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Leveraging RWE to Support Regulatory Decisions: An Update on Efforts to Inform Policy

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Clinical Professor, Fuqua School of Business
Editor-In-Chief, *Therapeutic Innovation and Regulatory Science (TIRS)*

Collaboratory Grand Rounds
March 15, 2019

What I’m Not Going to Cover (beyond this slide)

- Traditional RCTs are still the gold standard for drug development
- Definitions of RWD and RWE
  - Data and evidence are not the same
  - RWE includes observational and randomized designs
- Rationale for why RWE can be an important source of evidence for labeling and related regulatory decisions
  - Enables evidence development on longer term outcomes
  - Includes broader populations/uses more typical of routine practice
  - Incorporating RWE into product labeling can lead to better-informed patient and provider decisions w/more relevant information
  - Can me more relevant evidence to patients, caregivers, and providers
  - Can be developed in more cost-effective and efficient ways for certain clinical questions

2016 Congressional RWE mandate

21st Century Cures Act

- Passed in 2016 and twinned with ongoing PDUFA VI discussions
- Requires FDA to "establish a program to evaluate the potential use of RWE to…":
  - Help support approval of a new indication for a drug approved under section 505(c)
  - Help satisfy post-approval study requirements
- Established the general roadmap from 2016 passage to 2021:
  - Legislation -> Convening -> Framework -> Pilots -> Guidance

Priorities since 2016: Multistakeholder work

FDA Publications

Frameworks and Proceedings

Expert Commentary

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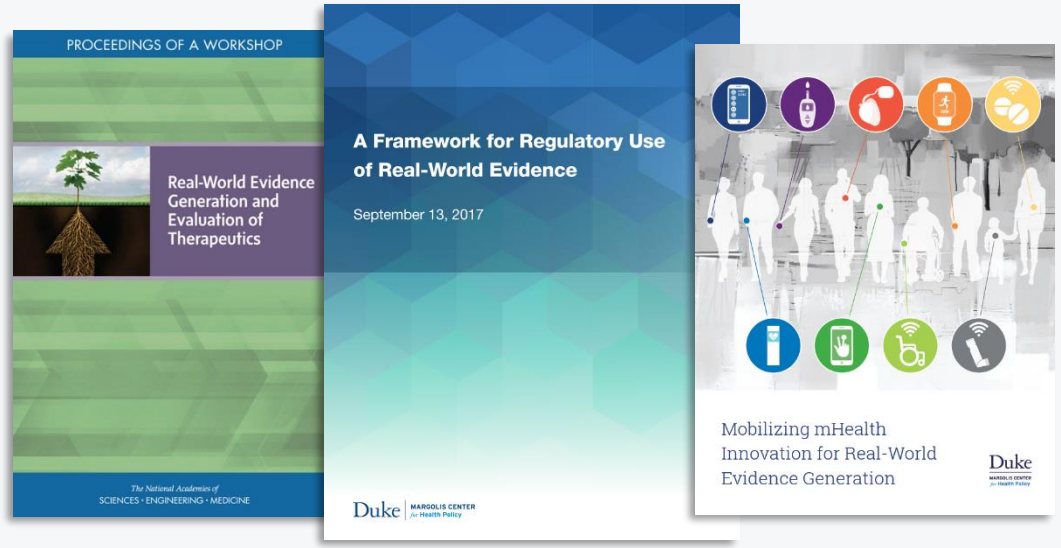

Expert Commentary

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Priorities since 2016: Multistakeholder work

FDA Publications

Viewpoint

August 22/29, 2017

Multidimensional Evidence Generation and FDA Regulatory Decision Making

Defining and Using "Real-World" Data

Jonathan

Real-World Evidence — What Is It and What Can It Tell Us?

Viewpoint

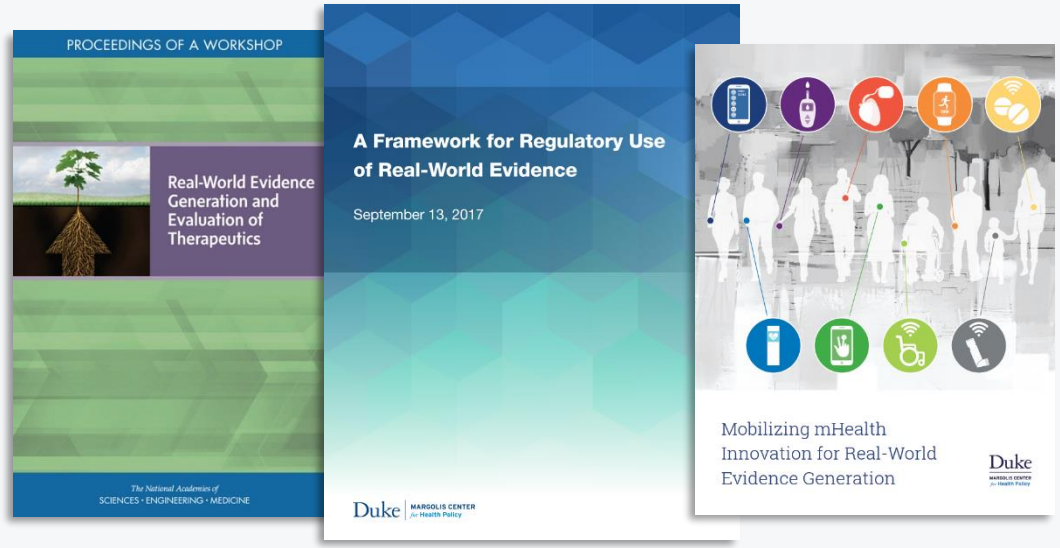
September 4, 2018

Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness

Jacqueline Corrigan-Curay, JD, MD[1]; Leonard Sacks, MD[1]; Janet Woodcock, MD[1]

h.D., Thomas Gross, M.D.,
elissa A. Robb, B.S.N., M.S.,

Frameworks and Proceedings



Expert Commentary

Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality

Rebecca A. Miksad[1] and Amy P. Abernethy[1]

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from SPOR-ISPE Special Task Force on n Health Care Decision Making

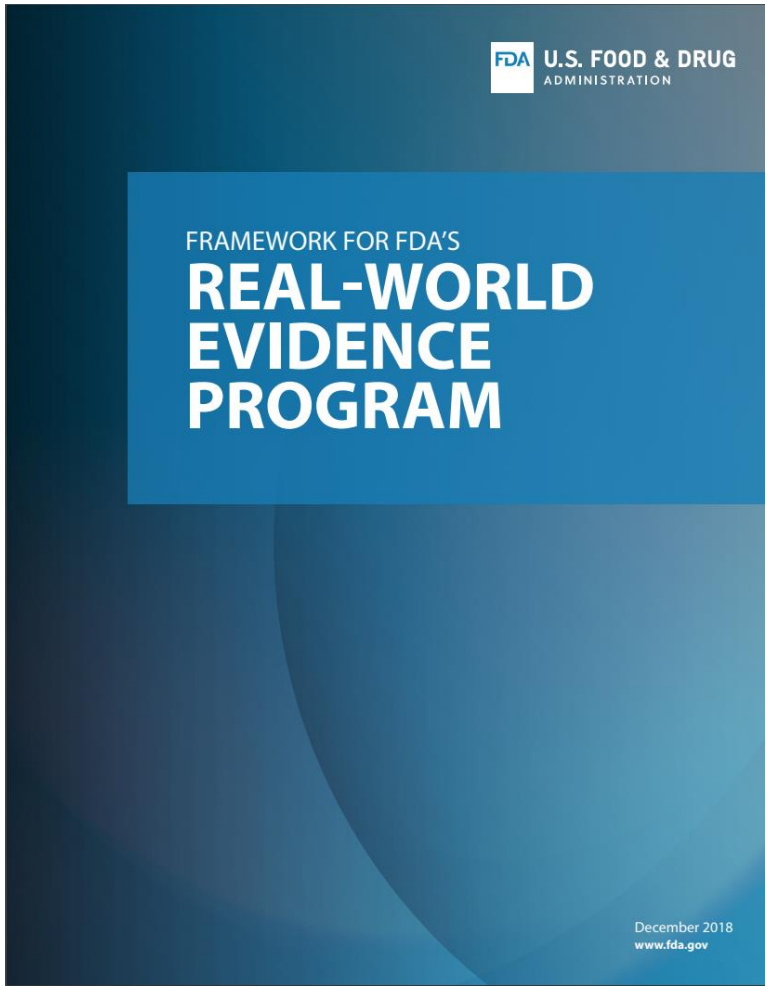
Harold Sox MD [2], Richard J. Willke PhD [3], Diana L. Bri
Goettsch PhD [6], David Madigan PhD [7], Amr Makady MSc [6], Se
a Tarricone MSc, PhD [9], Shirley V. Wang PhD, ScM [8], John W
hD [11]

Real World Data in Adaptive Biomedical Innovation: A Framework for Generating Evidence Fit for Decision-Making

S Schneeweiss, H-G Eichler, A Garcia-Altes, C Chinn, A-V Eggimann, S Garner, W Goettsch, R Lim, W Löbker, D Martin, T Müller, BJ Park, R Platt, S Priddy, M Ruhl, A Spooner, ... See all authors

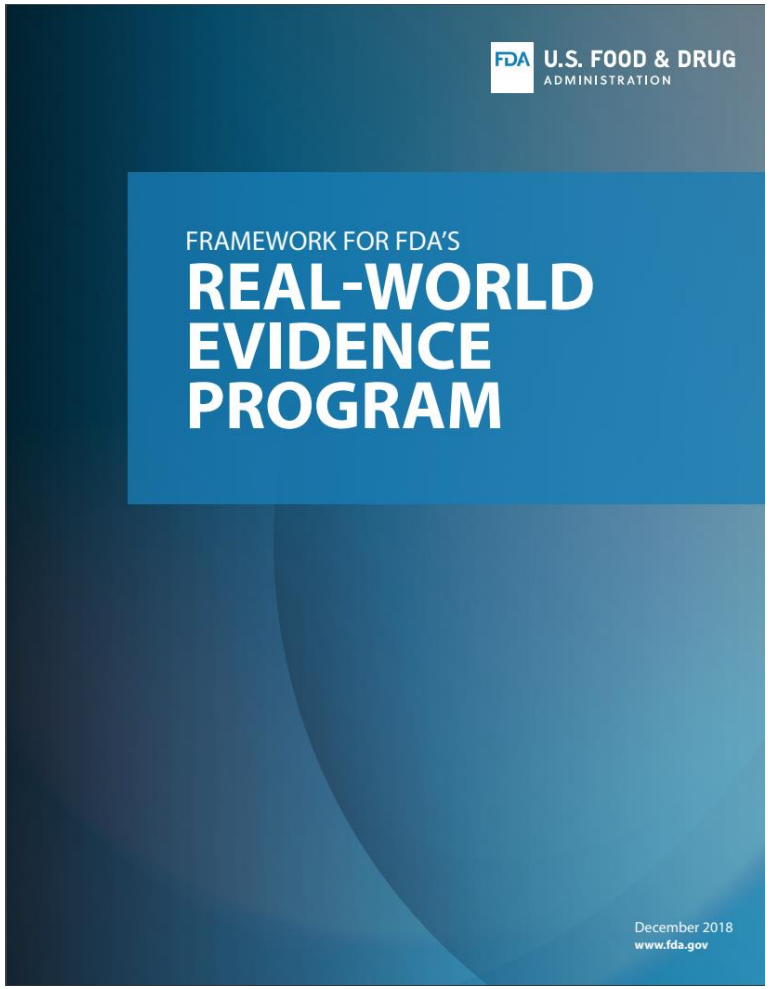
Scope of FDA's RWE Program

- Evaluates the potential use of RWE to support changes to labeling about drug product effectiveness, including:
  - Adding or modifying an indication, such as change in dose, dose regimen, or route of administration
  - Adding a new population
  - Adding comparative effectiveness or safety information



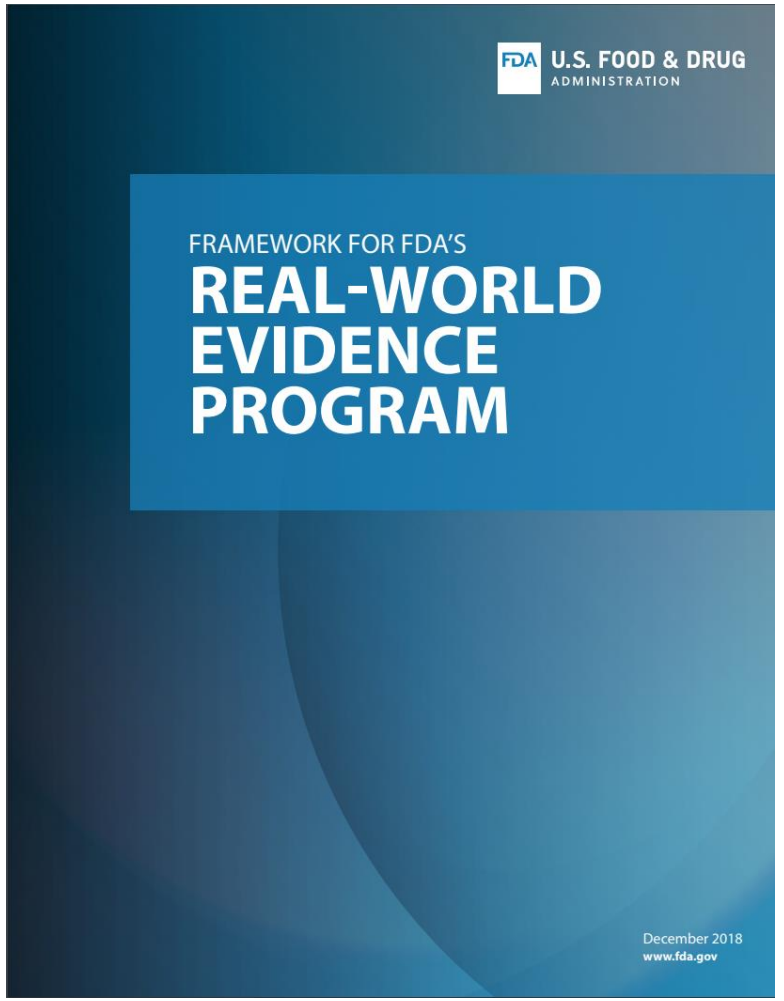
FDA has issued preliminary RWE framework

- Published Dec 2018
- Intended for drug and biological products
- Outlines FDA's plan to implement the RWE program
- Multifaceted program
  - Internal process
  - Guidance development
  - Stakeholder engagement
  - Demonstration projects



FDA has issued preliminary RWE framework

- The Agency's RWE Program will evaluate:
  1. Whether RWD are fit for use
  2. Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question
  3. Whether the study conduct meets FDA regulatory requirements



Several planned FDA guidances on RWD/RWE use to support regulatory decisions

RWD Fitness for Use in Regulatory Decisions

- Reliability and relevance of RWD from claims and EHR data
- Potential gaps in RWD sources and strategies to address them

Potential for Study Designs Using RWD to Support Effectiveness

- Considerations for including pragmatic design elements for each stage of a clinical trial (e.g., recruitment, outcomes assessment)
- RWD use for external control arms
- Observational study designs using RWD

Regulatory Considerations for Study Designs Using RWD

- Electronic source data*
- Regulatory considerations raised by different study designs using RWD*

*FDA will consider whether existing guidances on this topic address concerns relevant for using RWD to generate RWE, and whether additional guidance is needed

Data Projects

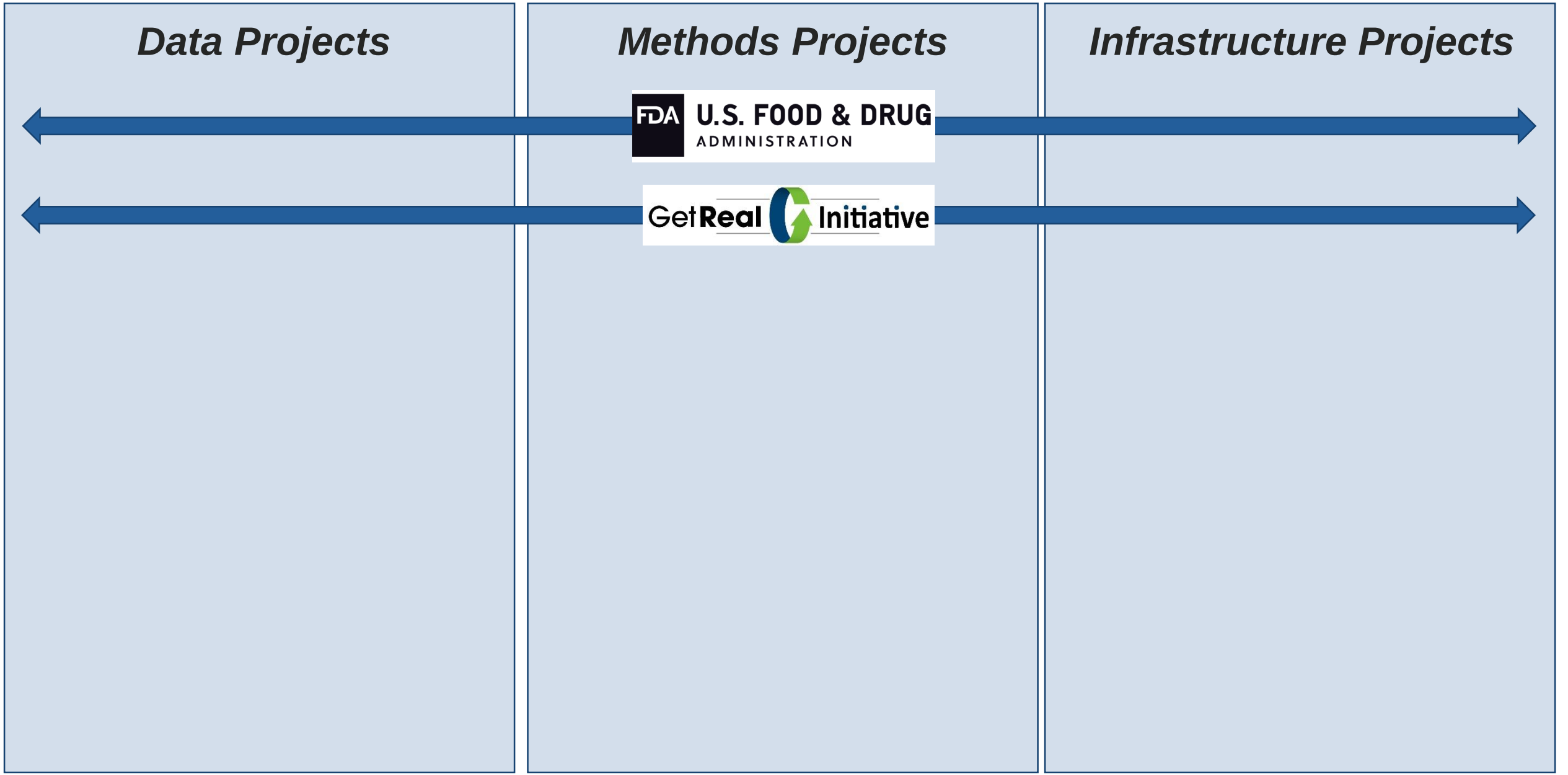
Methods Projects

Infrastructure Projects

Data Projects

Methods Projects

Infrastructure Projects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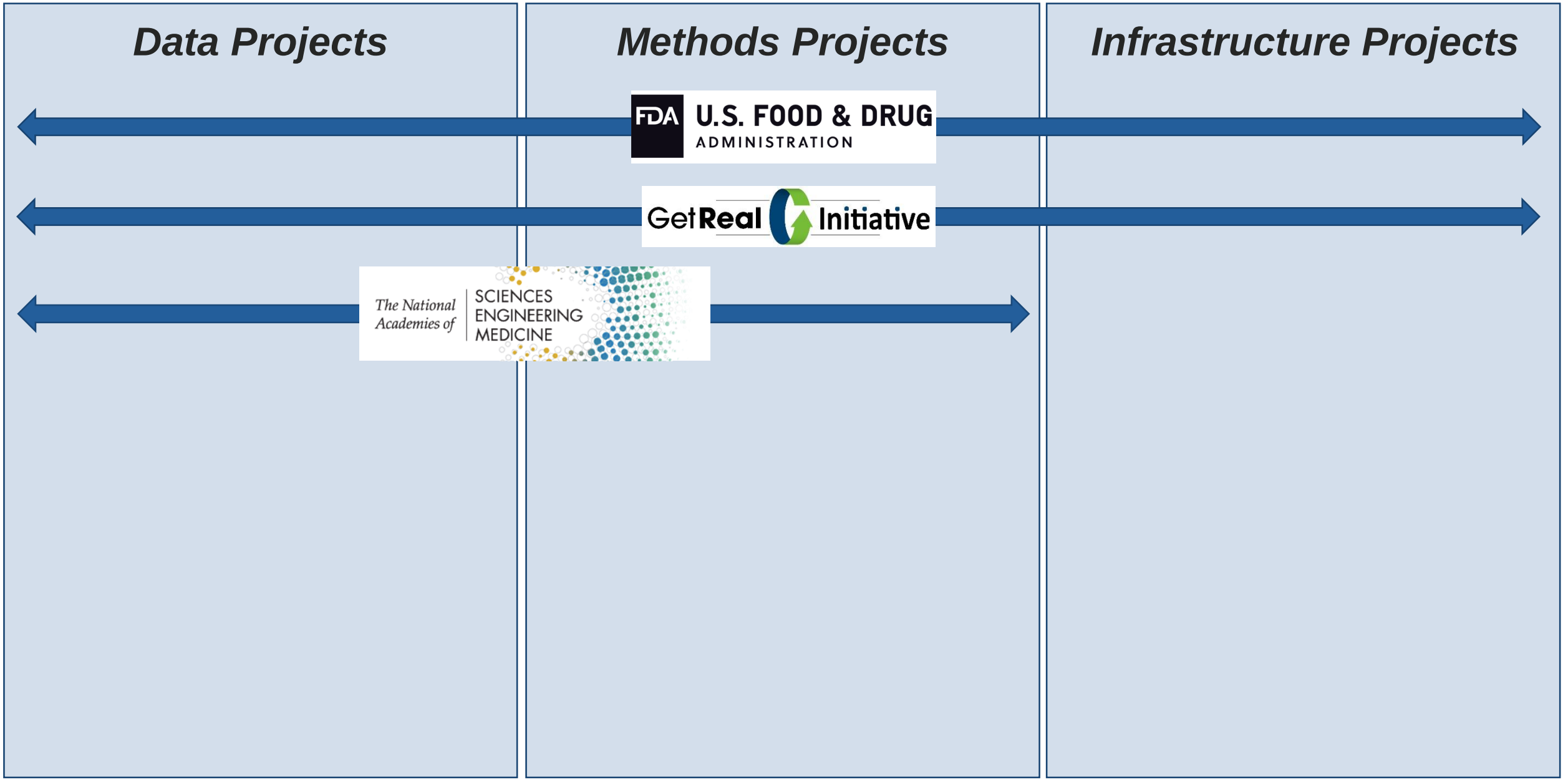
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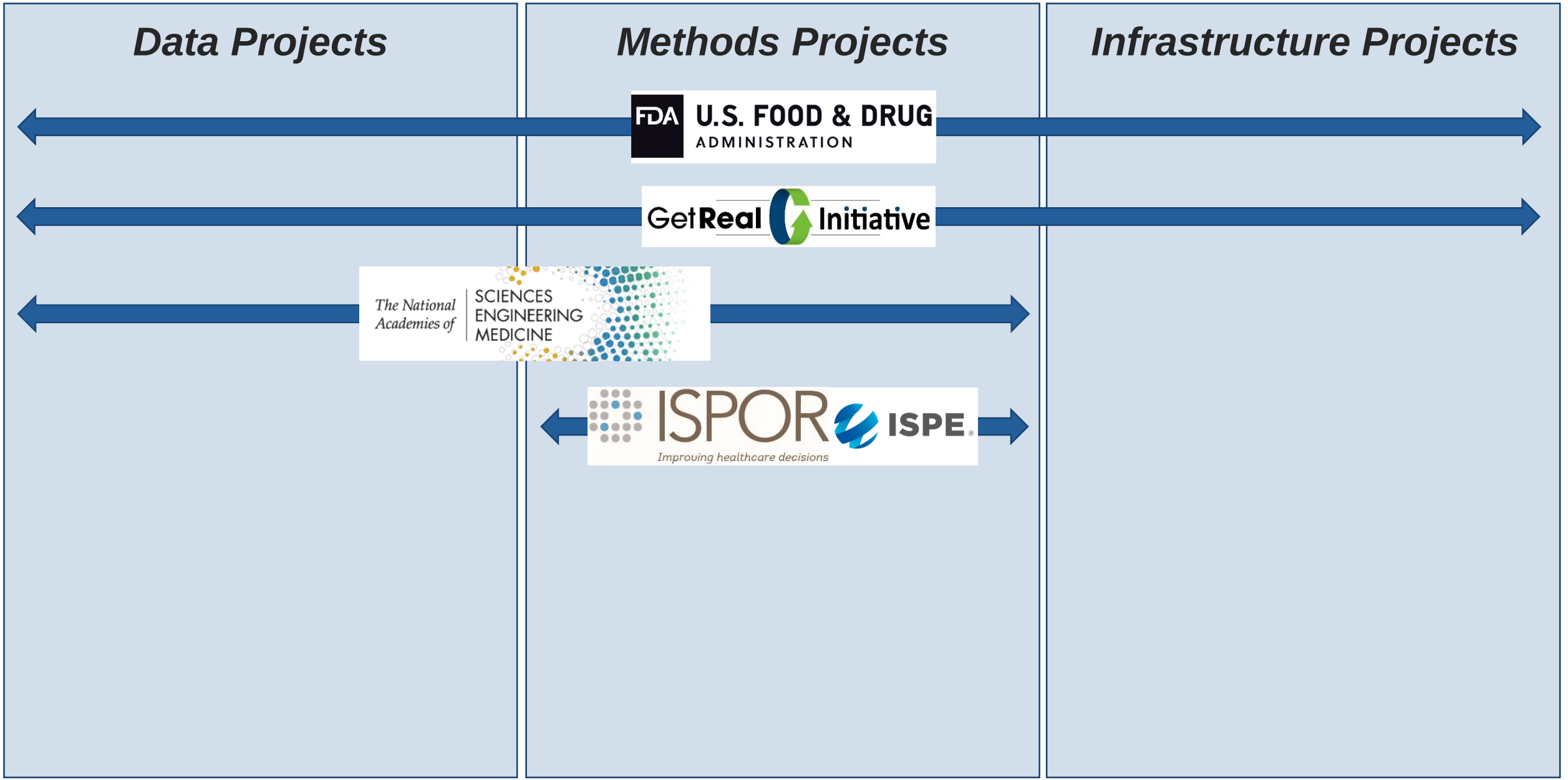
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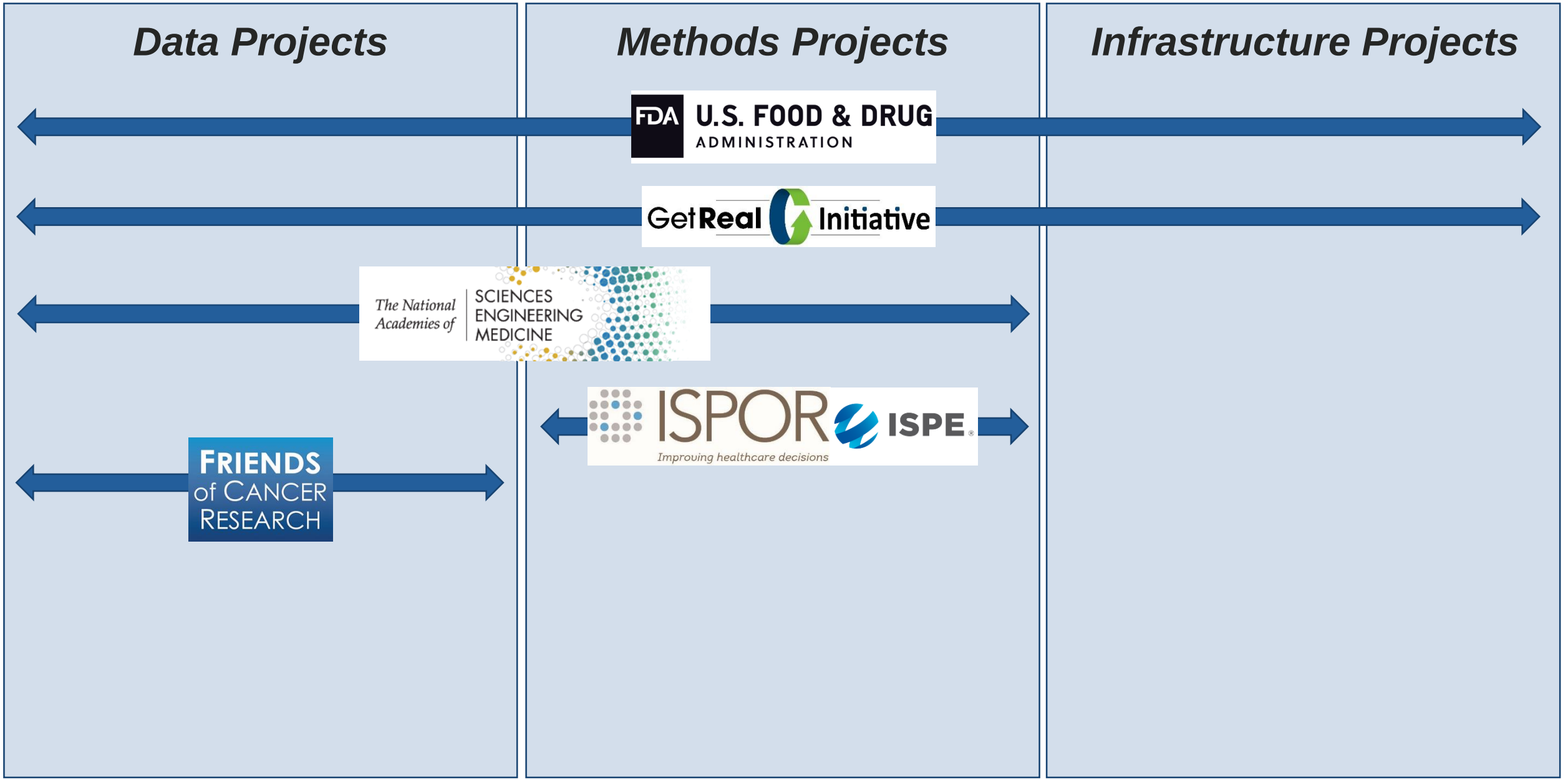
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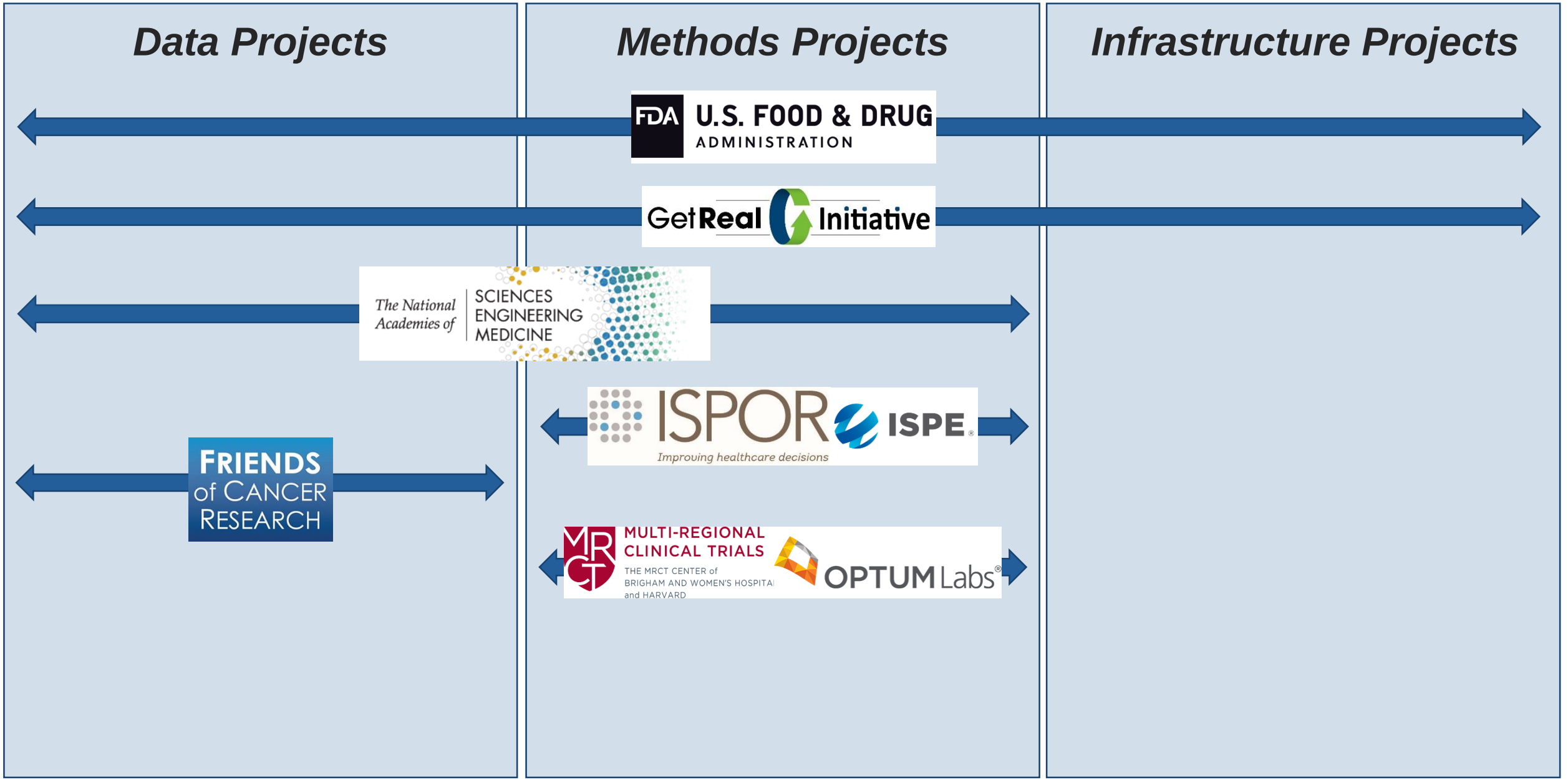
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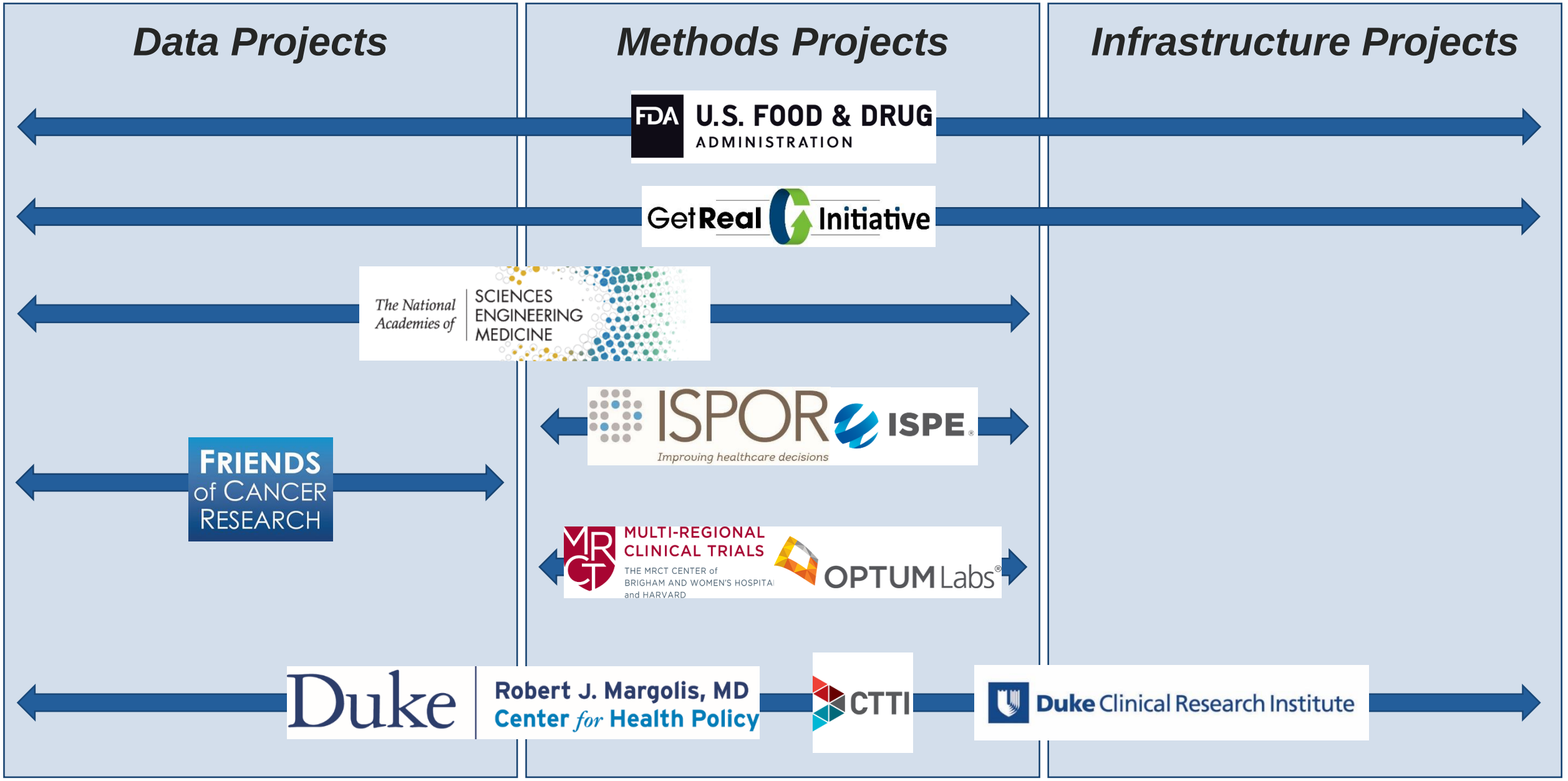
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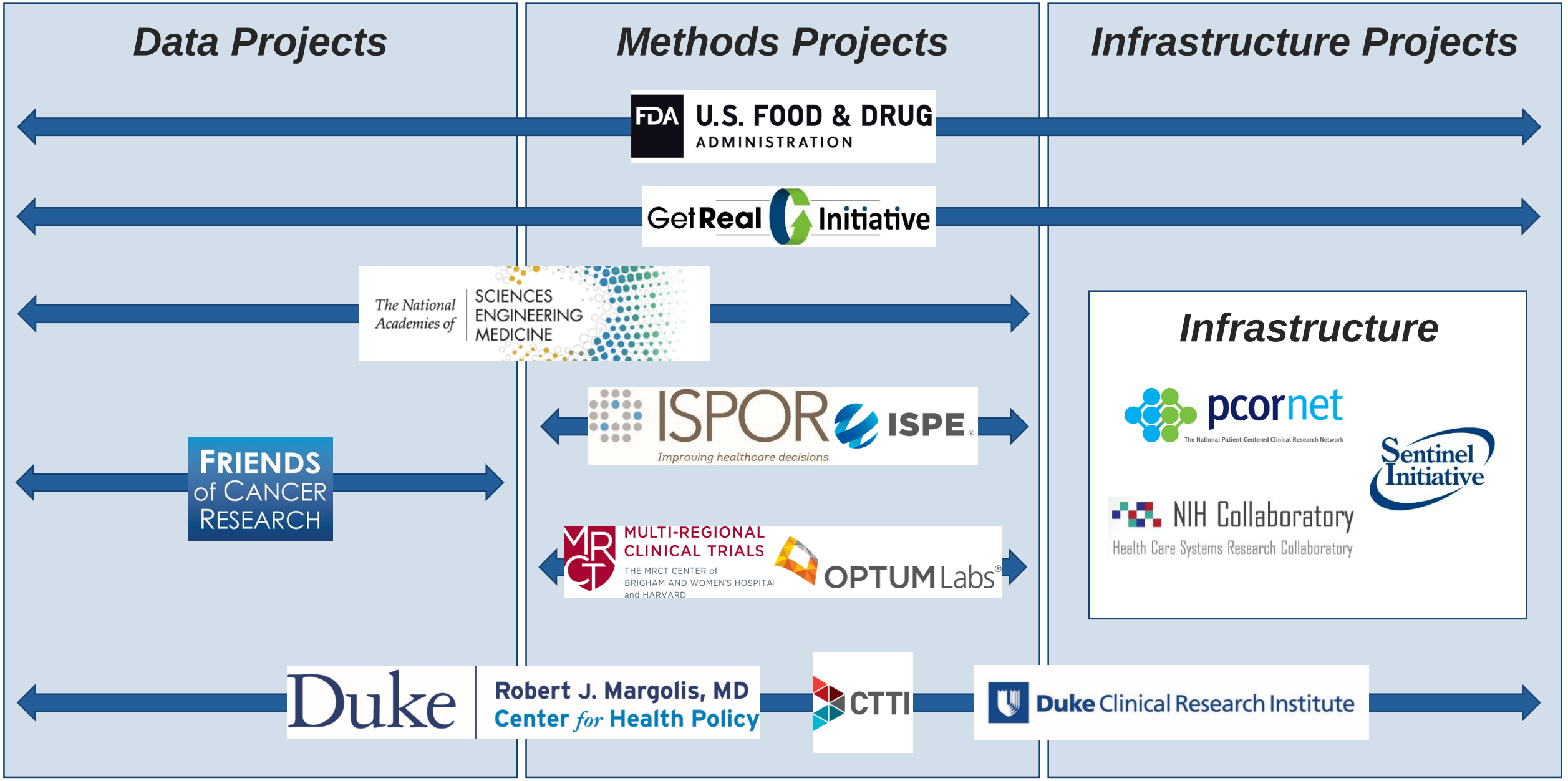
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CTTI
Duke Clinical Research Institute

Duke-Margolis RWE Collaborative Advisory Group includes leaders representing key stakeholders*

Data Curators

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*US Food and Drug Administration (FDA), Patient-Centered Outcomes Research Institute (PCORI), National Academies of Sciences, Engineering, and Medicine, and People-Centered Research Foundation act as observers

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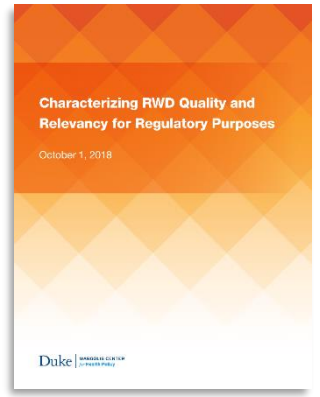
Fit-for-purpose data: quality and relevancy



Data Relevancy

- Availability of key data elements
  - Exposure
  - Outcome
  - Covariate
  - Patient-level linking (if applicable)
- Representativeness
- Sufficient subjects
- Longitudinality

Data Quality

- Accuracy
  - Validity
  - Conformance
  - Plausibility
  - Consistency
- Completeness
- Provenance
- Transparency of data processing

Fit-for-Purpose Data

Within the given clinical and regulatory context, the real-world dataset is of sufficient quality, as well as relevant, robust, and representative.

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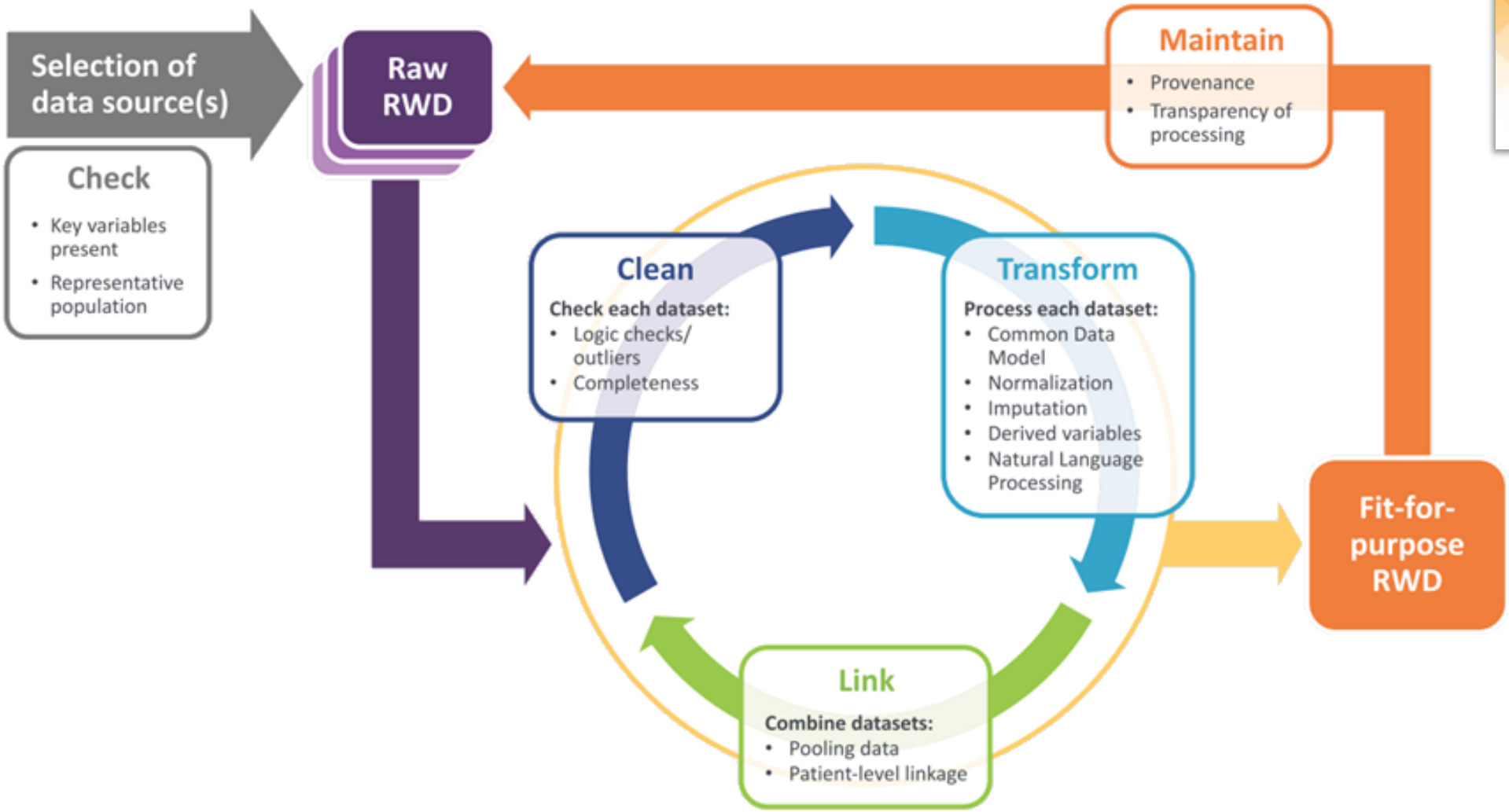
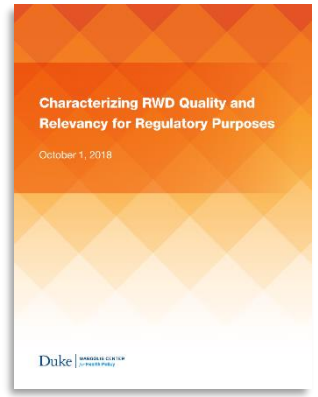
What are data curation best practices?





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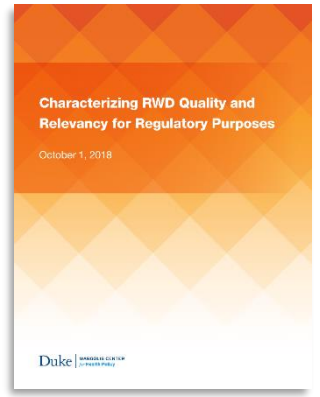
Curation is often complex and hard to explain



Raw RWD

Document
- Extent of provenance
- Protocols for data processing

Clean
Check each dataset:
- Logic checks/ outliers
- Completeness

Transform
Process each dataset:
- Common Data Model
- Normalization
- Imputation
- Composite variables
- Natural Language Processing

Link
Combine datasets:
- Pooling data
- Patient-level linkage

Stage 1

Research-ready RWD

Selection of data source(s)

Check
- Key variables present
- Representative population

Research-ready RWD

Stage 2

Clean
Check each dataset:
- Logic checks/ outliers
- Completeness

Transform
Process each dataset:
- Common Data Model
- Normalization
- Imputation
- Derived variables
- Natural Language Processing

Link
Combine datasets:
- Pooling data
- Patient-level linkage

Maintain
- Provenance
- Transparency of processing

Fit-for-purpose RWD

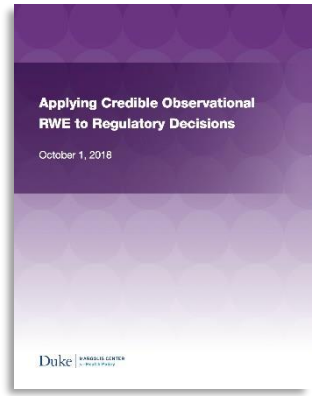
Establishing guideposts for RWD curation and reporting

- Jan 22 2019 Margolis-FDA workshop: “Unpacking Real-World Data Curation: Principles and Best Practices to Support Transparency and Quality”
- Driving questions: How would regulators evaluate RWD/RWE presented as part of an evidence package for a supplemental approval?
  - What data curation practices or approaches are organizations using to clean, transform, and link raw data sources into a fit-for-purpose dataset?
  - Can any commonalities or best practices be identified?
  - Are these steps being documented, and if so, how?

Emerging RWD curation and reporting concepts

- Individualized data curation processes might not be amendable to standardization or overly rigid best practices – the process by which we *adjudicate the quality of the curation process overall* might be
  - Some curation approaches might be better suited for certain data types (e.g. human abstraction for unstructured data vs automated processes for structured data).
  - Identify opportunities to push some Stage 2 curation activities into Stage 1 to improve efficiency and scaling of fit-for-purpose datasets.
  - Need to prove transformations worked, but also balance transparency of documentation with interpretability
- Developing common quality checks or “metrics” that can be used to determine whether the transformation worked may be best path forward

Strengthening observational research design and methods



Trust through Rigorous Methods

- Ability to elucidate causality versus correlation
- Ability to address confounding and bias
- Good study hygiene

Trust through Transparency and Process

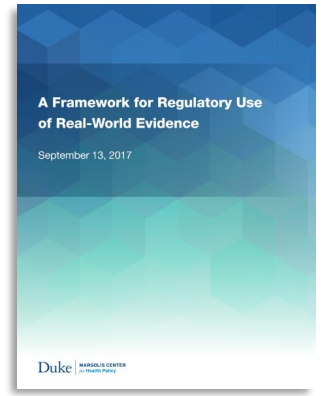
- Pre-register RWE studies like RCTs
- Avoiding “cherry-picking” of data
- Reproducibility
- Replicability

Will need consensus on how observational RWE can be considered ‘adequate and well-controlled’ to support decisions based on ‘substantial evidence’

2019 areas for Duke-Margolis Collaborative work

- **RWD Quality Checks, Curation, and Reporting** - Develop and describe quality checks for assessing overall RWD curation practices
- **Assessing Credibility for Individual Observational Studies** - Describe how individual observational studies can be strengthened for inclusion in evidentiary submissions per current statute
- **Understanding the Role of Observational Studies in a Totality of Evidence Approach** - Explore and put forward recommendations for how observational studies can best support regulatory considerations and decisions based on ToE
- **Establishing Guideposts for Developing Real-World Endpoints** - Establish generalizable principles or guidance for the development and use of real-world endpoints

Can we meet regulatory standards with credible, robust RWE?



Regulatory Context

What specific decision is FDA considering?

- New indication
- Labeling revision
- Safety revision
- Benefit-risk profile

Clinical Context

Can the clinical question be reliably addressed with RWE?

- Prevalence of the disease
- Clinical equipoise
- Expected treatment effect size
- Relevant prior evidence

Data Considerations

Is the real-world dataset fit for regulatory purpose?

1. **Is the data relevant?**
   - Representative of the population of interest
   - Contains key variables and covariates
2. **Is the data of adequate quality?**
   - Minimal missing data
   - Data reliability and validity is satisfactory for study purpose
   - Known provenance and transparency of data processing

Methods Considerations

Are the methodological approaches of sufficient rigor?

1. **Are the methods credible?**
   - Appropriate analytic approach
2. **Can the approach produce actionable evidence?**
   - Interplay of body of clinical evidence and tolerance for uncertainty

Fit-for-purpose RWE

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Questions?

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