Structured Registry Data for Valves

An Overview

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Disclosures and Disclaimer

John C. Laschinger, M.D.

I am a full time employee of the FDA. I have no financial conflicts of interest to report.

The views expressed in this presentation are those of the presenter and do not represent the official policies of the FDA.

Intersections

Regulatory and Clinical Uses of Registry Data

Common Goals:

- **Protect the public health** - Ensure the safety, effectiveness, and quality of medical devices
- **Advance the public health** by speeding and enhancing innovation
- **Provide the public with accurate information** about regulated products needed to improve and maintain health

Common Pathway:

- **Acquisition of Scientific Evidence** needed to make informed decisions

Regulatory Decision Making: Pre-Market

Providing The Evidence Needed to Reach Key Decisions

Three Key Decisions for Regulatory Approval:

- ❑ Is the drug/device **safe and effective in its proposed use(s)**, and do the drug/device **benefits outweigh the risks**
- ❑ What should the label should contain? Is the **proposed labeling (package insert) appropriate** for the drug/device,

Requires Pre-Clinical and Clinical Evidence

- ❑ Are the **methods used in manufacturing** the drug/device and the **controls** used to maintain the drug's/device's quality adequate to preserve the identity, strength, quality, and purity of the drug or the durability, performance, sterility and biocompatibility of the device

U.S. Drug and Device Approval Paradigm

Data vs. Evidence – Implications for Regulatory Approvals

- **Data**

  Raw Measurement

  Facts and statistics collected together for reference or analysis
  Meaningless by themselves, yet foundational
  - Complete, accurate, reliable and timely
  - Adjudication, core labs, auditing, monitoring

  } **Data Quality**

- **Information**

  Addition of critical context that provides relevance

  Knowledge communicated or received concerning a set of facts
  Understanding what is being measured, why and how
  Gives meaning to data

  } **Fitness to Purpose**

- **Evidence**

  Combination and analysis of information and facts

  Interpretable using informed clinical/scientific judgment
  Can be applied to answer clinical or scientific questions - guides decision-making
  Makes data useful - Indicates whether a belief or proposition is true or valid
  Required for Clinical and Regulatory Decisions

http://blogs.fda.gov/fdavoice/index.php/2015/12/what-we-mean-when-we-talk-about-data

New Device Approvals: Regulatory Threshold

Can Registry Data be Considered Evidence?

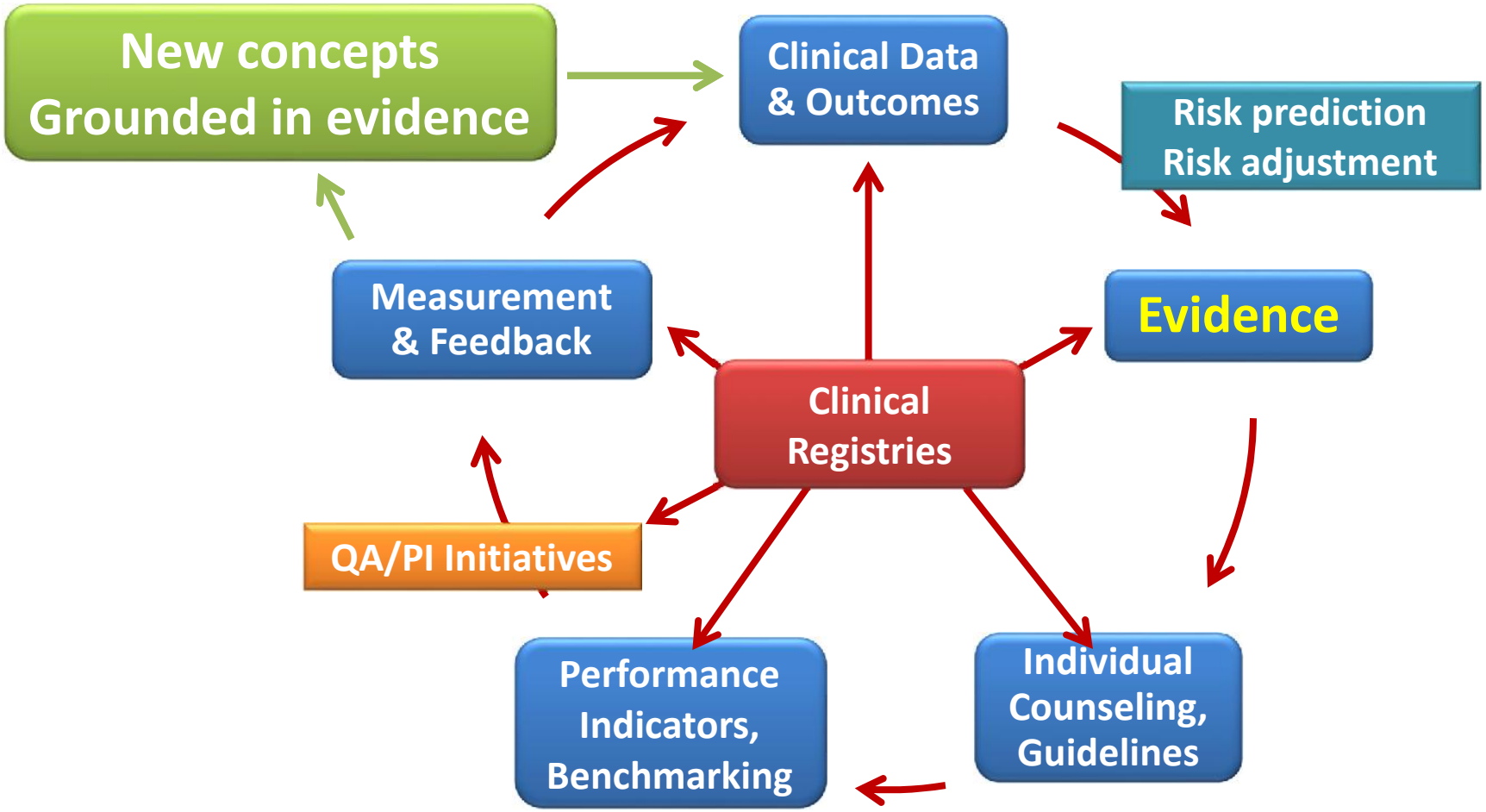
New Devices

21 CFR 860.7(c)2

"**Valid scientific evidence** is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and **reports of significant human experience with a marketed device**, from which it can fairly and responsibly be concluded by qualified experts that there is **reasonable assurance** of the **safety and effectiveness** of a device under its conditions of use. The **evidence required may vary** according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use."

Clinically Sustainable Registries

Proven Role in the Cycle of Quality



Adapted from: Califf et al. JACC 2002;40:1895–901
Bhatt et al. JACC 2015;68:2230-2245

Regulatory Evidence from Existing Registry Data

Retrospective Registry Assessment – The 3 R's

- ✓ Accrual
- ✓ Accuracy
- ✓ Assurance

Reliable

- ❑ Purpose (why)
- ❑ People
- ❑ Processes
- ❑ Common Definitional and Temporal Framework
- ❑ Data Checks
- ❑ Monitoring/auditing
- ❑ Patient Protections

Is it Good Data?

- ✓ Aggregation
- ✓ Acceptability

Robust (medical community determination)

- ❑ Validated Predictive Risk Modeling
- ❑ Benchmarking and Quality Assurance
- ❑ Performance improvement
- ❑ High Penetrance (sustainable)
- ❑ Post-market surveillance
- ❑ Informs Practice Guidelines
- ❑ Generates Peer reviewed publications

Does the data generate Useful Information?

If Yes….

- ✓ Adequacy
- ✓ Analysis

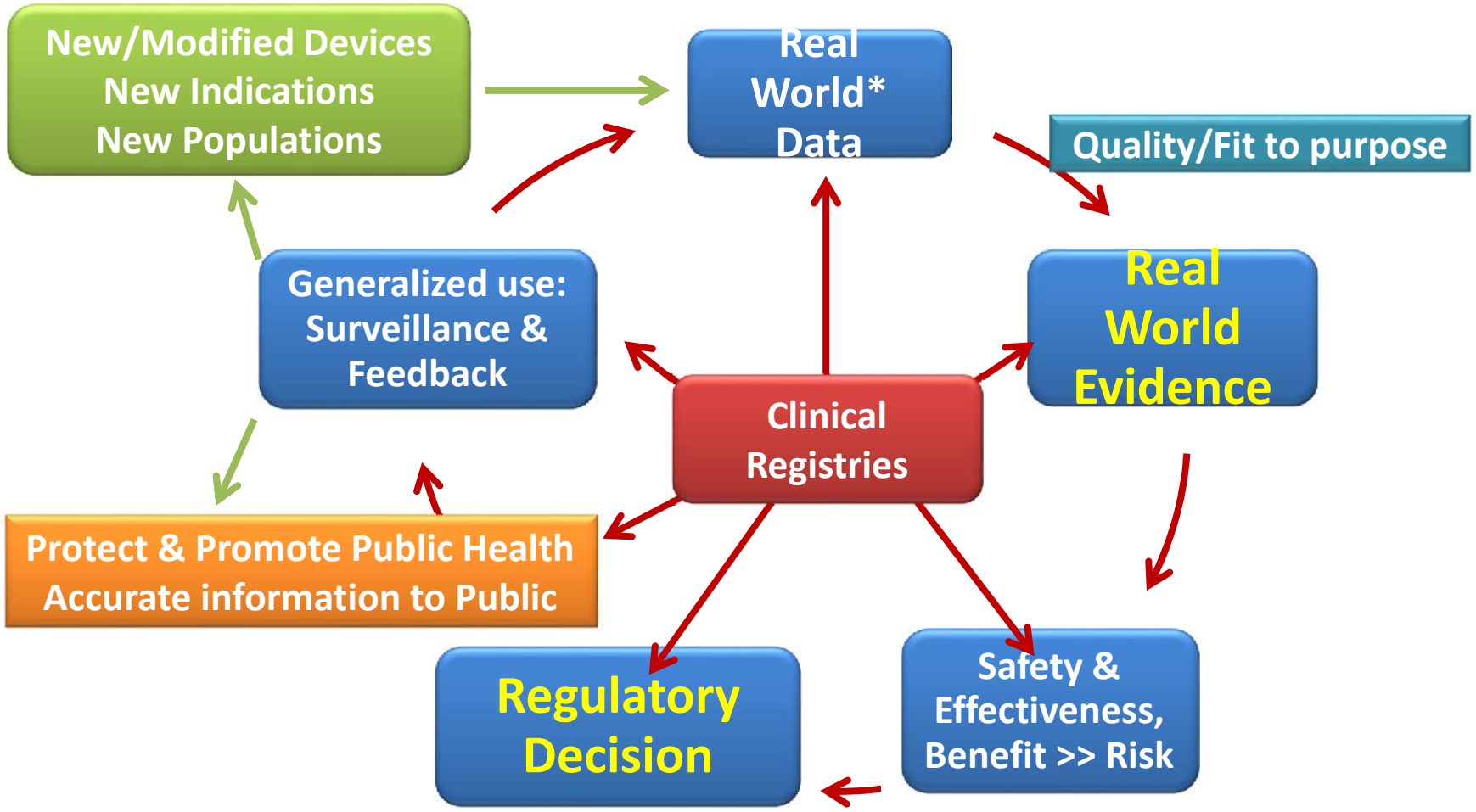
Relevant

- ❑ Applies to question at hand – Fit to purpose
- ❑ Amenable to sound analysis
- ❑ Interpretable using Informed Clinical Judgment

Is Relevant Evidence produced?

Clinically Sustainable Registries

Is There a Role in New Device Development



*Data from diverse populations under diverse clinical circumstances

Use of a Registry as a Research Platform

Acquisition of Prospective Data Within a Registry

Prospectively Designed Randomized Clinical trials:

Pro: Control of bias, confounding, facilitates blinding

A basis for causal inference (randomization)

Con: Imposed restrictions – population and clinical circumstances

Important limitations in understanding and generalizability

Key Questions for Device Approval – addressing the cons:

- Can a prospective Randomized Control Trial be embedded within an existing Registry (i.e. Conducted in a Real World Population)
  - Can needed data be collected accurately
    - Modular data sets, core-labs, adjudication and monitoring
  - Is evidence from real-world data appropriate to assess safety and infer causal relationships for effectiveness

Data Quality and Fitness to Purpose

- Patient Protections; Data governance, access, and sequestration

Sustainable and Robust Infrastructure Platforms

Building for the Future Together

"FDA is thoroughly committed to working with the many partners in our ecosystem to help **build and sustain an infrastructure that produces the high-quality scientific evidence needed to guide FDA's decisions** about the drugs, medical devices, tobacco products, and food products it's charged with regulating, **as well as the decisions that healthcare providers, patients, and consumers make about their health and well-being.**"

R.M Califf, MD

FDA Voice 3/30/16

http://blogs.fda.gov/fdavoice/index.php/2016/03/priorities-teamwork-to-achieve-common-goals/?source=govdelivery&utm_medium=email&utm_source=govdelivery

Registry Adaptation and Development

Acquisition of Evidence – Begin with the End in Mind

Establish quality by design

- Define and answer relevant questions
  - Baseline dataset
  - Data Completeness (fit to purpose) – Modular add-ons, Linkages
- Develop uniform definitions and CRFs
  - Data interoperability - Common definitional and temporal framework
- Processes to ensure data quality (complete and accurate)
  - Training, Logic checks, auditing
  - Monitoring and adjudication, core labs

Sustainability

- Develop incentives and utility for routine use
  - Penetrance (representativeness)
  - Risk prediction and risk adjustment
  - Device assessment/approval, Surveillance

Patient Protections

- Informed consent – Flexibility to address relevant issues
- Privacy – patient and data

Acquisition of Clinical Evidence

Large Efficient Pre-Market Trials - "Real World" Evidence

Usable "Real World" Data

- Reliable
- Robust
- Relevant

} Quality Data → Fit to Purpose (Useful Information) → Evidence

Sustainable and Robust Infrastructure Platform

- **Quality by Design**
- **Interoperability /Flexibility**
  - Baseline and Modular data set add-ons
  - Auto-population by EHR
  - Linkages to other data sources
- **Allows Multiple Regulatory and Clinical Uses**
  - **Retrospective Analyses** - De-identified aggregate data
    - Outcomes
    - Risk prediction, risk adjustment and benchmarking
    - Guidelines, QA/PI
  - **Surveillance** –late events/outcomes, real world performance, signal generation
  - **Prospective Studies**
    - Embedded in Platform
    - Randomization
    - Modular add-ons/core labs
    - Informed Consent
    - Ownership of Data
    - Pre-Post Market balance

Acquisition of Valid Scientific Evidence

Potential of Pre and Post-Market Registries

Focus on the Total Product Life Cycle

↓

Focus on the Total Evidence Life Cycle

Thank You!

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Essential Elements of Data Collection

Prospective Clinical Investigations

The 10 A's to Consider*

- Agreement to participate: Informed Consent
- Assignment of Therapy – processes for randomization, blinding
- Access – control/ownership of proprietary data & sequestration, patient privacy, outside access to line-item data (e.g., investigators, industry, FDA, CMS)

Data Quality (Reliable):

- Accrual of data – collection processes and procedures
- Accuracy of data – completeness and accuracy
- Assurance – enhanced auditing & monitoring of study data, DSMB
- Accountability of study subjects - minimize withdrawals & lost to follow-up
- Adjudication of key adverse events - CEC, Core labs

Fit to Purpose (Relevant):

- Adequacy - needed information/evidence is generated to answer question at hand
- Analysis – pre-specified endpoints & SAP, totality of the data, interpretable results.

Registry is the CRF with Modular Add-Ons if needed

* Modified from Andy Farb