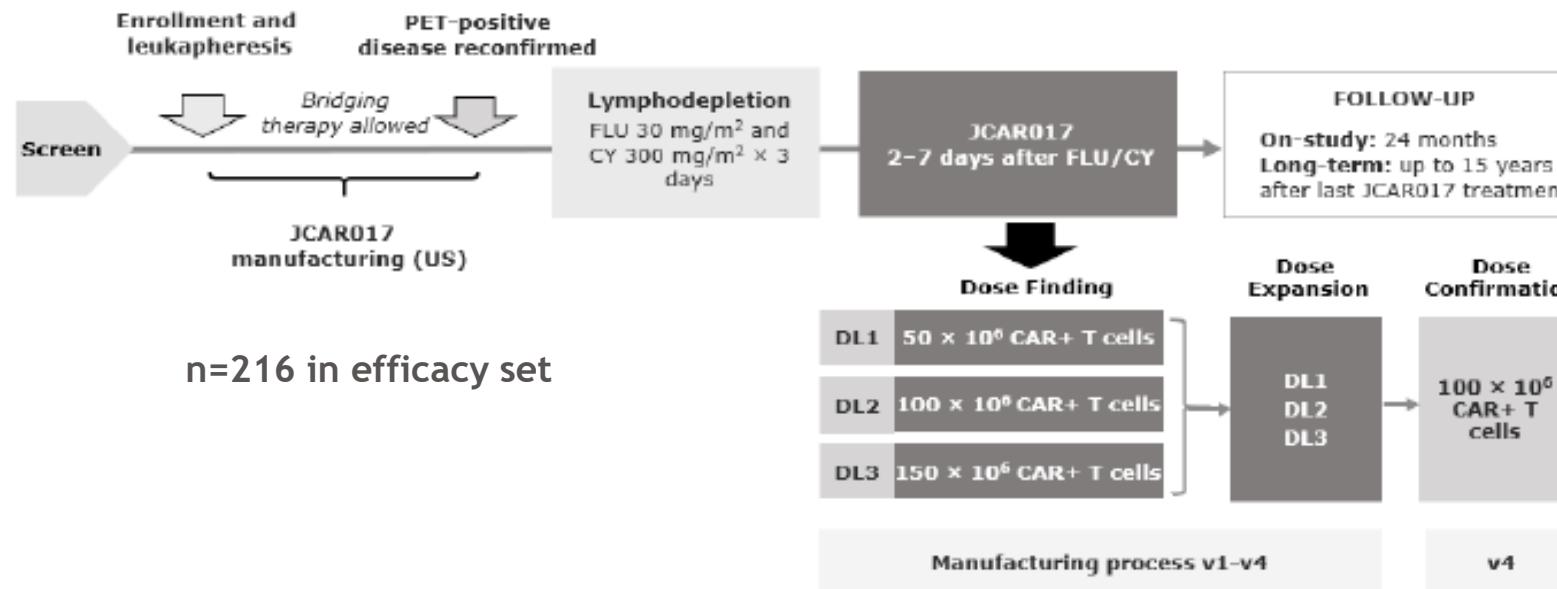


Liso-cel DLBCL 3L+ Comparator Cohort: NDS_NHL_001

- DLBCL is an aggressive lymphoma accounting for ~31% of all non-Hodgkin lymphoma.²
- Approximately 20-50% of DLBCL patients are R/R 1st line of therapy, and once a patients 3rd line OS < 7 months.³
- SCHOLAR-1, large international multicohort retrospective study reported R/R DLBCL patients had ORR of 26% and CR of 7% with median OS of 6.3 months.⁴
- Prior to the approval of Breyanzi, the treatment landscape was starting to improve, with approvals of Yescarta & Kymriah, but incidence of DLBCL marginally, yet steadily decreasing on average 0.9% over the past 10 years with age-adjusted death rates being.⁵

External Control in r/r LBCL as part of EMA filing (Apr-2022 EC Approval)

TRANSCEND NHL 001 was a single arm trial investigating Breyanzi in relapsed/refractory NHL, including DLBCL/PMBCL/FL3B:



- Primary endpoint: ORR
- Secondary endpoints: CR, DoR, PFS, OS

EMA Engagement During Development

- PRIME Meeting: historical control, inclusion of patients representative of EU setting, and statistical considerations, including pre-specification of covariates and analyses, as well as reference to the NICE guidelines for indirect comparisons
- Scientific Advice Meeting: data sources (RWD and Systematic Literature Review) for external control and the associated statistical analysis methods to support comparative evidence for MA; post-marketing registry data collection strategy

Breyanzi EFPAR Public Assessment Report. https://www.ema.europa.eu/en/documents/assessment-report/breyanzi-epar-public-assessment-report_en.pdf

Objectives

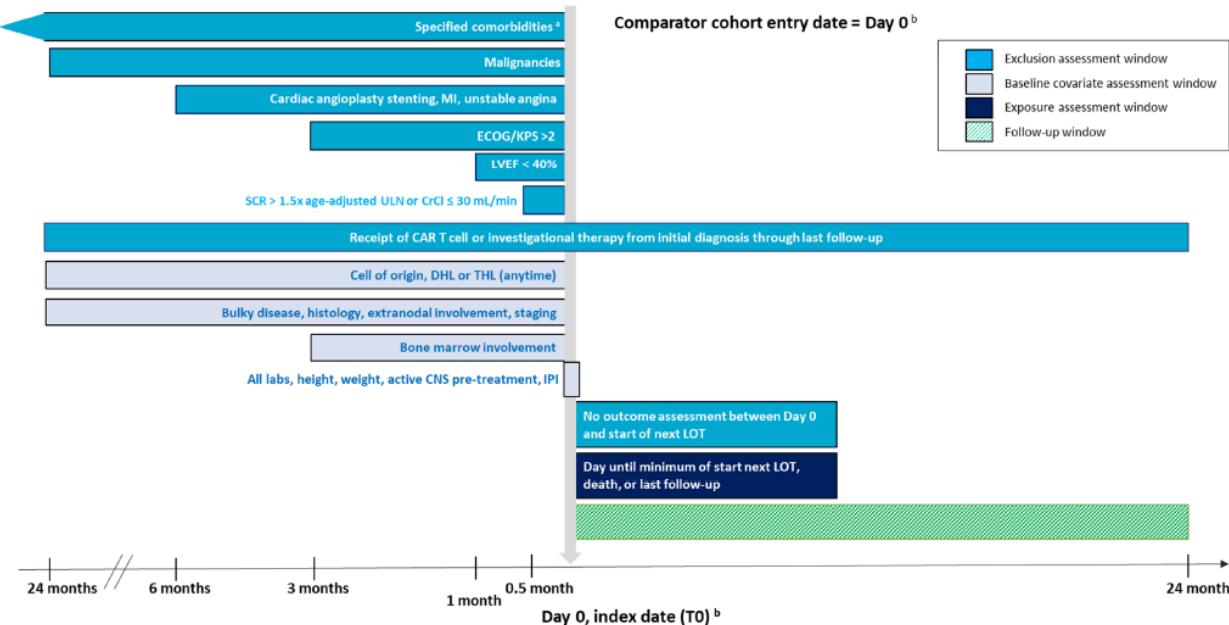
Primary objective: To describe demographic and clinical characteristics, treatment patterns and clinical outcomes of subjects with R/R B-NHL who are treated in RW clinical oncology settings.

Secondary objective: To assess the comparative effectiveness of liso-cel versus external controls.

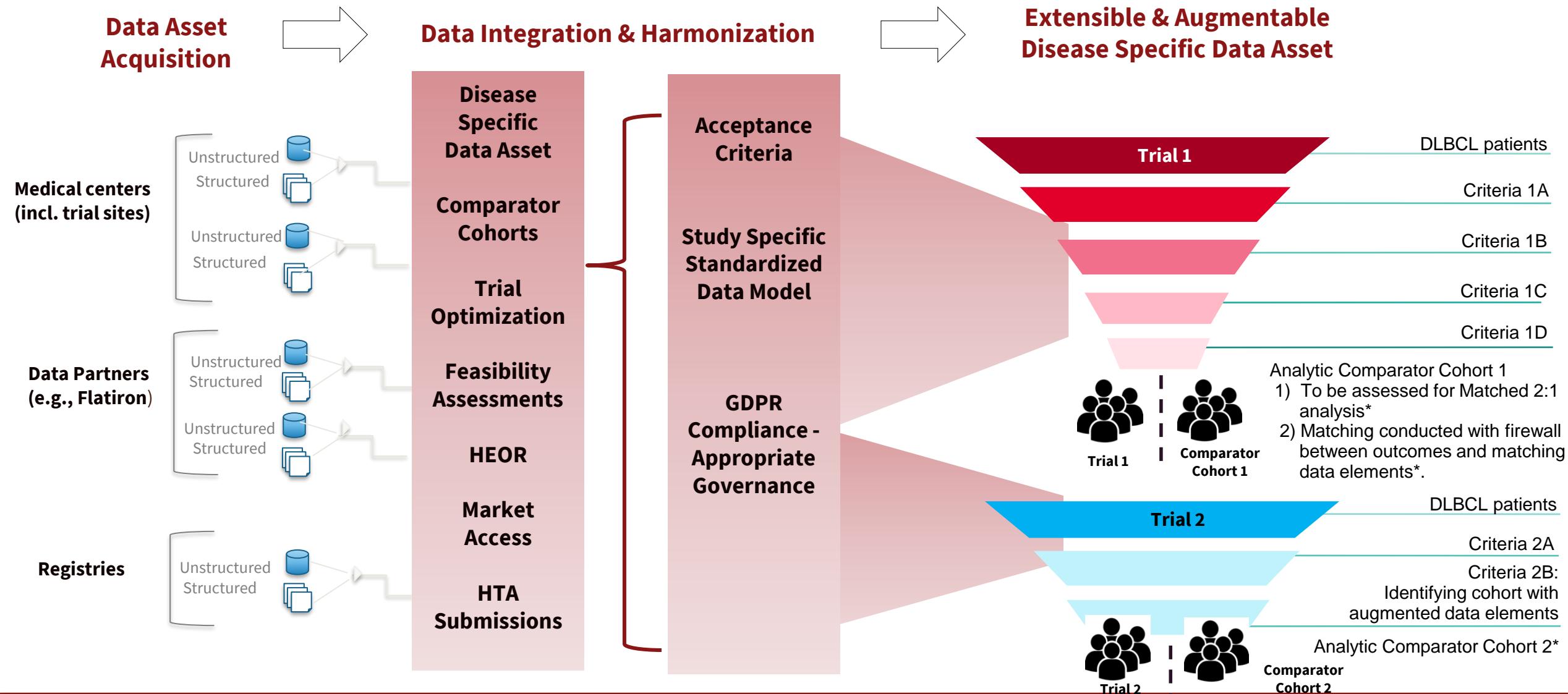
Van Le H, Van Naarden Braun K, Nowakowski M, et al. Use of a real-world synthetic control arm for direct comparison of lisocabtagene maraleucel and conventional therapy in relapsed/refractory large B-cell lymphoma. *Leuk Lymphoma*. 2023 Mar; 64(3): 573-585.

Study design

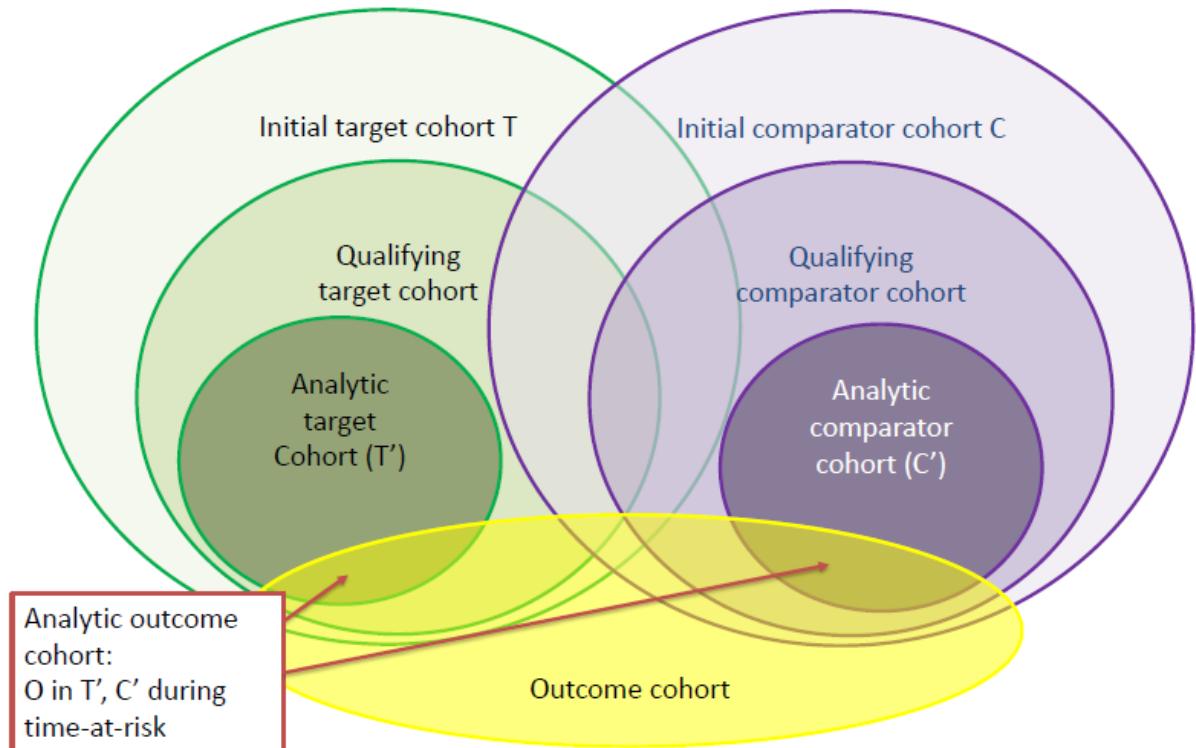
- Global, non-interventional, retrospective study with RW subjects from a larger cohort with eligibility similar to subjects in TRANSCEND trial; generation of comparator cohort reflecting non-cellular therapy standard of care
- Pre-specified study protocol and SAP for comparison of clinical trial single arm to RWD comparator arm.



Data Strategy: Operational and Technical



Data Strategy: Conceptual framework for cohort construction



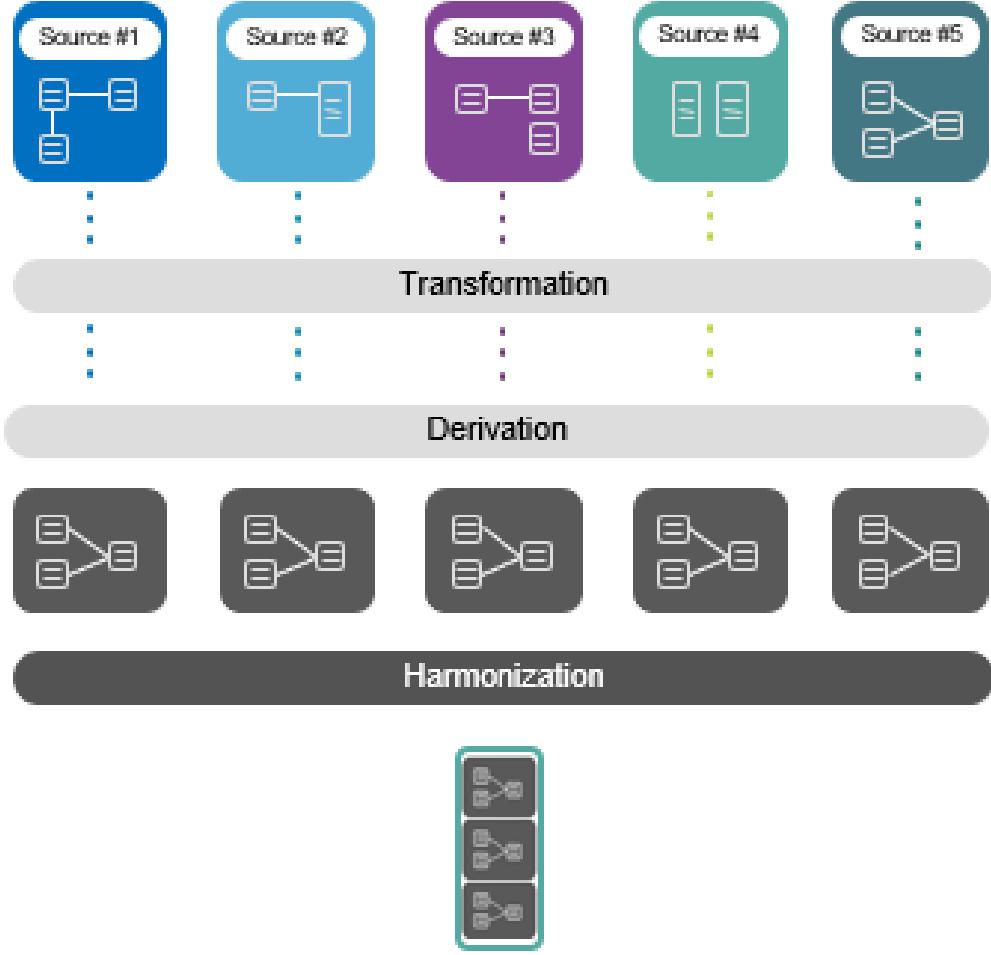
Conceptual framework of tiered cohort construction affords ability to understand the representativeness of RWD and details and implications of various criteria filters.

Initial Comparator Cohort (ICC) defined by criteria that will ascertain the population of interest at a broader level than the clinical trial arm. Equivalent in the clinical trial population would be the entire screened and enrolled patient population.

Qualifying Comparator Cohort (QCC) is a subset of the ICC defined by additional, more refined clinical measures closely aligned with the clinical trial inclusion and exclusion criteria.

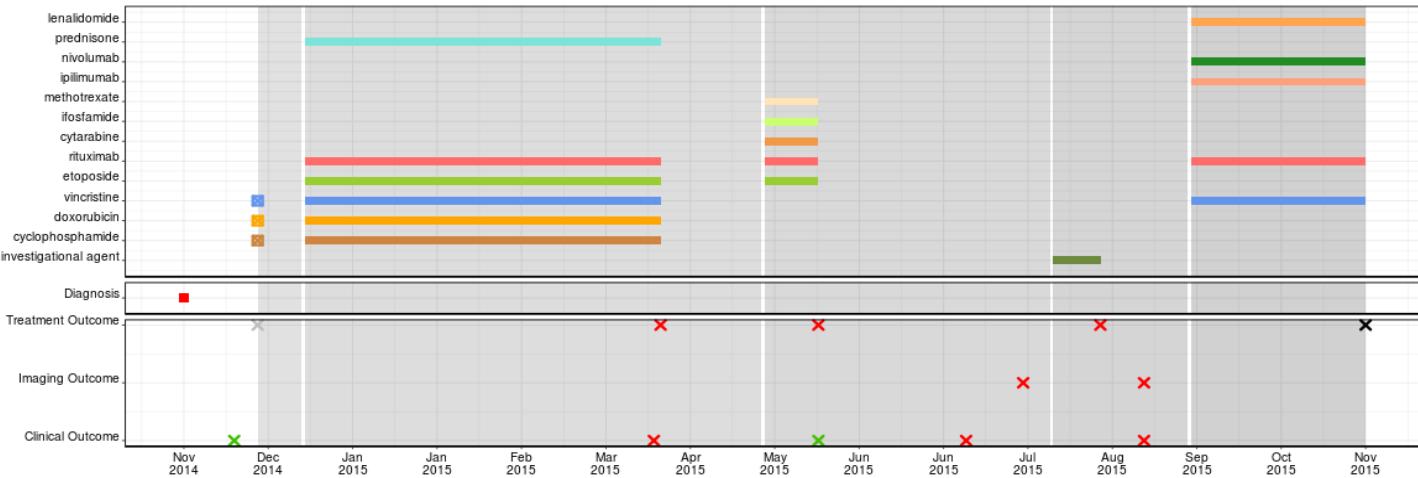
Analytic Comparator Cohort (ACC) is a subset of QCC matched to the baseline characteristics of the clinical trial arm.

Data Integration and Harmonization



- Data structure and variable standardization
- Variable conversion: valid values, date, unit, lab type,
- Managing unstructured data

- Operational definitions: derive clinical variables: LOT, progression and response
- Imputation rules for missing values



Data Harmonization: De-duplication



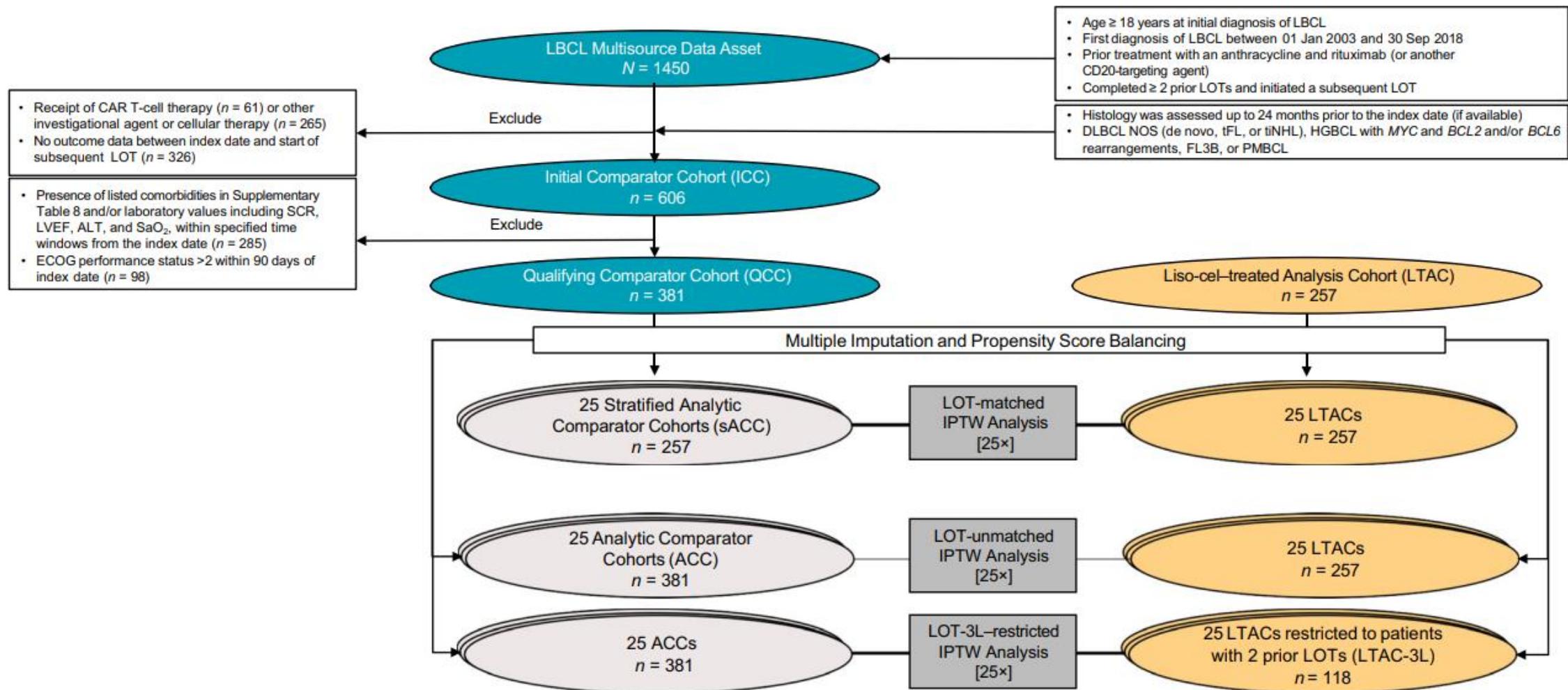
All patient data de-identified by multiple partners using different methods.

Three methods developed to identify potential duplicate patients:

1. Deterministic matching
2. Probabilistic matching using weighted similarity scores
3. Probabilistic matching using unweighted similarity scores

Input Data Sets					Cartesian Product Output				
Table A		Table B			Table C				
A	B	C	D	E	A	B	C	D	E
α	1	α	10	a	α	1	α	10	a
β	2	β	10	a	α	1	β	10	a
		β	20	b	α	1	β	20	b
		γ	10	b	α	1	γ	10	b
					β	2	α	10	a
					β	2	β	10	a
					β	2	β	20	b
					γ	2	β	10	a
					γ	2	β	20	b
					γ	2	γ	10	a
					γ	2	γ	20	b

Comparator cohort attrition



Challenges with RWD Index Dates

Patient #1

RWD –Retrospective assignment of index date



Patient #1

Clinical trial – Prospective assignment of index date



Stratified Random Assignment of Index Line of Therapy

- Eligibility for the clinical trial occurred prospectively and required DLBCL patients to have received at least 2 LOTs prior to receipt of liso-cel. Thus, patients were enrolled in the clinical trial at 3rd LOT or greater (LOT3+)
- Conversely, eligibility and index LOT for RW patients were defined retrospectively. This assignment of index LOT resulted in a different distribution of prior LOTs in the comparator arm.

Demographic and Baseline Characteristics

- Comparability between sACC and LTAC on age (median age = 62.0 and 63.0) and sex (63% and 66% males).
- sACC included patients from Europe (30%) while TRANSCEND only US.
- Differences between sACC and LTAC in prior HSCT (18% vs. 34%) and presence of bulky disease (20% vs. 11%).
- Differences in index date assignment in QCC, median number of prior lines and time from initial diagnosis to index date differed.

Prior Lines of Therapy: Primary and Sensitivity Analyses

	Primary Analysis		Sensitivity Analysis 1		Sensitivity Analysis 2	
	sACC (n = 257)	LTAC (n = 257)	QCC (n = 381)	LTAC (n = 257)	QCC (n = 381)	LTAC-2L (n = 118)
No. of prior LOTs						
Median	3.0	3.0	2.0	3.0	2.0	2.0
Min-max	2.0, 4.0	1.0, 8.0	2.0, 2.0	1.0, 8.0	2.0, 2.0	2.0, 2.0
No. of prior LOTs, n (%)						
1	0 (0.0)	9 (3.5)	0 (0.0)	9 (3.5)	0 (0.0)	0 (0.0)
2	127 (49.4)	118 (45.9)	381 (100.0)	118 (45.9)	381 (100.0)	118 (100.0)
3	67 (26.1)	67 (26.1)	0 (0.0)	67 (26.1)	0 (0.0)	0 (0.0)
4	63 (24.5)	39 (15.2)	0 (0.0)	39 (15.2)	0 (0.0)	0 (0.0)
5	0 (0.0)	11 (4.3)	0 (0.0)	11 (4.3)	0 (0.0)	0 (0.0)
6	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
≥7	0 (0.0)	11 (4.3)	0 (0.0)	11 (4.3)	0 (0.0)	0 (0.0)

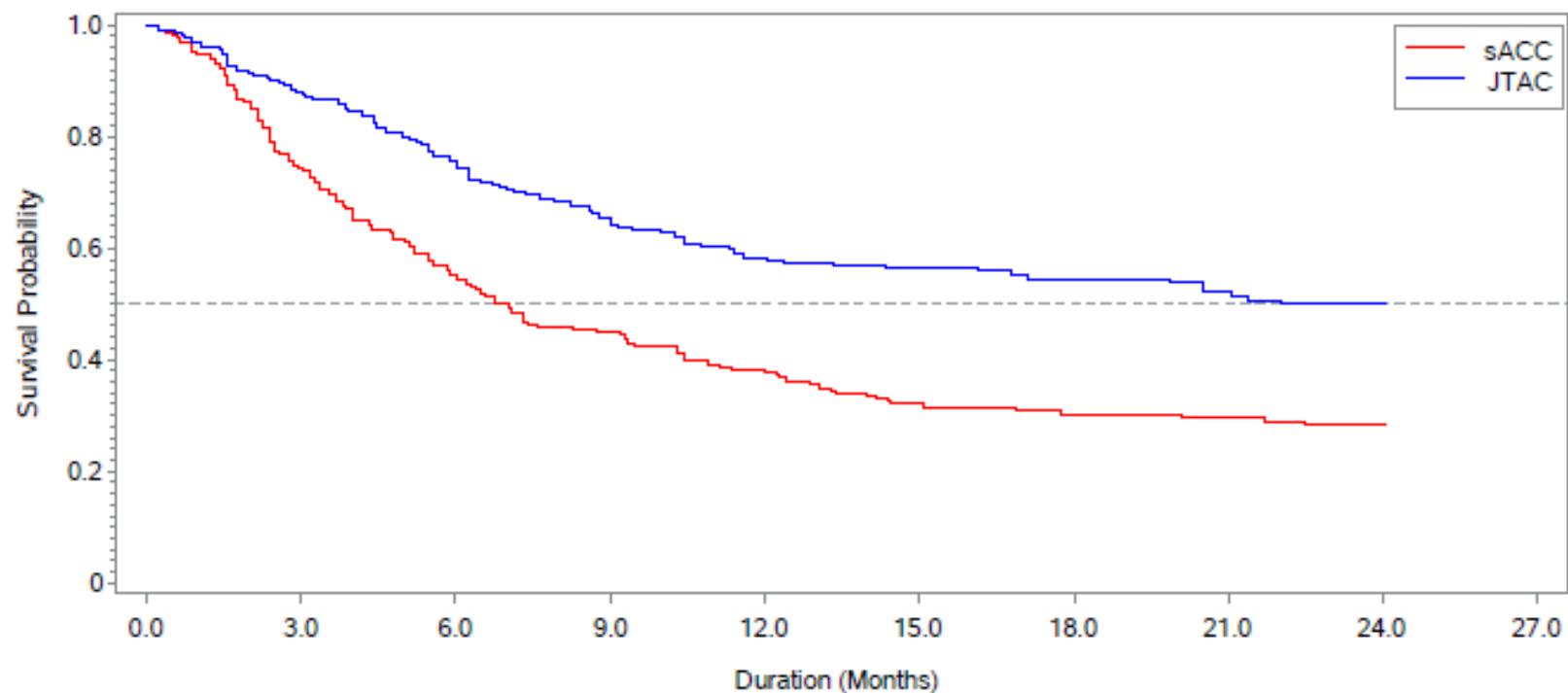
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≥7	0 (0.0)	11 (4.3)	0 (0.0)	11 (4.3)	0 (0.0)	0 (0.0)

Prior Lines of Therapy: Primary and Sensitivity Analyses

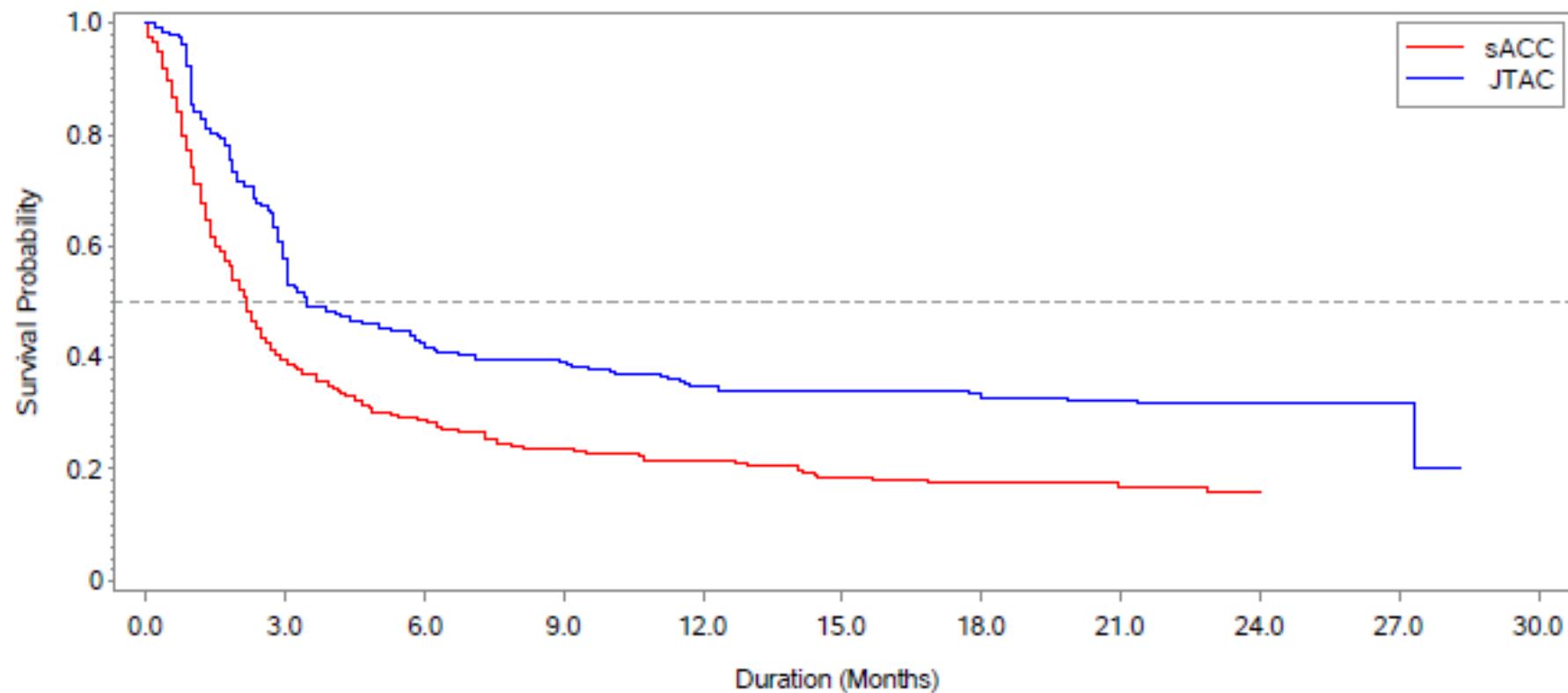
	Primary Analysis		Sensitivity Analysis 1		Sensitivity Analysis 2	
	sACC (n = 257)	LTAC (n = 257)	QCC (n = 381)	LTAC (n = 257)	QCC (n = 381)	LTAC-2L (n = 118)
No. of prior LOTs						
Median	3.0	3.0	2.0	3.0	2.0	2.0
Min-max	2.0, 4.0	1.0, 8.0	2.0, 2.0	1.0, 8.0	2.0, 2.0	2.0, 2.0
No. of prior LOTs, n (%)						
1	0 (0.0)	9 (3.5)	0 (0.0)	9 (3.5)	0 (0.0)	0 (0.0)
2	127 (49.4)	118 (45.9)	381 (100.0)	118 (45.9)	381 (100.0)	118 (100.0)
3	67 (26.1)	67 (26.1)	0 (0.0)	67 (26.1)	0 (0.0)	0 (0.0)
4	63 (24.5)	39 (15.2)	0 (0.0)	39 (15.2)	0 (0.0)	0 (0.0)
5	0 (0.0)	11 (4.3)	0 (0.0)	11 (4.3)	0 (0.0)	0 (0.0)
6	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
≥7	0 (0.0)	11 (4.3)	0 (0.0)	11 (4.3)	0 (0.0)	0 (0.0)

Overall Survival (sACC vs LTAC)



- After median follow-up times of 24.0 months in the LTAC and 17.9 months in the sACC for all surviving subjects, 52.2% of subjects and 36.7% of patients, respectively, were alive
- The median OS was statistically significantly longer in the LTAC as compared with the sACC (23.5 months versus 6.8 months; $p = 0.0001$)

Progression Free Survival – (sACC vs. LTAC)



- After median follow-up times of 10.6 months in the LTAC and 6.5 months in the sACC for all surviving subjects, 32.3% of LTAC subjects and 19.1% of sACC patients, respectively, were progression free.
- The median PFS was statistically significantly longer in the LTAC as compared with the sACC (3.5 months versus 2.3 months; $p = 0.0001$)

Discussion/Conclusion

- This study confirms the high unmet medical need for patients with 3L+ R/R LBCL.
- Assignment methods of index LOTs impacted the median overall survival in RW.
- Significantly improved outcomes were demonstrated with liso-cel treatment in the TRANSCEND cohort vs similar RW cohort.
- These findings support the conclusion that liso-cel provides significant and meaningful benefit for patients with 3L+ R/R LBCL relative to available therapies.

EMA Assessment of submitted RWE (EPAR) (Apr-2022 EC Approval)



Limitations

- When the significant clinical and biological **heterogeneity** of aggressive large B-cell lymphomas is considered, results from these indirect comparisons can only be accepted to “**contextualise**” the **results** observed with JCAR017, yet their **contribution to inform B/R evaluations is necessarily limited.**”

Conclusions

- With the intrinsic limits of naïve indirect comparisons, the results observed with JCAR017 in terms of response rate, depth and duration of response, although not clearly outstanding, **can still be considered of relevance when contextualised in the current treatment landscape**, as highlighted by the provided SLR, MAIC and by a recent meta-analysis investigating the efficacy of second-generation CAR T-cell therapy in DLBCL). Adjusted analyses from historical study NDS-NHL-001 also **showed higher ORR, CRR, PFS and OS in the reference dataset from study 017001 compared to the historical cohorts.**

Full Approval Granted

- Registry-based study also included as one of the post-marketing commitments for long-term safety & efficacy

Breyanzi EFPAR Public Assessment Report. https://www.ema.europa.eu/en/documents/assessment-report/breyanzi-epar-public-assessment-report_en.pdf

RWD Takeaways for Comparator Cohorts

- Address RWD methodologic challenges within study design
- Pre-specify analytic objectives
- Thoughtfully approach endpoint measurement
- Document, document, document



Q&A (5 min)

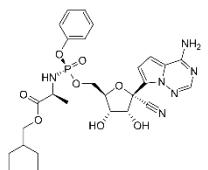
Deep Dive Breakout 3:

Characterizing real world effectiveness post-authorization: Remdesivir for COVID-19

Remdesivir is a Polymerase Inhibitor of SARS-CoV-2



SARS-CoV-2: single stranded positive-sense enveloped RNA virus, beta-coronavirus family^{1, 2, 3}



Remdesivir (RDV): prodrug of nucleoside analog that inhibits viral RNA-dependent RNA polymerase. Broad spectrum antiviral activity *in vitro* against members of several viral families

- filoviruses (e.g. Ebola)
- coronaviruses (e.g. SARS-CoV and MERS-CoV)⁴

RDV Mode of Action

- RDV intracellularly undergoes rapid conversion to the pharmacologically active nucleoside triphosphate (RDV-TP), GS-443902⁴
- RDV-TP is efficiently incorporated into the nascent RNA chain by viral RNA-dependent RNA polymerase (RdRp) resulting in delayed RNA chain termination during viral replication^{4,5}

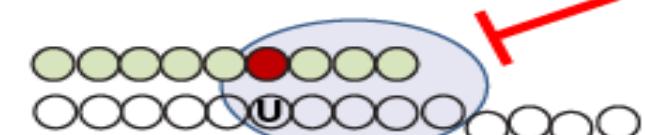
1 RNA synthesis



2 ATP/RDV-TP



3 Delayed chain termination



1. Zhu, Na; et al. *New England Journal of Medicine*. United States. 382 (8): 727–733. doi:10.1056/NEJMoa2001017.

2. Zhou et al *Nature* Feb 3, 2020

3. Lu et al. *Lancet* 2020

4. Warren TK, et al. *Nature* 2016;531:381-5.

5. Gordon, et al. 2020 <https://www.jbc.org/cgi/doi/10.1074/jbc.AC120.013056Lo> MK, et al. *Sci Reports* 2017;7:43395.

Rationale for Remdesivir Use for COVID-19

January 2020

Non Clinical

- 96% sequence homology in polymerase gene between SARS-CoV and SARS-CoV-2
- Demonstrated potent *in vitro* and *in vivo* activity against other coronaviruses (SARS and MERS)

Clinical

- Well characterized safety (N>500)
 - Patients w acute Ebola virus disease
 - Healthy volunteers

Use of RWD *Early* in a Pandemic

Benefits

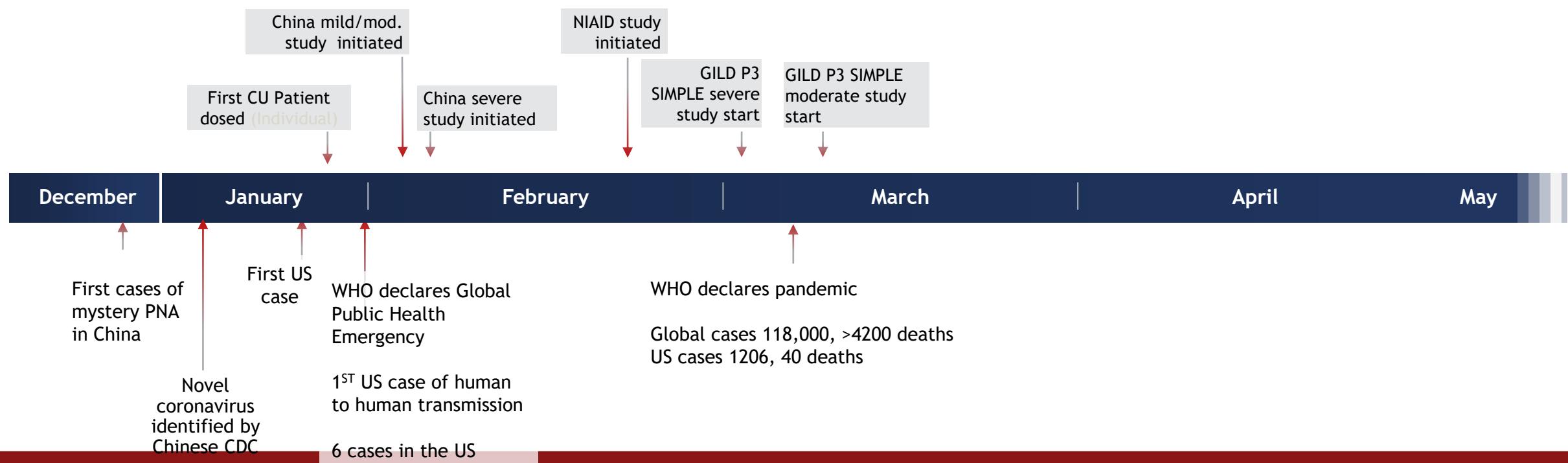
- Speed understanding of potential efficacy/safety
 - Internal decision-making, course corrections
 - Regulatory/external conversations

Challenges

- Evolving understanding of disease
 - Definitions, outcomes
- Logistics
 - For administrative data
 - Delay in initiation of coding
 - Slow data refreshes
 - Quarters → months → weeks
- For primary data
 - Scope of data collection
 - Data cleaning
- Interpretation
 - Generalizability/reliability



COVID-19 Pandemic Timeline – 2019-2020



Compassionate Use Program

Compassionate Use (Individual)

Jan 25
First CU Requests



Total CU Requests 115



CU in 20+ countries

Expanded Access (Institution)

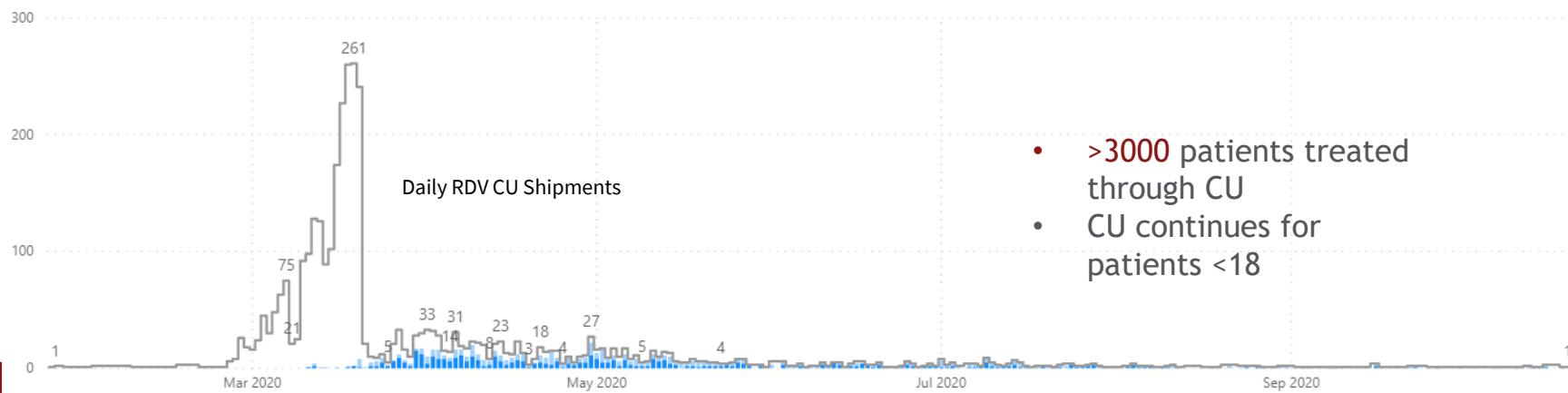
Mar 22

JANUARY

FEBRUARY

MARCH

April / May



- >3000 patients treated through CU
- CU continues for patients <18

Collecting Data in a Compassionate Use Program

Informing Clinical Development

Rationale

- Clinical trials not due to read out until April/May
- By mid-March, more patients treated on CU than in all clinical trials combined
- Early characterization in special populations

Challenges

- Initiating and inserting EDC into ongoing CU program
- Ensuring data integrity, mitigate bias
- Maintaining speed of shipments
 - Target: 24 hrs from request receipt
- Pandemic conditions
 - Transport/logistics
 - Panic/confusion
 - Some sites unaccustomed to clinical research, many queries
- Comparison group



Compassionate Use: Outcomes

By baseline oxygen support status

		Baseline Oxygen Support Status			
	n (%)	Invasive n=104	Noninvasive n=24	Suppl Air n=31	Room Air O2 sat <94% n=3
Post-treatment Oxygen Support Status	Death	27 (26)	5 (21)	1 (3)	0
	Invasive	39 (38)	5 (21)	1 (3)	0
	Noninvasive	8 (8)	4 (12)	0	0
	Suppl air	6 (6)	1 (12)	3 (10)	0
	Room air	12 (12)	0	2 (7)	0
	Discharge	12 (12)	9 (38)	24 (77)	3 (100)
	Improvement	38 (37)	10 (42)	26 (84)	3 (100)

- 48 % of patients showed an improvement* in oxygen support class
 - Median 14 days follow-up (Q1, Q3: 10, 17) from 1st RDV dose
 - 24% with clinical worsening

Patients with documented RDV start on or before 14 March 2020

*including 1 subject without baseline ventilation status who was discharged



Severe and Critical COVID-19 from Compassionate Use Special Populations

Pediatric	N=77
Male, n (%)	46 (60)
Median age, years (range)	14 (0-17)
<2 months	4 (5)
2 months to <1 year	8 (10)
1 year to <5 years	4 (5)
5 years to <12 years	20 (26)
>12 years	41 (53)
Duration of symptoms at baseline, days (IQR)	8 (6, 10)
Pregnant N=67	Postpartum N=19
Age, years	33 (21-43) 34 (20-41)
Gestational age, weeks	28 (14, 39) 30 (27, 36)
Days of hospitalization	3 (2, 5) 3 (2, 6)
ICU setting, n (%)	44 (67) 19 (100)
Duration of symptoms before RDV, D	9 (7, 11) 9 (6, 11)
Any medical condition history, (%)	45 (67) 10 (53)

* Causes of death were reported as COVID-19 for 2 patients, brain herniation, and multi-organ failure in context of COVID-19 + nosocomial sepsis

† A postpartum woman aged 30 y died due to severe acute respiratory distress syndrome (ARDS) and associated cytokine storm (unrelated to RDV).

1.Chiotos K, et al. IAS 2020. PE11763

2.Burwick R, et al. CID 2020



Pediatric (N=77)¹

- **Outcome:** Clinical recovery was observed in 80% of patients on invasive and in 87% not on invasive O₂ support
- **Safety:**
 - Any AE: 25 (32)
 - Any Serious AE 12(16)
 - Deaths 4(5)*



Pregnant Women (N=67)²

- **Outcome:** 93% recovered, 96% had clinical improvements, and no deaths reported
- **Safety**
 - Any AE: 22 (33)
 - Any serious AE: 12 (18)
 - AE leading to D/C: 7 (10)
 - Death: 0



Postpartum Women (N=19)²

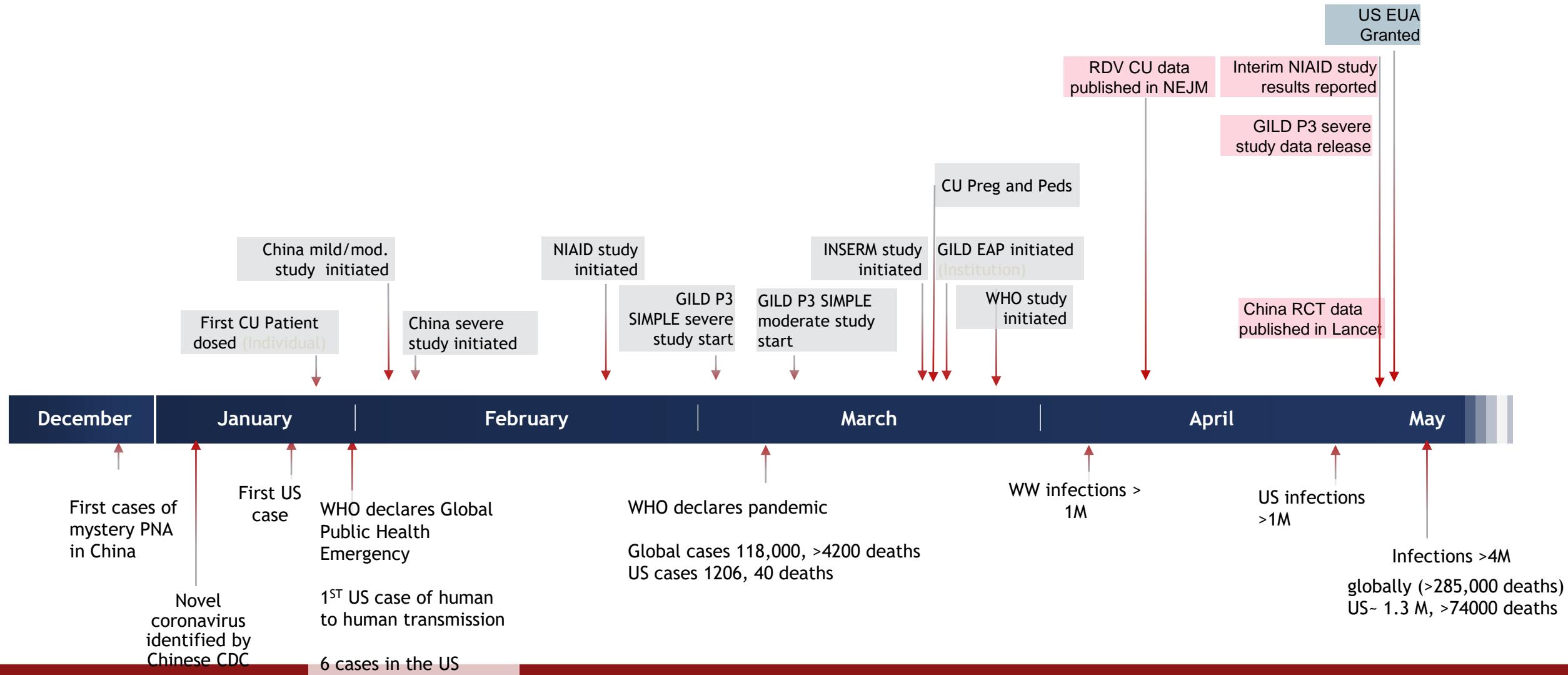
- **Outcome:** 90% recovered and 84% were discharged
- **Safety**
 - Any AE: 3 (16)
 - Any serious AE: 2 (11)
 - AE leading to D/C: 0
 - Death: 1 (%)†

Pediatric patients and pregnant and postpartum women treated with RDV in compassionate use had high rates of recovery and RDV demonstrated no new safety signals



CERSI
UCSF-Stanford

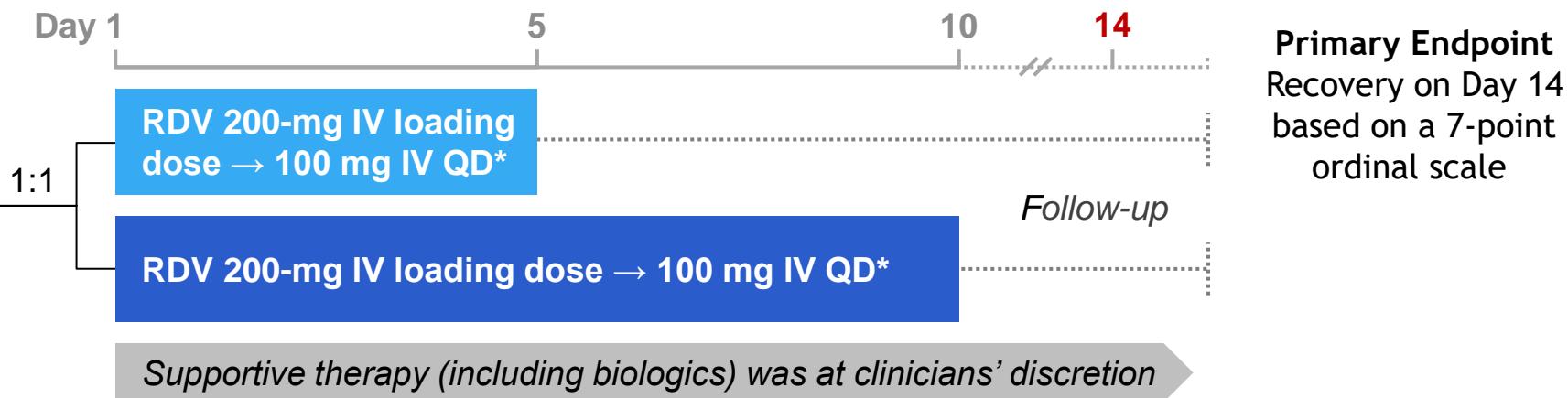
COVID-19 Pandemic Timeline



SIMPLE Severe Study GS-US-540-5773

Hospitalized adults with severe COVID-19 (target N=400)

- Confirmed SARS-CoV2 by rtPCR ≤4 days before enrollment
- SpO₂ ≤94% on room air
- Radiographic evidence of pulmonary infiltrates



*Recommended dosing; not all patients received 5- or 10-day treatment. rtPCR, reverse transcriptase–polymerase chain reaction assay; SpO₂, peripheral oxygen saturation.

- Phase 3, randomized, open-label, multicenter study (enrollment Mar 6-26): 55 sites in 8 countries
- Key eligibility criteria: creatinine clearance ≥50 mL/min
 - Patients with screening ALT or aspartate aminotransferase (AST) >5x the upper limit of normal (ULN) were excluded

Evolution of a (frenzied) search for an external comparator

Published cohorts

- Generalizability/comparability in SoC pandemic's impact (Asian cohorts)
- Data access/use
- Insufficient granularity of aggregated data

Secondary RWD data assets

- Small sample sizes early on
- Delayed data reporting
- Comparability (US-only datasets)

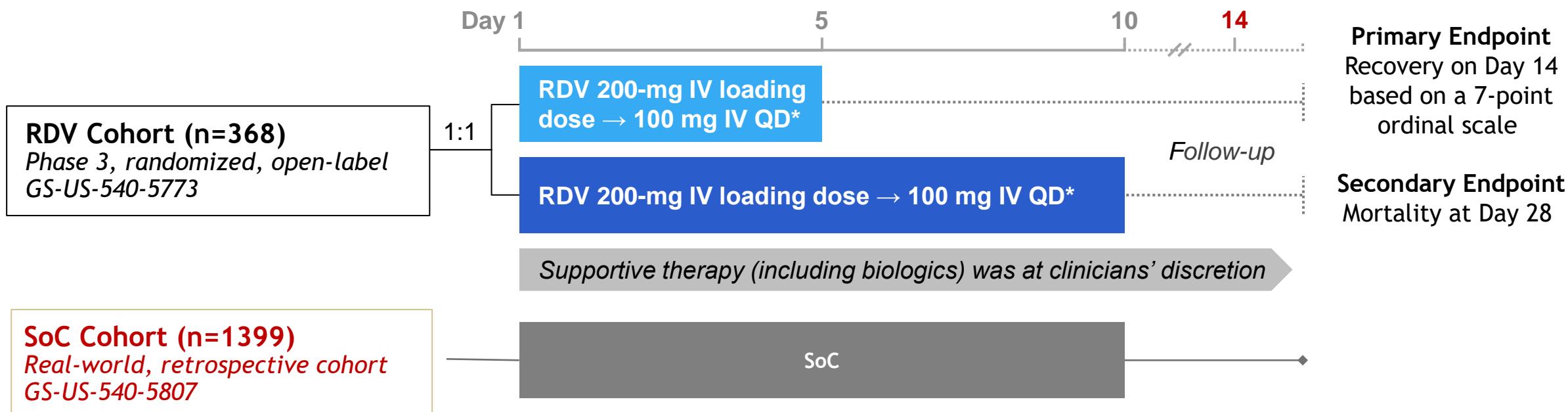
Develop fit for purpose data collection

		Study 5773 ¹ (NCT04292899/GS-US-540-5773)	Study 5807* (EUPAS34303/GS-US-540-5807)
		✓ Phase 3, prospective, randomized (5 vs 10 days), open-label trial	✓ Real-world, retrospective, longitudinal cohort
		✓ SARS-CoV-2 infection confirmed by PCR ✓ Hospitalized with severe COVID-19 ✓ ≥18 years of age	
		✓ SpO ₂ of ≤94% on room air or requiring supplemental oxygen ✓ Radiographic evidence of pulmonary infiltrates	
		✓ SOC plus IV RDV ^t (RDV cohort)	✓ SOC according to local practice at that time (non-RDV cohort)
		✓ FPI Mar 9, 2020; analysis cut-off Apr 10, 2020	✓ FPI Feb 6, 2020, analysis cut-off Apr 10, 2020

*Exclusion criteria were retroactively applied to Study 5807 to ensure study populations were comparable, specifically: venoarterial extracorporeal membrane oxygenation (ECMO) on D1; ALT/AST >5x the upper limit of normal on D1; creatinine clearance <50 mL/min (Cockcroft-Gault) at D1; and pregnancy/breastfeeding. Patients were allowed medications that may potentially treat COVID-19, excluding RDV: 1200 mg on D1, followed by 100 mg daily on D2–5 or D2–10. ALT: alanine aminotransferase; AST, aspartate aminotransferase; D, day; FPI, first patient in; IV, intravenous; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO₂, oxygen saturation

RDV for Severe COVID-19 vs Real World SoC

Comparing efficacy in adults with severe COVID-19 using data from a phase 3 trial and a retrospective cohort of patients with severe COVID-19 treated with SoC



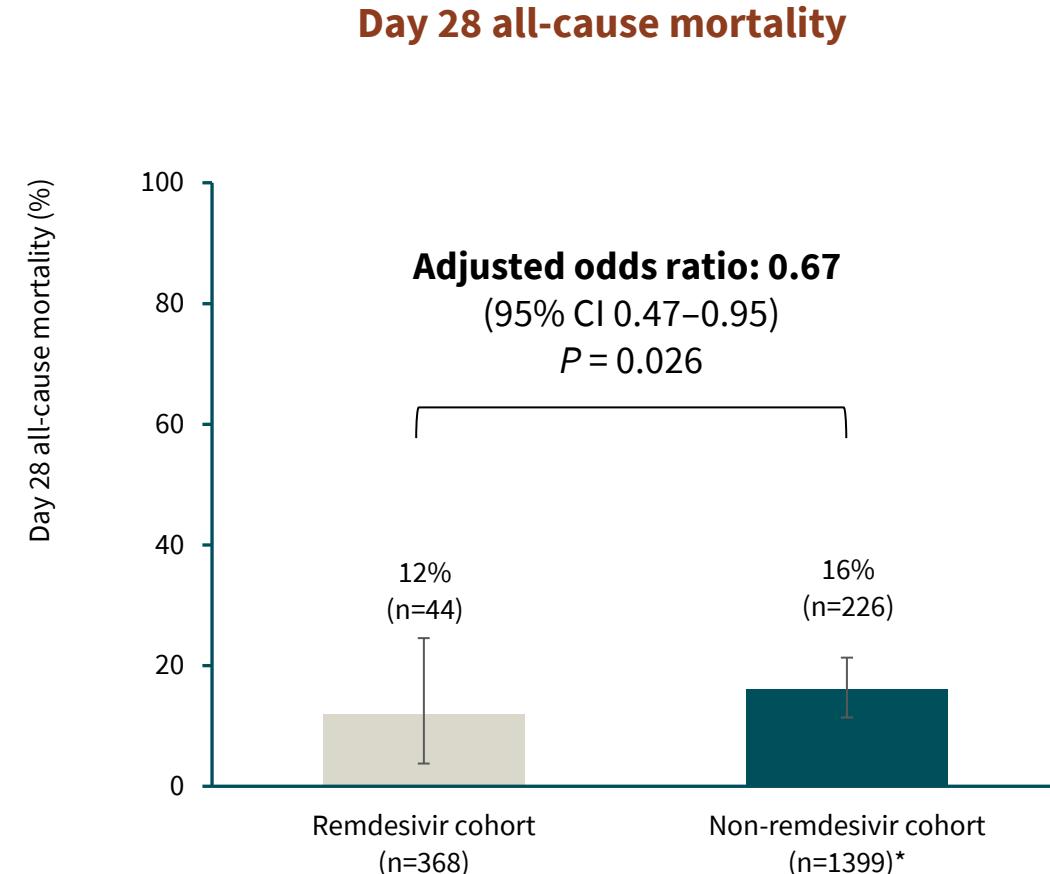
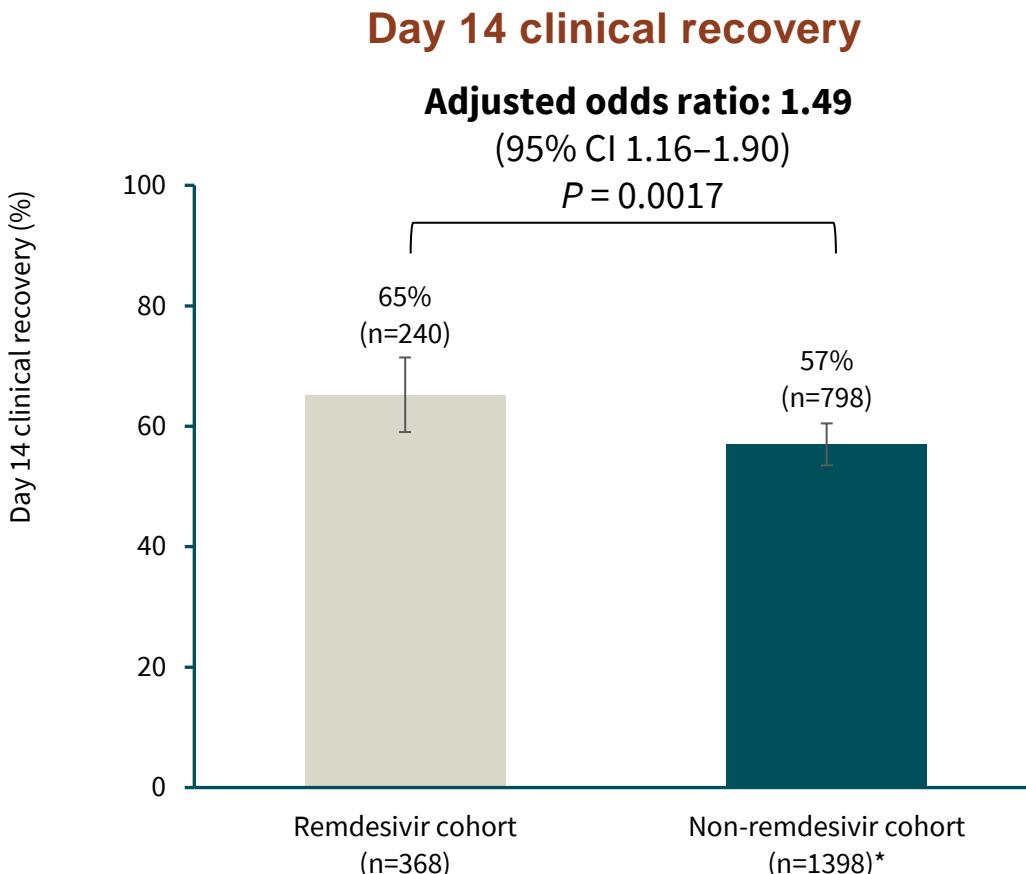
- PS-matched multivariable logistic regression used to estimate the treatment effect of RDV vs SoC

SoC, standard of care

1. Olander SA, et al. Clinical Infectious Diseases, 24 July 2020 <https://doi.org/10.1093/cid/ciaa1041>

2. National Library of Medicine (U.S.). (2020 July). Identifier NCT04292899 <https://clinicaltrials.gov/ct2/show/NCT04292899>

RDV for Severe COVID-19 vs Real World SoC 5773A vs 5807 - Final Results



*Weighted statistics
CI, confidence interval

Patients in the remdesivir cohort had significantly higher Day 14 clinical recovery rates and significantly lower Day 28 all-cause mortality rates compared with the non-remdesivir cohort

Olander et al, CROI 2021, Presentation 01295

Creating and Using a RWD External Comparator During a Pandemic

Benefits

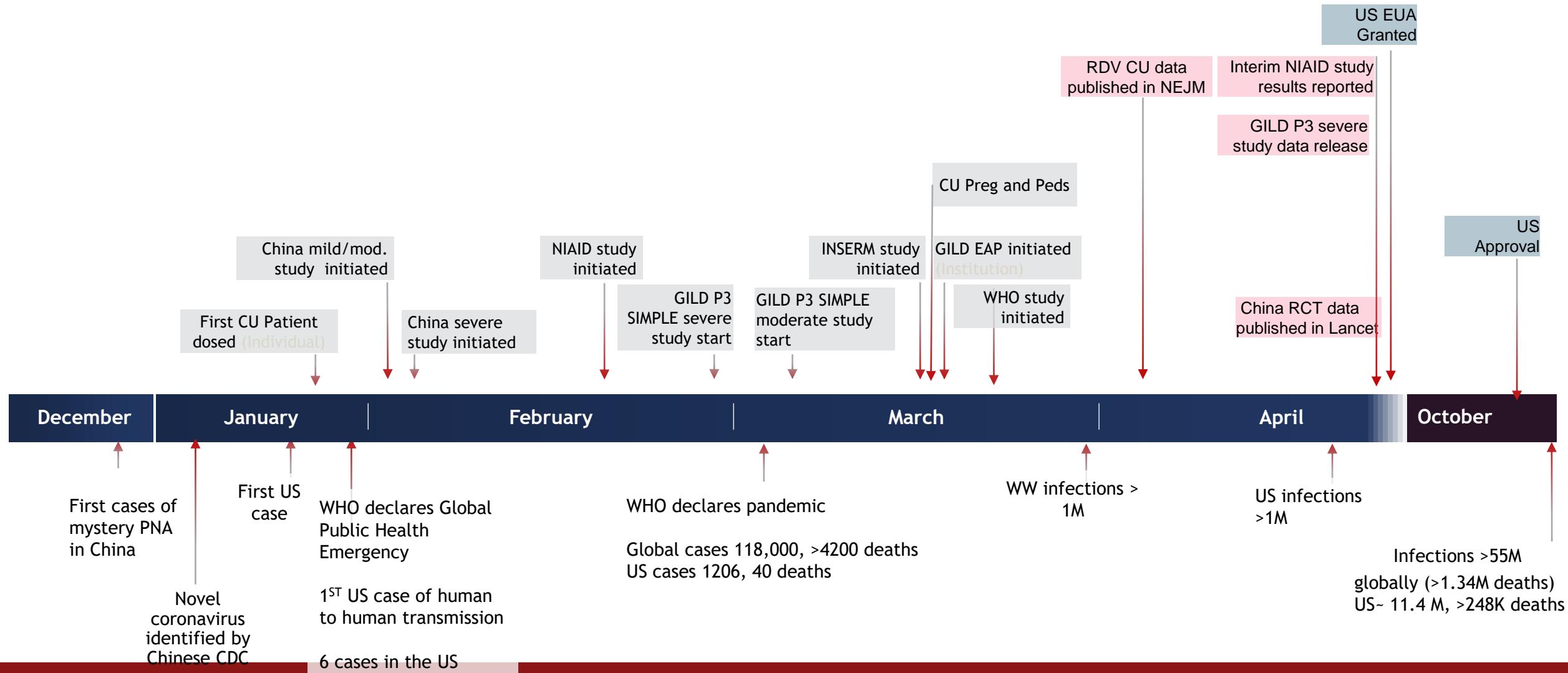
- Permits comparisons
 - Esp where assignment to SOC or PBO might slow enrollment or pose ethical challenges
- Data receipt remarkably fast
 - Once protocol and data elements finalized
 - If can rely entirely on a single existing source, can be even quicker

Challenges

- Advanced statistical methods used for comparisons
 - Propensity score weighting
 - Complicates acceptance
- *De novo* collection can be extremely resource intensive
 - Combination of EDC entry and bulk EHR transfers
 - Data querying and harmonization very intense
- Growing understanding of disease may shift focus of outcomes, covariates



COVID-19 Pandemic Timeline: 2019-2020



Post-Authorization RWD Analysis



Later use of RWD

State of Data

At this point, we are “later” in the pandemic

- Many RWD datasets available, 10,000 to >100,000 COVID-19 cases
- Codes more widely used, better specificity
 - For disease (and confirmed disease)
 - For individual therapies
- Disease understanding has changed
 - Therapies (RDV, corticosteroids, plasma, mAbs, biologics, etc) widely used
 - Originally other meds were being used, with little to no evidence
 - Timing of treatment
 - Disease management

Methods

HealthVerity Comparative Effectiveness Analysis

Study design: comparative effectiveness analysis using a matched cohort design in US-based hospital claims data for hospitalized COVID-19 patients with or without RDV treatment during stay

Data source: HealthVerity data ecosystem ^a

Study population: patients hospitalized with newly diagnosed COVID-19 (May 1, 2020 ^b – May 3, 2021)

Key eligibility criteria: patients ≥ 18 y with COVID-19 diagnosis on their hospitalization record and ≥ 12 months enrollment or claims before index date, with ≥ 1 medical encounter during this period, and no evidence of clinical trial participation

Matched comparator: RDV-exposed patients were matched 1:1 to referent patients using a 2-stage process:

1 RSS for exact balance on key variables

- Calendar time (+/- 3 days)
- Patient demographics (age, gender)
- COVID-19 disease severity (baseline O₂ requirement, ICU status)
- No. of days between admission, RDV exposure
- Corticosteroid use

2 PS matching to control for confounding

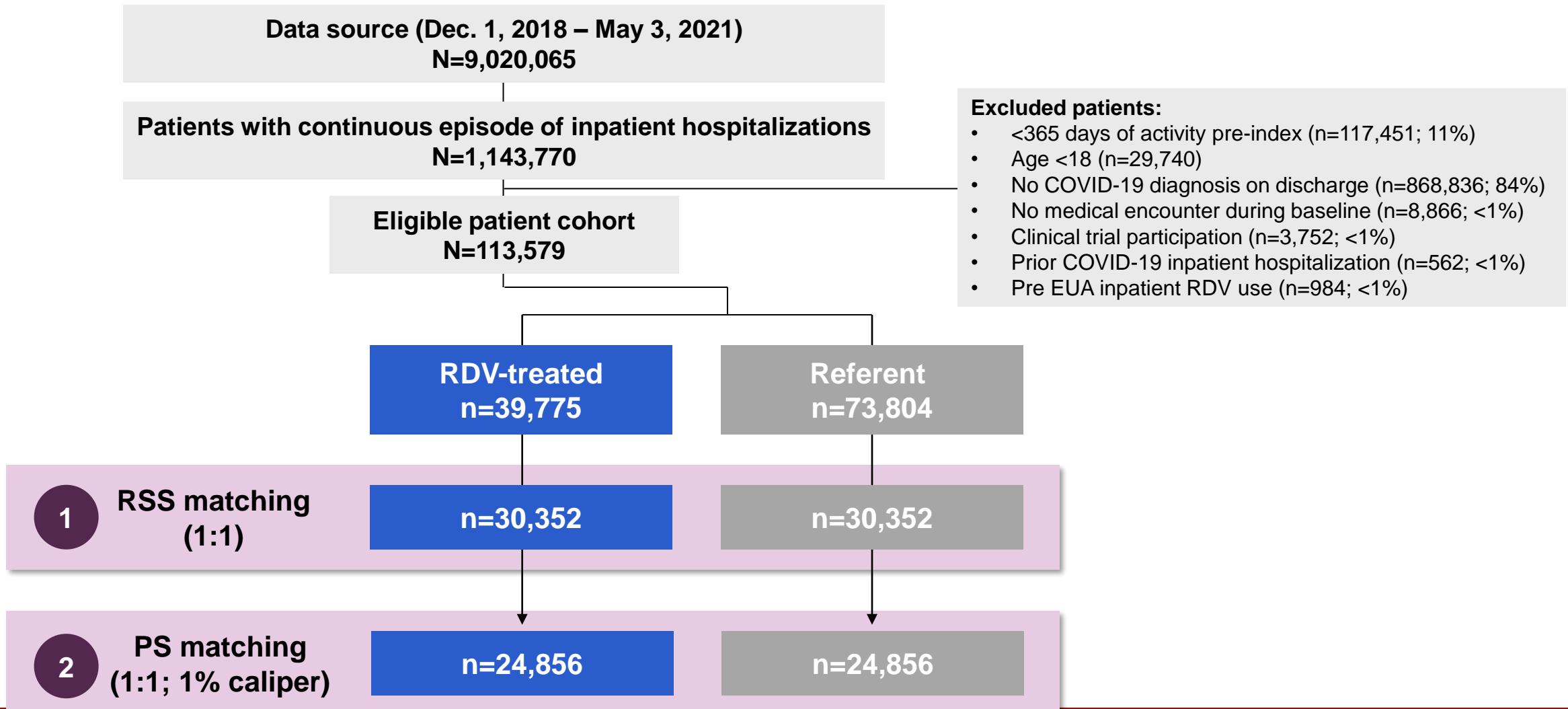
- Patient demographics
- Clinical characteristics
- Comorbidities
- Concomitant medications

PS matching was repeated for each subgroup analysis

^a De-identified US-based hospital chargemaster, medical and pharmacy claims, laboratory, and EHR data, including Veradigm claims and EHR data, for patients with activity between Dec 1, 2018 and May 3, 2021; ^b RDV emergency use authorized on May 1, 2020; PS, propensity score; RSS, risk set sample.

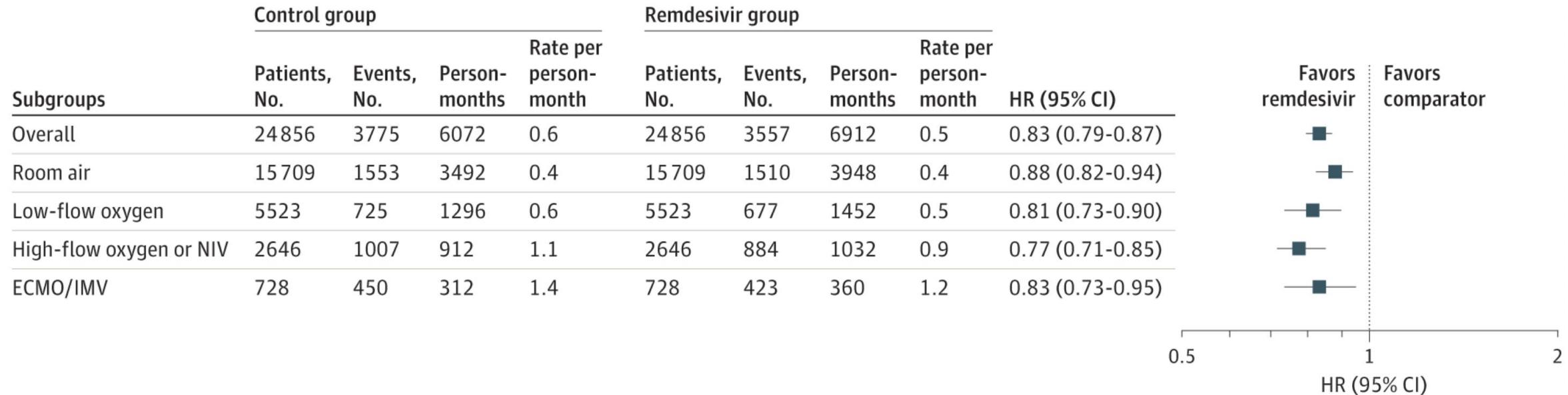
Patient Disposition

HealthVerity Comparative Effectiveness Analysis



Primary Outcome Results

Mortality by Baseline O₂ Support Subgroup: Primary Analysis



RDV was associated with a statistically significant reduction in mortality in patients hospitalized with COVID-19

Statistically significant mortality reductions were observed in each subgroup

Lessons Learned

RWE in Future Pandemics

Inside the organization

Seek support from leadership for bold moves/investments/resources

Invest in scaling labor-intensive processes

Seek partnerships to speed RWD refreshes

RWE useful internally and externally

Outside the organization

Accelerate adoption of coding schema

Spread understanding of and appreciation for RWE

RWE fluency needed across all stakeholders

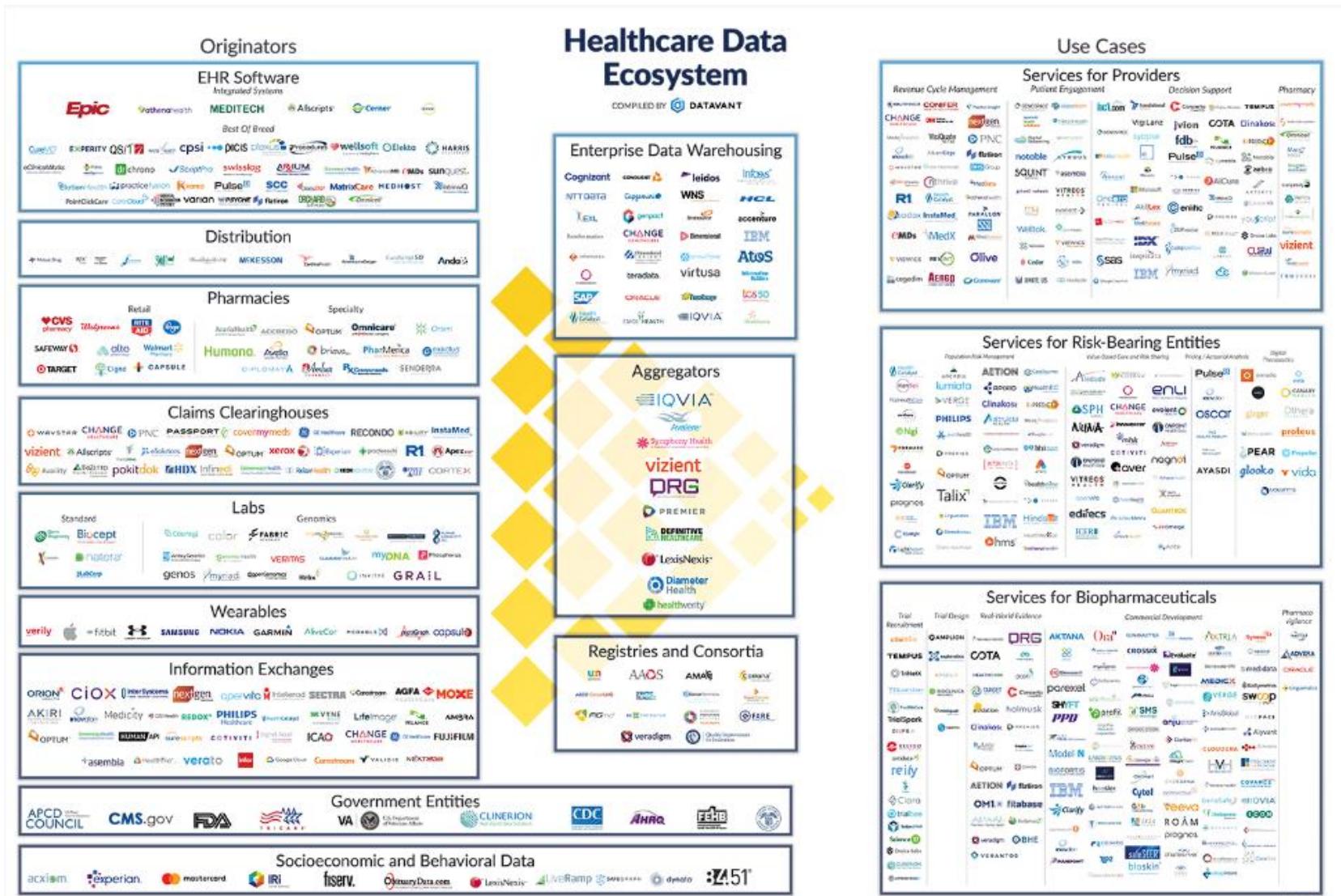




Q&A (5 min)

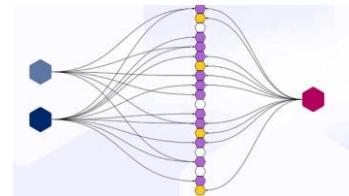
Wrap Up: Looking Ahead

Growing RWD Ecosystem Becoming Less Fragmented

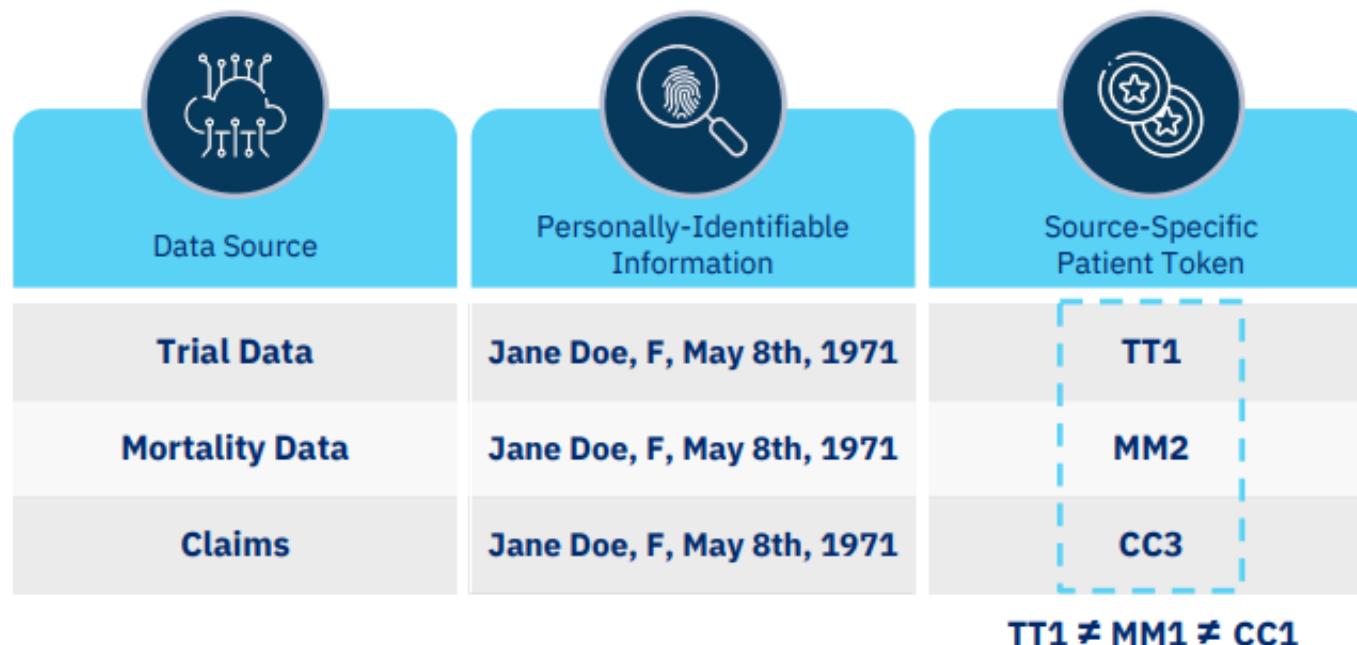


Major Real-World Data Types: <https://datavant.com/resources/blog/how-americas-health-data-infrastructure-is-being-used-to-fight-covid-19/>

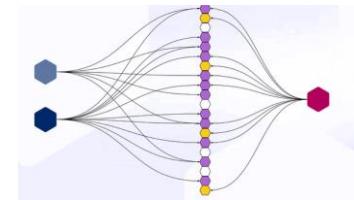
Tokenization of Disparate RWD



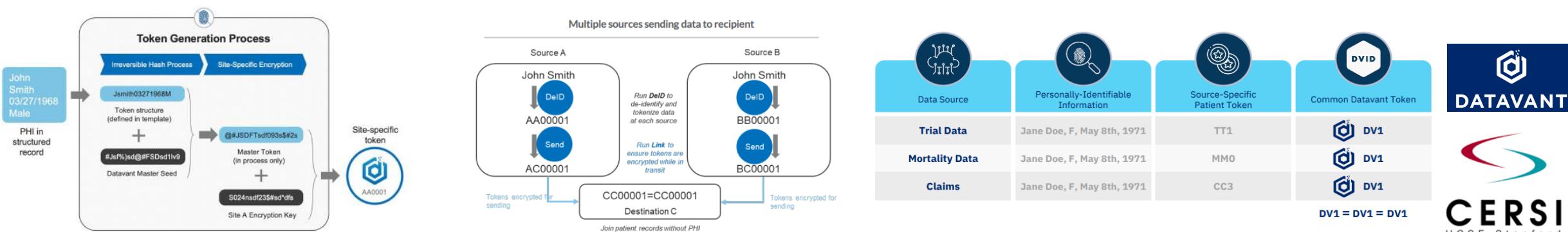
- RWD is de-identified, hence no way to link patient level data together across disparate data sources.
- Tokenization affords the ability to match patient-level data from disparate data sources while maintaining privacy requirements (no sharing of PII) via site-specific, encrypted token.



Tokenization Process

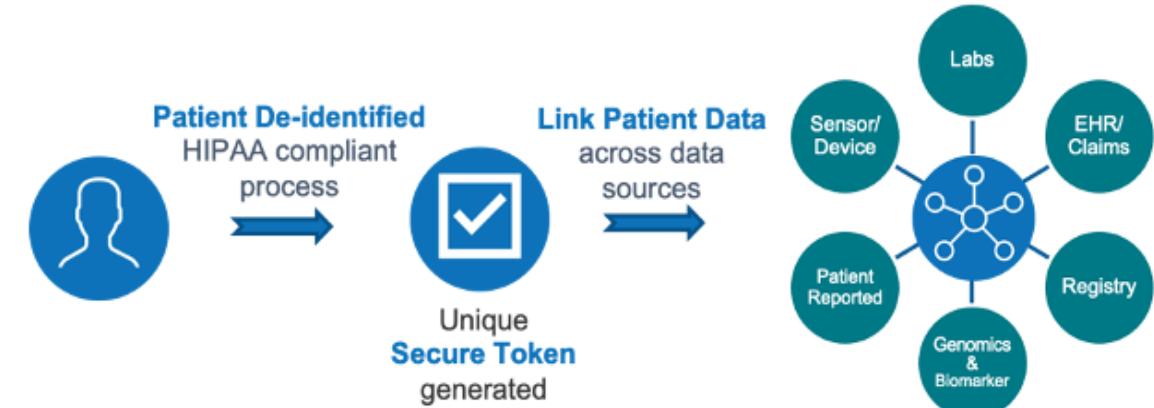


- Creation of specific, encrypted patient token that can not be reversed engineered for patient re-identification.
- Site-level control of token usage by other organizations.
- Patient key is never exposed; if token ever exposed only impacts origination site.



Impacts on RWD Ecosystem

- Increase single source data density by linking across disparate data sources.
- Identify more diverse patients for clinical trial recruitment.
- Facilitate rapid and direct site engagement and confirmation of patient eligibility.
- Connect prospectively collected clinical trial data with RWD to understand full patient journey, conduct long-term follow-up on safety and efficacy.



In closing

Today we learned about what RWD is, how it used across the drug discovery pipeline, and the tremendous advantages these data types bring to delivering better medicines to the marketplace.

While there is a lot to cover, some key points to remember.

- Real world data are generated across the health care ecosystem.
- While complexities exist in their generation and extraction, RWD are now a crucial part of the drug discovery, development, and regulatory pipeline.
- The field of RWD and the evidence derived from it requires an in depth understanding of how the data were generated, and best data management and analysis practices.





C E R S I
U C S F - S t a n f o r d