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# Considering Data Qualities in Determining FFP – Can We Converge on an Approach?

ISPOR Real-World Evidence Summit 2023

May 7, 2023

**Moderator: Marc Berger,** MD

**Speakers:**

- **John Concato,** MD, MS, MPH, Food and Drug Administration
- **Daniel Morales,** MD, PhD, EMA
- **Laurie Lambert,** MPH, PhD, Canadian Agency for Drugs and Technologies in Health
- **Gracy Crane,** PhD, Roche Products Limited

# Agenda

- Opening Statements
- Discussion Questions
- Audience Questions

U.S. FOOD & DRUG ADMINISTRATION

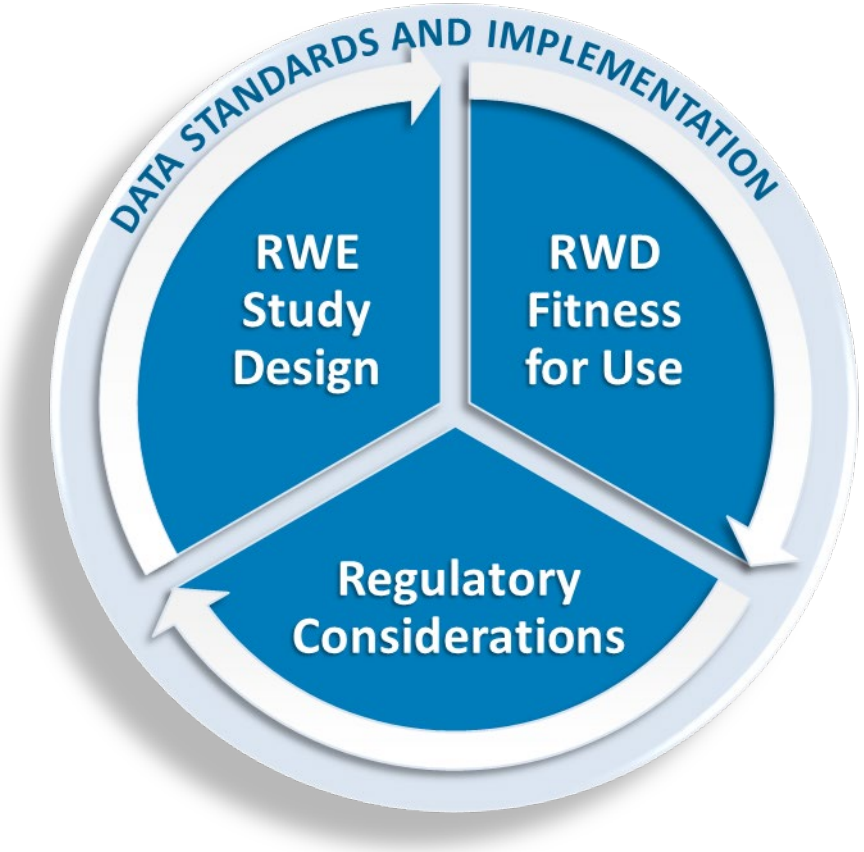
*ISPOR RWE Summit – 7 May 2023*

# FDA Perspectives on Fit-for-Use Data

**John Concato, Office of Medical Policy, CDER-FDA**

**Note: Views and opinions expressed are those of the presenter and should not be attributed to the Food and Drug Administration**

# RWE for Effectiveness: Overview of FDA Approach




**Key considerations (from 2018 Framework):**

- **Whether the RWD are fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

https://www.fda.gov/media/120060/download

# RWE Submissions to FDA: Representative Problems

**Real-world data sources:**

- issues related to data reliability and clinical relevance
- need for linkage to other data sources
- missing or "mistimed" data
- suitable capture of endpoints

**Non-randomized study designs:**

- threat of residual confounding
- problems with index date ("zero time")
- use of inappropriate comparator

**Conduct of non-randomized studies:**

- insufficient confirmation of *pre-specified* protocol and analysis plan
- issues related to FDA inspection

Based on: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

# Draft FDA Guidance on Registry Data: Nov 2021

**Excerpts on fit-for-use data (lines 166-171):**

- **"Before using any RWD (including registry data) for regulatory decision-making, sponsors should consider whether the data are fit-for-use by assessing the data's relevance and reliability."**

- **"[The] term *relevance* includes the availability of key data elements (patient characteristics, exposures, outcomes) [and] representative patients for the study, […] the term *reliability* includes data accuracy, completeness, provenance, and traceability."**

https://www.fda.gov/media/154449/download

# Draft FDA Guidance on EHR/Claims Data: Sep 2021

**Excerpts on validation (lines 482-490):**

- **"The protocol should include a detailed description of the planned validation, including [approach, methods, processes]."**
- **"If a previously assessed operational definition is proposed, additional information should be provided, including [details on data source, time frame, performance measures, and whether performance measures are applicable to the proposed study]."**
- **"FDA also recommends including in the protocol prespecified sensitivity analyses [regarding operating characteristics]."**

https://www.fda.gov/media/152503/download

# Draft FDA Guidance on 'Substantial Evidence': Dec 2019

**Excerpts regarding substantial evidence of effectiveness standard:**

- **[From Intro]: "The approaches discussed in this guidance can yield evidence that meets the statutory standard for substantial evidence and reflect the evolving landscape of drug development."**
- **[Regarding regulatory flexibility]: "In all cases, FDA must reach the conclusion that there is substantial evidence of effectiveness to approve a drug; however, the degree of certainty supporting such a conclusion may differ, depending on clinical circumstances (e.g., severity and rarity of the disease and unmet medical need)."**

https://www.fda.gov/media/133660/download

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# Daniel Morales, MD, PhD, EMA

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# Considering data qualities in determining FFP



## HMA EMA Big Data Steering Group recommendations

- Develop guidelines
- Strengthen process for data qualification
- Promote uptake of electronic health records, registries, genomics data, and secure data availability

## EMA has two major initiatives focusing on

- Data quality and representativeness (Data Quality Framework)
- Data discoverability (Guide for the Use of Real World Metadata)

# EMA Data Quality Framework

EUROPEAN MEDICINES AGENCY

- **Two important aspects** of data quality of the primary data:

### Reliability

Based on e.g. the detection and correction of errors, missing data and implausible values (characteristic of the data source independent from its use for a specific study)

### Relevance

Data source to provide adequate and valid evidence informing a specific research question following the application of appropriate epidemiological and statistical techniques (may be required for some studies and not for others)

| | | |
|---|---|---|
| **Reliability** | **Coherence** | **Extensiveness** |
| **Relevance** | **Timeliness** | |

# Good practice guide for the use of real world metadata

EUROPEAN MEDICINES AGENCY

| Use case | Content |
|---|---|
| ***An investigator wants to identify suitable data sources for a planned study*** | Outline of the steps recommended for a catalogue user in order to select a suitable data source for a particular study |
| ***A study protocol submitted for a study mentions a data source and the assessor needs to understand the suitability of the data source proposed*** | Description of the data elements useful for the assessment of the suitability of data source in the assessment of a study report |
| ***An investigator writes a study reports for which they need to describe the data source(s) proposed to be used or used in the study*** | Proposal of solutions when a comparison between the characteristics of several databases used in the study is difficult to perform |
| ***A data holder wants to compare the features of a specific data source with other ones covering fully or partially the same population*** | Recommendations on benchmarking several data sources – use of the harmonised description of the characteristics of each data source |

Canada's Drug and
Health Technology Agency

# Considering data qualities in determining FFP - Can we converge on an approach?

## The HTA perspective

Laurie Lambert, MPH, PhD
Lead Real-World Evidence
CADTH

*International Journal of Technology Assessment in Health Care*

**cambridge.org/thc**

# The new definition of health technology assessment: A milestone in international collaboration

Brian O'Rourke[1], Wija Oortwijn[2], Tara Schuller[3] and the International Joint Task Group

- HTA is a multidisciplinary process that uses explicit methods to determine the value of a health technology **at different points in its lifecycle**.

- The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system.

# RWE may serve a variety of purposes to help determine the value of a health technology

- Efficacy of a health technology
  - Clinical effectiveness and safety
  - Costs and economic implications

- Contextual/Implementation Issues
  - Ethical, social, cultural, legal, organizational, environmental

- Wider implications for the patient, relatives, caregivers, the population

- Potential unintended consequences

Canada's Drug and
Health Technology Agency

# We can't appraise fitness for purpose without transparent reporting about the generation and results of RWE!

# New Canadian Guidance for Reporting Real-World Evidence will promote convergence on an approach

1) Ensure **regulators and HTA agencies** have sufficient information to evaluate a study for its appropriateness of use for decision-making;

2) Provide core reporting standards for RWE studies **that align with global standards**;

**3) Prioritize transparency in reporting** while accounting for practical challenges related to RWD and RWE.

cadth symposium

# Shaping Future-Ready Health Systems

**May 16 to 18, 2023**

Shaw Centre, Ottawa, Ontario

**symposium.cadth.ca**

# Considering data qualities in determining FFP - Can we converge on an approach?

## The Industry Perspective

Gracy Crane, M.Sc., Ph.D
Global Regulatory Policy Lead (Roche)
Member of the ISPOR RWE Transparency Initiative



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# Industry position

Components of the multifaceted nature of F4P RWD results in many "moving parts" that need to work together to enable use of RWD for regulatory & HTA decision making by industry

**Must be Reliable**

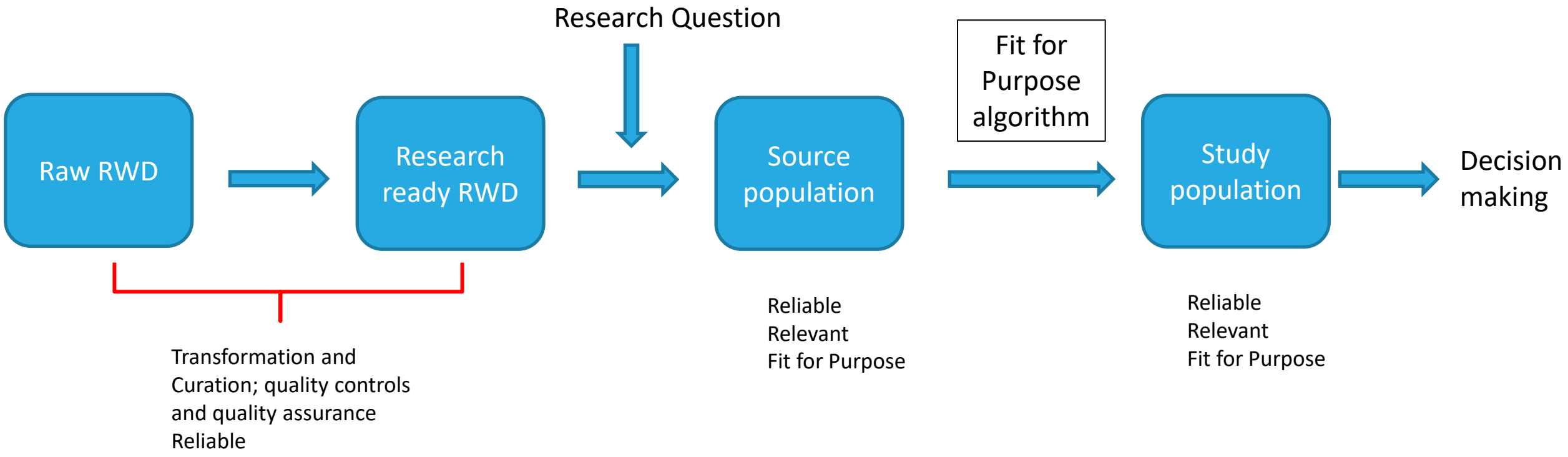
**Must be Relevant (related to the research question)**

- Regulatory context or HTA context
  - Role of RWE in context of RCT or non-randomized study
  - Role of RWD – substantial vs supportive
- Filing strategy
  - US only filing, EU only or global filing package
- Clinical context
  - Availability or paucity of data (sources)
- Data source(s)
  - How to bring harmonize multiple data sources (eg rare diseases)?
  - Re-use of data sources – can experience increase confidence and reduce uncertainty?
  - Linkage with heterogenous or multimodal data eg genomics; imaging etc
- Methods
  - Pre-specification
  - Transparency
  - Algorithms

Must meet **established data standards** by regulators (FDA's data standards for RWD and EMA's data standardization strategy)

# Industry Ask






We need convergence on common principles for characterizing data quality to aid global drug development

# Discussion Questions

- What is the relationship between the standards for Data Quality and F4P? Do these not vary with nature of the regulatory decision?
- While the criteria for F4P may be bespoke for a particular regulatory question, doesn't one consider what has been learned about the "operating characteristics" of particular data sources based on their track record for producing credible RWE?
- DQ and F4P standards will likely vary when there exists RCT data related to the therapeutic in question as opposed to when standard RCTs are not available or feasible (ex. detection of rare adverse events, orphan/rare disease drugs, etc.). Does this mean that there are different standards for sufficient (substantial) evidence?