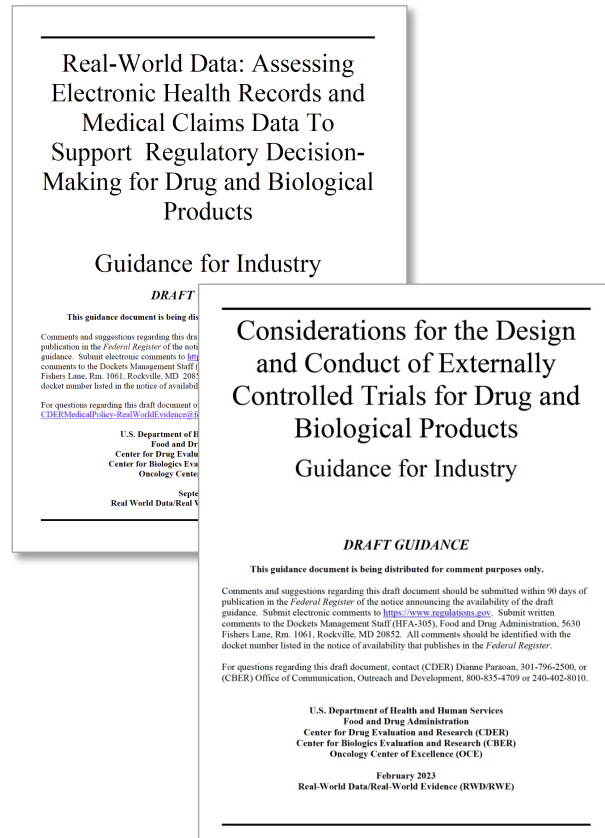


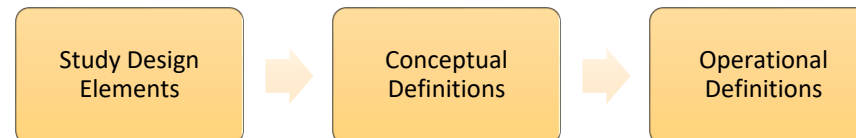
Clear, Consistent, and Computable Operational Definitions: Defining the Purpose and Data Needs for Real-World Evidence Generation

Aaron Kamau MD MS MPH

FDA Draft Guidance (Sept 2021 & Feb 2023)



- Reiteration of Relevance and Reliability
- Focus on
 - key data variables: inclusion criteria, outcome measure, covariates, etc
 - internal & external validity, completeness & accuracy, bias and confounding
 - data provenance, data accrual quality, data curation quality, into final study-specific dataset
- Requirement for documentation in the protocol
- Recommendation to engage the FDA early regarding study design & data source qualification
- Conceptual definitions → Operational definitions



Conceptual & Operational Definitions

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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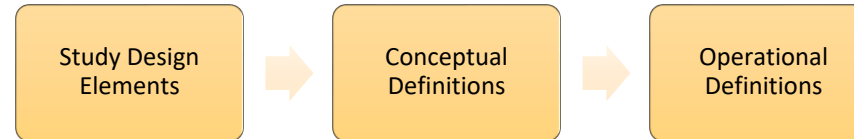
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September 2021
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- Conceptual definitions → Operational definitions



III. GENERAL CONSIDERATIONS

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FDA RWE guidances focused on study design and analysis. This guidance addresses issues that are essential to determining the reliability and relevance of the data and that should be addressed in the protocol, including:

1. The appropriateness and potential limitations of the data source for the study question and to support key study elements.
2. Time periods for ascertainment of study design elements.
3. **Conceptual definitions** and **operational definitions** for study design elements (e.g., inclusion/exclusion criteria for study population, exposure, outcomes, covariates) and the results of validation studies. See Section V, Study Design Elements, for examples of conceptual and operational definitions for study design elements.
4. Quality assurance and quality control (QA/QC) procedures for data accrual, curation, and transformation into the final study-specific dataset.

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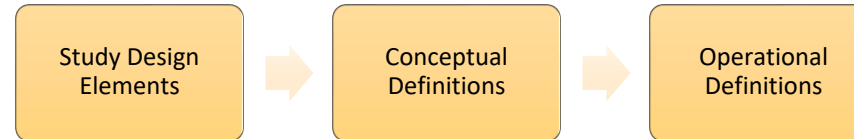
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VII. GLOSSARY

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Conceptual Definition: Explains a study construct (e.g., exposure, outcomes, covariates) or feature in general or qualitative terms.

...

Operational Definition: The data-specific operation or procedure a researcher followed to measure constructs in a particular study

Conceptual, Operational & Query Definitions

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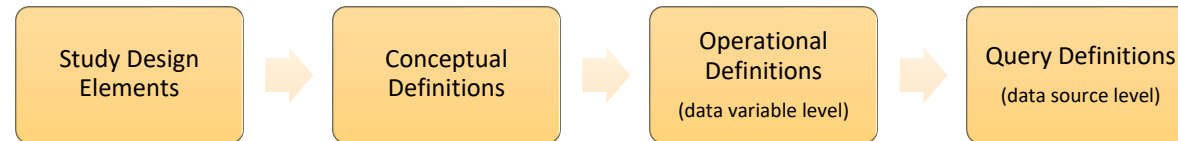
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According to Aaron ;-)

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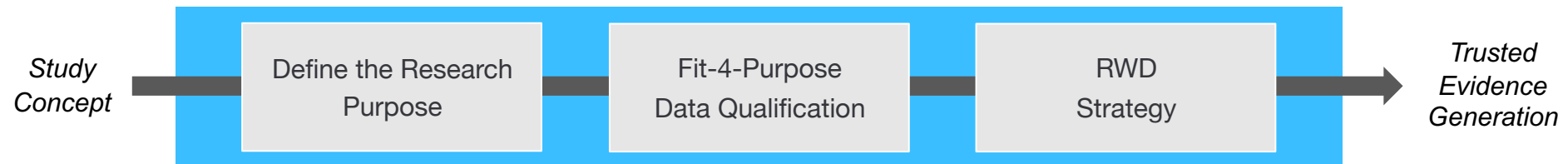
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Operational Definition: The data-specific operation or procedure a researcher follows to measure constructs in a particular study

Query Definition: the application of a data-specific operational definition to a specific dataset, database, or data source

Conceptual, Operational & Query Definitions

Why do we need clear operational definitions?



The Research Purpose

- Target patient population
- Study objectives
 - Research questions
 - Rationale
- Audience / Stakeholders
- Intended outcome of the study
- RWD use case(s) alignment

Study Elements

- I/E criteria & subgroups
- Exposure
- Comparator cohort(s)
- Endpoints
 - Characteristics
 - Outcomes
- Covariates for cohort matching

Data Needs

- Relevance
- Reliability
- Data availability
- Data completeness
- Provenance & traceability

How to best utilize the selected data sources/partners specific to the study purpose

- Data access
- Data management needs
 - Data integration, data model(s), linkage
- Deduplication
- Etc., etc.
- Analysis needs/methods
- Interpretation & presentation of results

Documentation, documentation, documentation

Computable Operational Definitions

A computation is a process that obeys finitely describable rules.

~ Rudy Rucker

Study Element	Source Wording	Conceptual Definition	Operational Definition	Related Value Sets
Inclusion	Patients who have had a solid organ transplant	Receipt of a solid organ transplant	<div>≥ 1 Procedure Record for Solid Organ Transplant Procedures, any time prior to the index date OR ≥ 1 Diagnosis Record for Solid Organ Transplant Diagnoses, any time prior to the index date; any encounter type, any diagnosis position</div>	<ul style="list-style-type: none">• Solid Organ Transplant Procedures• Solid Organ Transplant Diagnoses

≥ 1 Procedure Record for Solid Organ Transplant Procedures, any time prior to the index date
OR
≥ 1 Diagnosis Record for Solid Organ Transplant Diagnoses, any time prior to the index date; any encounter type, any diagnosis position

Granular components:

- Data variable
- Quantity / magnitude
- Target value, concept or code list / value set
- Time period qualifier
- Other relevant qualifiers based on the data variable or type of operational definition

Expression to describe how the related components relate to each other

Example: Solid Organ Transplant Definitions

Study Element	Source Wording	Conceptual Definition	Operational Definition	Related Value Sets
Inclusion	Receipt of solid organ or islet transplant	Receipt of a solid organ transplant	<p>≥ 1 Procedure Record for Solid Organ Transplant Procedures, any time prior to the index date</p> <p>OR</p> <p>≥ 1 Diagnosis Record for Solid Organ Transplant Diagnoses, any time prior to the index date; any encounter type, any diagnosis position</p>	<ul style="list-style-type: none"> •Solid Organ Transplant Procedures •Solid Organ Transplant Diagnoses
Inclusion: subgroup	Subgroup: Receipt of solid organ or islet transplant and taking immunosuppressive therapy	Receipt of a solid organ transplant AND Treatment with an immunosuppressive therapy	<p>≥ 1 Procedure Record for Solid Organ Transplant Procedures, any time prior to the index date</p> <p>OR</p> <p>≥ 1 Diagnosis Record for Solid Organ Transplant Diagnoses, any time prior to the index date; any encounter type, any diagnosis position</p> <p>AND</p> <p>≥ 1 Medication Record for Immunosuppressive Therapies, within the 12 months prior to the index date</p>	<ul style="list-style-type: none"> •Solid Organ Transplant Procedures •Solid Organ Transplant Diagnoses •Immunosuppressive Therapies
Inclusion: subgroup	>Subgroup: Solid organ transplant, high risk	Receipt of a solid organ transplant AND (Age 65 years or older OR Diagnosis of Graft vs. Host disease (GVHD)	<p>≥ 1 Procedure Record for Solid Organ Transplant Procedures, any time prior to the index date</p> <p>OR</p> <p>≥ 1 Diagnosis Record for Solid Organ Transplant Diagnoses, any time prior to the index date; any encounter type, any diagnosis position</p> <p>AND</p> <p>Age ≥ 65 years old, at index date</p> <p>OR</p> <p>≥ 1 Diagnosis Record for Graft-vs-Host Disease Diagnoses, any time prior to the index date; any encounter type, any diagnosis position</p>	<ul style="list-style-type: none"> •Solid Organ Transplant Procedures •Solid Organ Transplant Diagnoses •Graft-vs-Host Disease Diagnoses

Example: Myocardial Infarction Definitions

Study Element	Source Wording	Conceptual Definition	Operational Definition	Related Value Sets
Baseline Characteristic: Comorbidity: MI	Myocardial infarction	Diagnosis of myocardial infarction	<div> ≥ 1 Diagnosis Record for Myocardial Infarction (CCI) Diagnoses, within the 12 months prior to the index date; hospitalization/inpatient encounter type, any diagnosis position OR ≥ 2 Diagnosis Records for Myocardial Infarction (CCI) Diagnoses, within the 12 months prior to the index date; any encounter type, any diagnosis position </div>	•Myocardial Infarction (CCI) Diagnoses
Outcome: Safety: MI	Myocardial infarction	Diagnosis of myocardial infarction	<div> ≥ 1 Diagnosis Record for Myocardial Infarction (CCI) Diagnoses, within the 6 months after the index date; any encounter type, any diagnosis position </div>	•Myocardial Infarction (CCI) Diagnoses
Outcome: Safety: MI (for determining prevalence/incidence)	Myocardial infarction	Diagnosis of myocardial infarction	<div> ≥ 1 Diagnosis Record for Myocardial Infarction (CCI) Diagnoses, within the 24 months prior to the index date; any encounter type, any diagnosis position </div>	•Myocardial Infarction (CCI) Diagnoses

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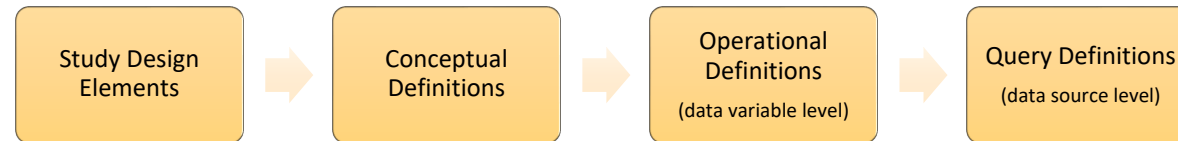
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Mahalo

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Join an informal discussion on Clubhouse 

hosted by the RWD & RWE Club

Every Wed @ 11-12 (Eastern Time)

