Pragmatic Clinical Trials for Regulatory Decisions

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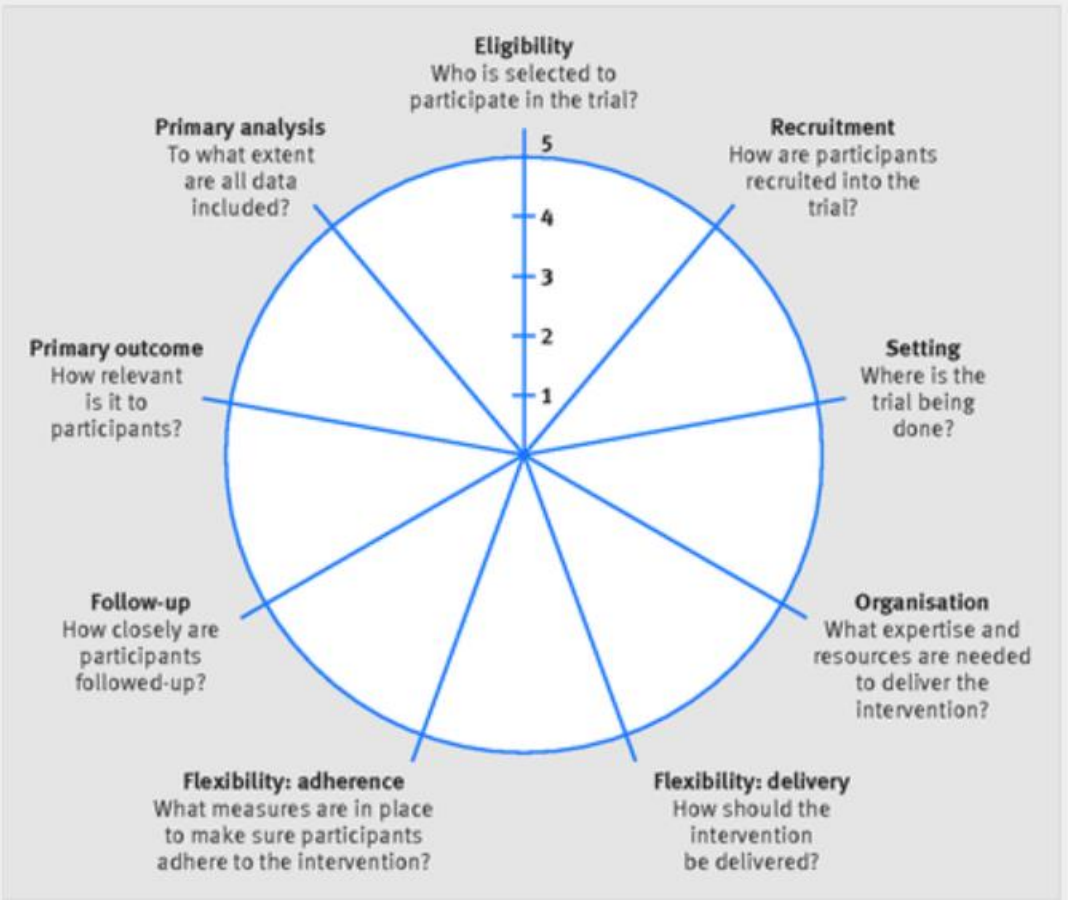
Pragmatic Clinical Trials

- **“Pragmatic” in reference to trials means many things to many people**
- **Broadly, refers to an attempt to make the result of the trial applicable to a broad “real” population**
- **“Pragmatism” is a range of characteristic with many different domains**
- **It is not a single design**
- **An important question is whether some or all of these flexibilities will work for regulatory questions**



Keep it Simple

Put another way, considering both applicability and simplification of trials

- **Can we integrate research into clinical practice**
  - **Enroll a more diverse population**
  - **Potentially increase efficiency and lower costs through use of clinical data already being collected**
  - **Understand how products work when administered as part of clinical practice**

  AND
- **Provide substantial evidence for a labeling claim**

There is a Model to Build on

LARGE-SCALE RANDOMIZED EVIDENCE: LARGE, SIMPLE TRIALS AND OVERVIEWS OF TRIALS*

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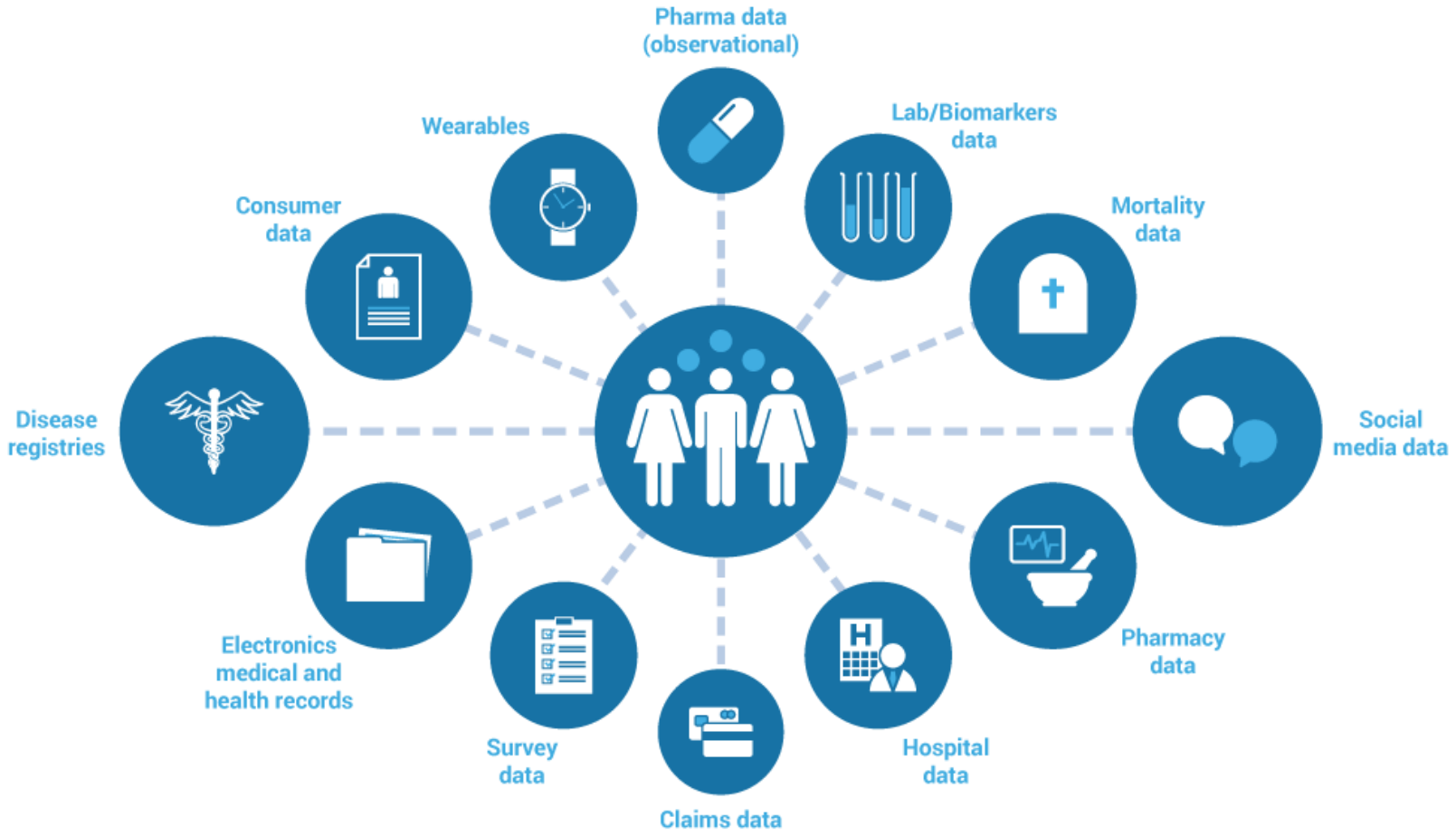
THE LANCET

Volume 332, No. 8607, p349–360, 13 August 1988 Next Article >

RANDOMISED TRIAL OF INTRAVENOUS STREPTOKINASE, ORAL ASPIRIN, BOTH, OR NEITHER AMONG 17 187 CASES OF SUSPECTED ACUTE MYOCARDIAL INFARCTION: ISIS-2

ISIS-2 (SECOND INTERNATIONAL STUDY OF INFARCT SURVIVAL) COLLABORATIVE GROUP[1]

The Opportunity and Challenge



Potential Components for RCTs in real world clinical practice settings for label expansion

- **Primary hypothesis well-defined, relevant to participating HCPs: consistent with non-placebo controlled non-blinded design**
  - **When is lack of blinding unlikely to impact the results?**
- **Approved medication, widely available, and therapeutic alternatives being studied acceptable to practices and to patients**
  - **Intervention studied "fits" within healthcare system; practice visit frequency adequate to data collection and monitoring**
  - **Can this be integrated into the work flow**
- **Straightforward dosing and administration**
- **Study enrollment criteria easily applied and appropriately defines target patients**

Study Design Elements

Potential Components for RCTs in real world clinical practice settings for label expansion

- **Primary endpoint and other key clinical outcomes *easily ascertained* from practice (eHR) and/or claims datasets (can consider embedded eCRF)**
  - **Can the physician/investigator reliably capture the endpoint of interest?**
  - **Will there be challenges with measuring disease progression/changes versus more objective measures, labs, imaging?**
  - **Can mobile technologies be leveraged to fill in the gaps?**
- **Network "captures" all outcomes – drug dispensing, ER visits hospitalization, death, PCP or specialist care interactions--limited patient movement out of system**
  - **How much missing data is acceptable? Will we know it is unknown?**

Data accuracy and complete-ness

Potential Components for RCTs in real world clinical practice settings for label expansion

- **Streamlined AE reporting acceptable (e.g., reporting only serious events, use of reporting waivers, routine practice setting safety monitoring appropriate)**

  FDA Guidance – Determining the extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations

- **Central site monitoring appropriate with more + limited on-site monitoring / risk-based monitoring**

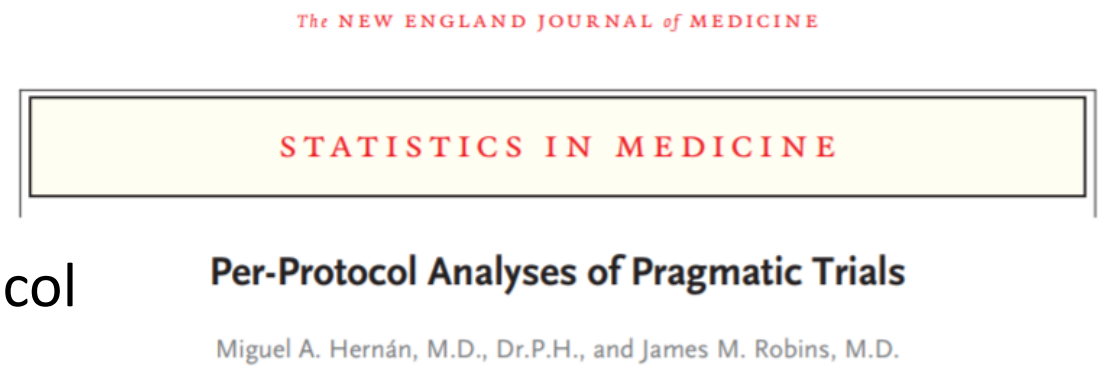
Study Monitoring

The question matters

- **Is Drug A equivalent to Drug B?**
  - What is the non-inferiority margin in the real world setting?
  - Can one be confidence that treatment variability, compliance and missing data do not drive the result?

Statistical considerations

- Does the actual adherence or lack of adherence in clinical practice warrant different statistical approaches?
  - Per-protocol analyses - The validity of per-protocol analyses depends not only on the choice of the appropriate method but also on:
    - an explicit definition of the per-protocol effect,
    - an a priori specification of the statistical plan, and
    - the collection of high-quality data on adherence and prognostic factors.



Considerations for the Clinician/Investigator

- **Will clinicians agree to be Investigators under FDA regulations? Sub-investigators?**
  - VA HCTZ/Chlorthalidone Study: study functions were established such that no personnel at VA medical centers from which patients are enrolled are considered “engaged in research.” This consideration was facilitated by our decision to obtain consent from primary care clinicians to serve as study participants
- What roles aside from clinical care will practitioners be willing to undertake? e.g. AE reporting
- Will there be any ethical concerns raised by a blurring of the investigator/clinician roles?

Putting it All Together

- Identification of relevant questions for practitioners and patients
- Selection of an intervention that can be appropriately delivered in a clinical setting
- Normalization of the integration of clinical practice/research
- Integration of clinical data across health care systems, with appropriate patient protections to maximize data capture
- Potential use of mobile technologies to fill in the gaps, e.g. to capture patient reported outcomes

Many trials can have 'pragmatic elements' while maintaining rigorous standards for data collection and assessment

Thank You

Acknowledgements

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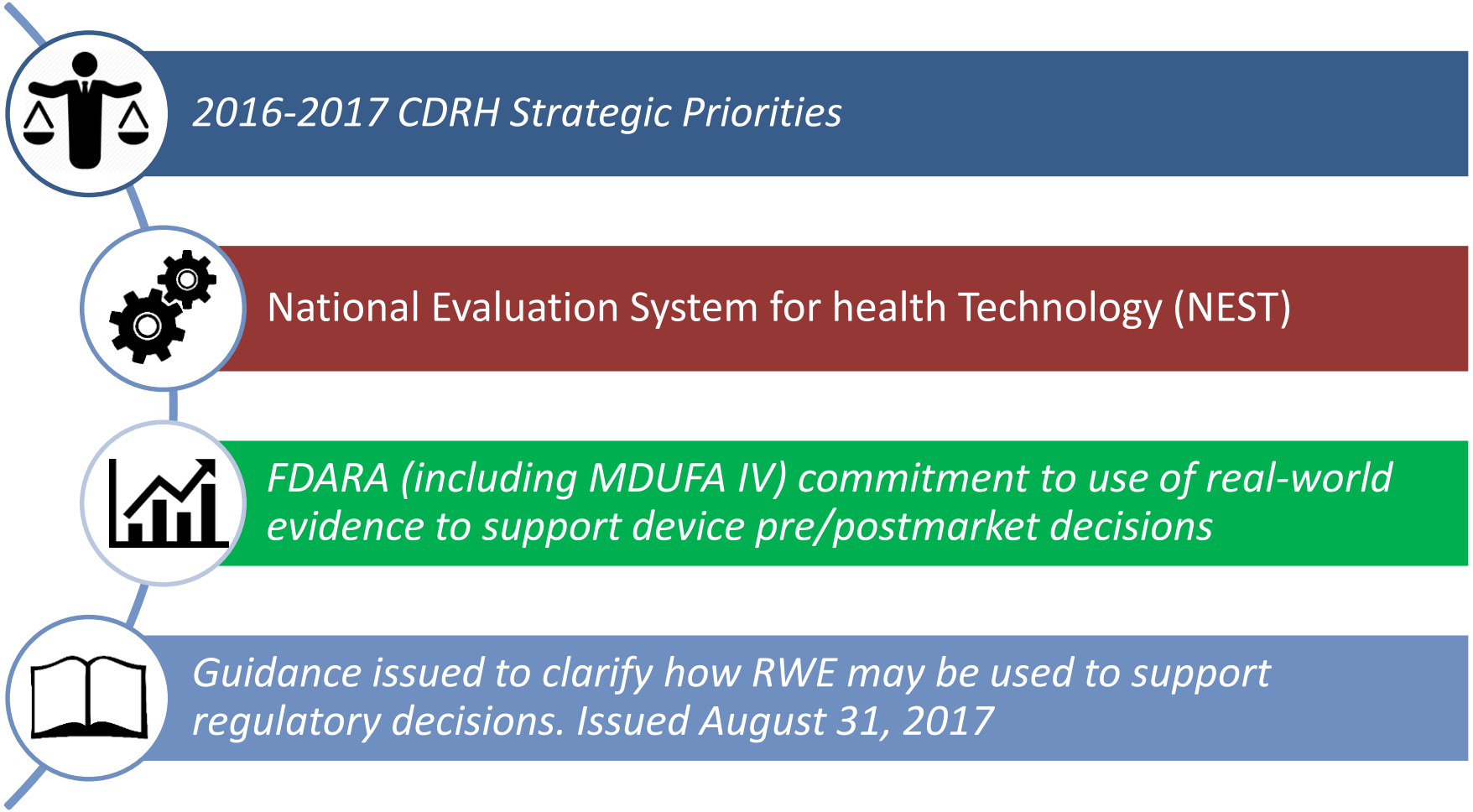
- Bob Temple

The Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

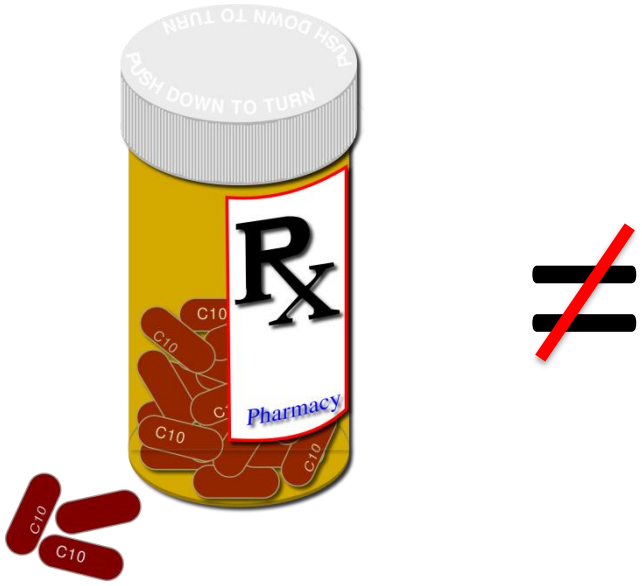
Owen Faris, Ph.D.
Director, Clinical Trials Program
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

Context for RWE Guidance



Devices Are Different from Drugs

- Many devices are highly dependent on clinician knowledge, experience, and skill
- Devices and techniques iteratively and rapidly improve (sometimes even during a trial)
- Gold-standard RCT often not practical



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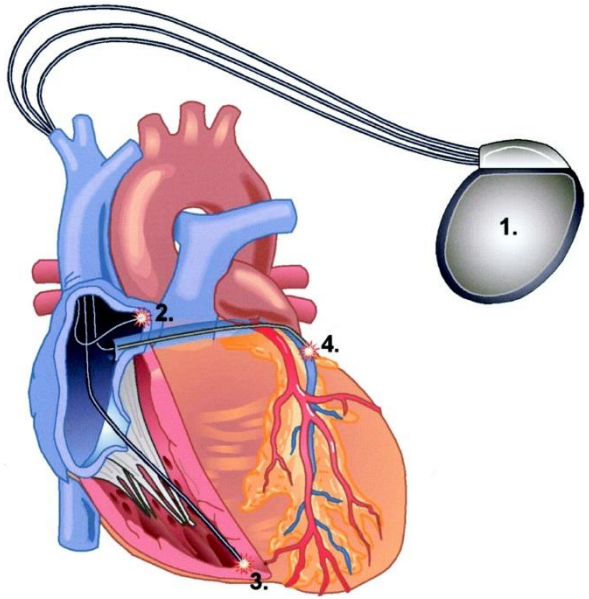


What are the opportunities?

Flexibility

- "Can't always get what you want…."
- But if we are flexible, we can "get what we need"

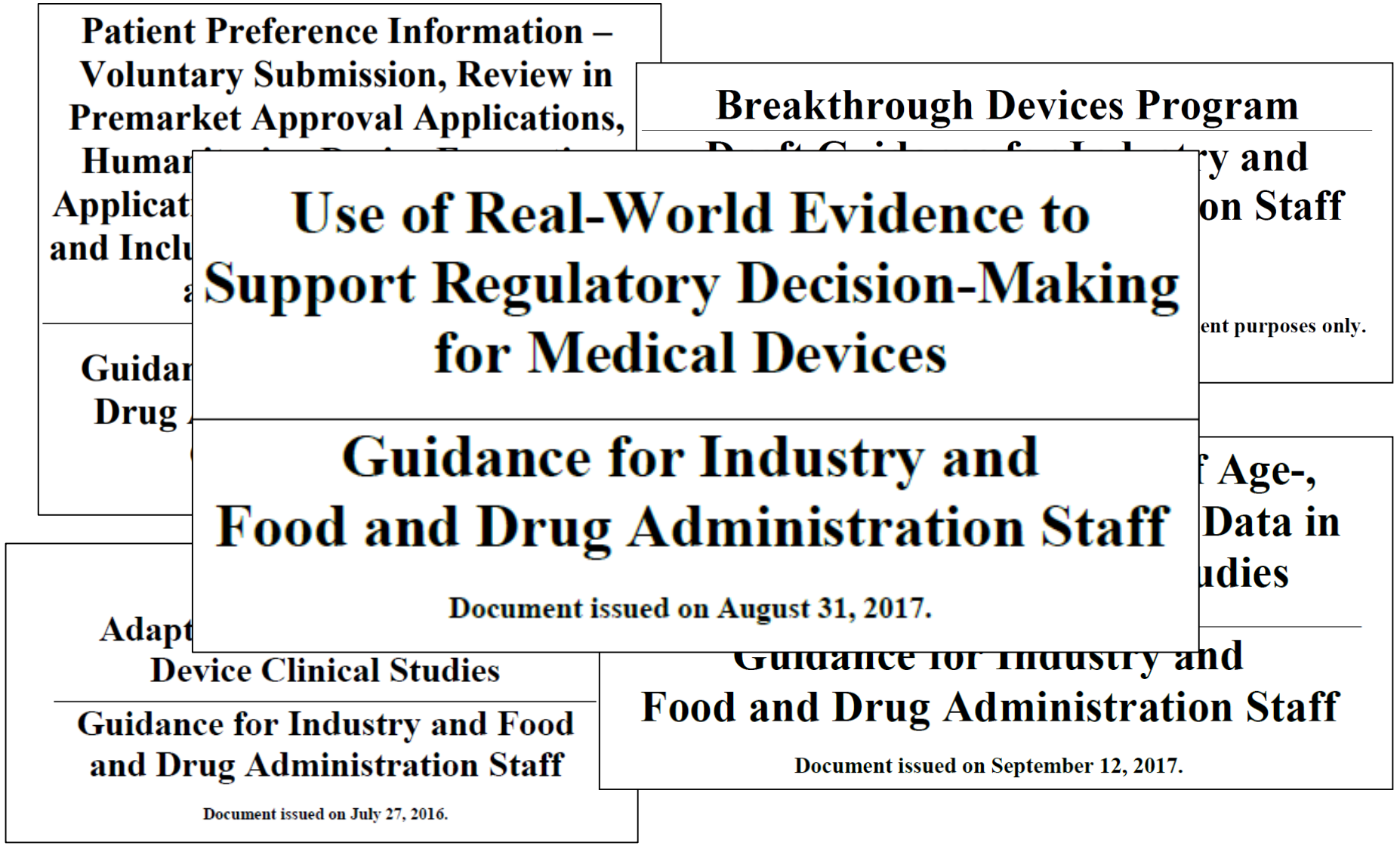
Innovation

- Modeling
- Adaptive designs
- Real-world evidence

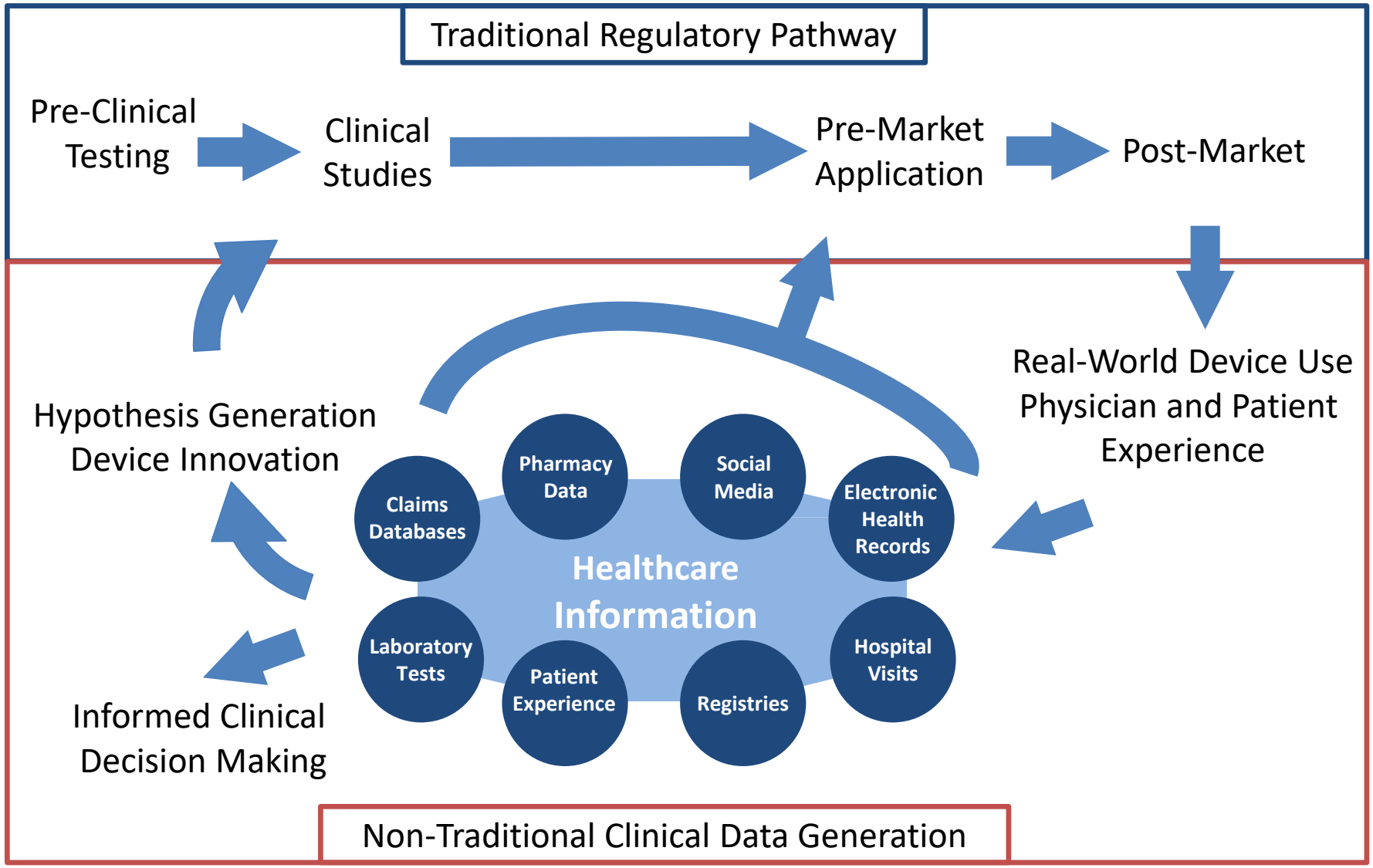
Collaborations

- NEST
- Industry groups
- Patient and clinician groups

Clinical Trial Innovation



Evidence in Regulatory Decisions



Data Quality

'Fit for Purpose'

Data should be assessed for completeness, consistency, accuracy, and whether it contains all critical data elements needed to evaluate a medical device and its claims.

Relevant & Reliable

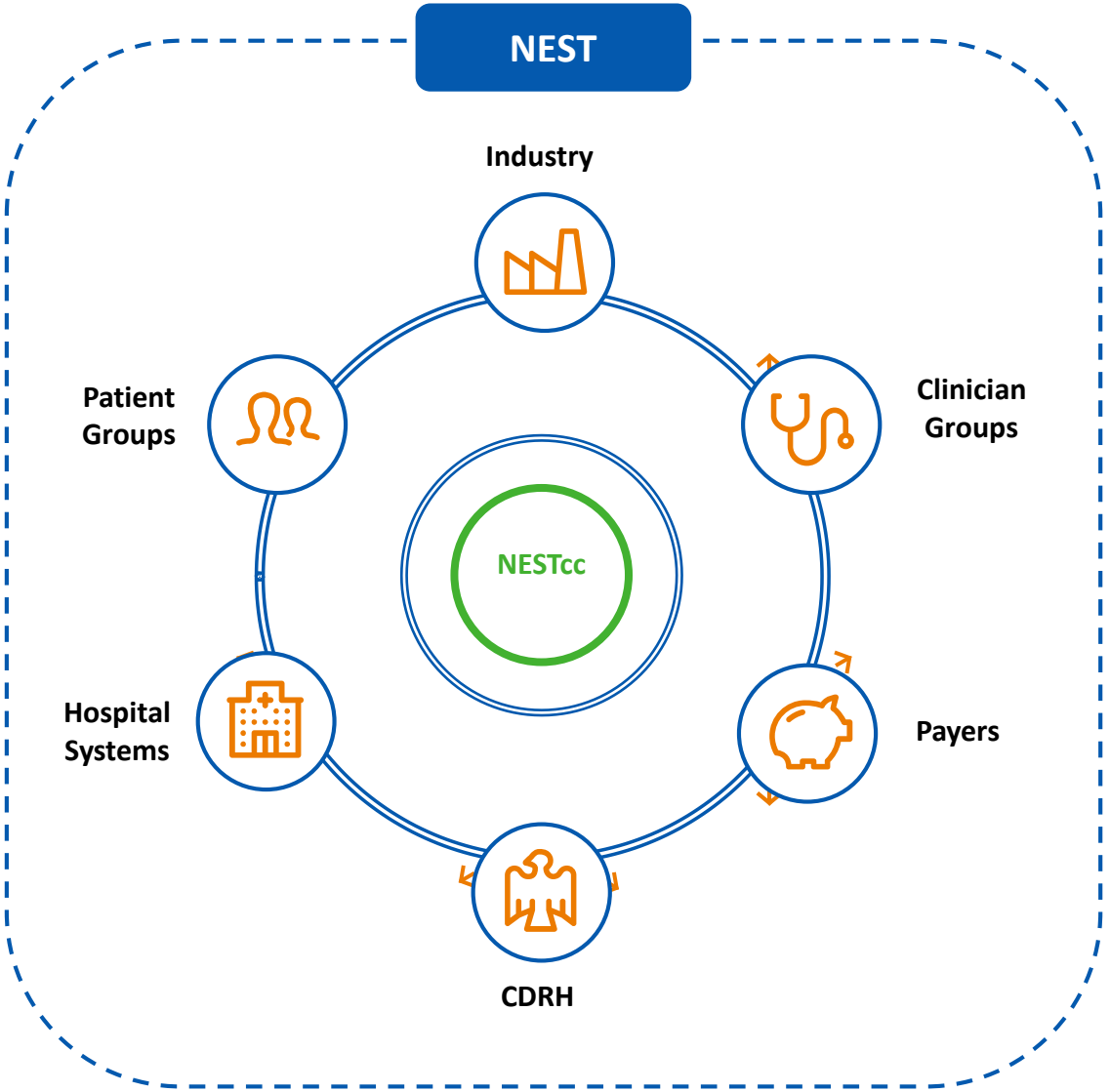
Benefit

Risk

Some Regulatory Uses for RWE

- Control arm for pivotal clinical study
- New indications for approved devices
- Studying new improvements to devices
- Replacing post approval study
- Adverse event reporting
- Shifts to pre-postmarket balance

National Evaluation System for health Technologies (NEST)



Cardiac Device Coordinated Registry Network – CDCRN

- To provide uniquely reliable prospective clinical and regulatory evidence about the effects of studied treatments on important outcomes over long periods of time
- To allow access to data for all stakeholders that will promote appropriate regulatory approval and clinical application of medical devices for therapeutic interventions
- Do it in a way that provides flexibility and affordability

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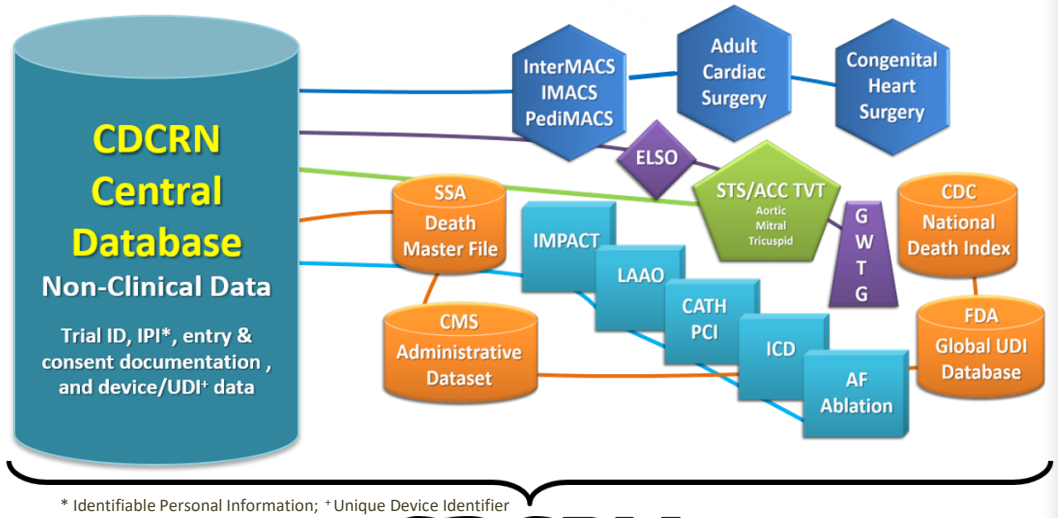
CDCRN – A Reusable Infrastructure for Clinical and Regulatory Evidence Generation

(1) New CDCRN Central Database **(2) Existing CV Registries and Administrative Datasets #**



* Identifiable Personal Information; + Unique Device Identifier

CDCRN

2 Components + Linkages (—)

CDCRN Results In:

- ***NO CHANGE*** to current governance or business models of any registry
- ***NO DISRUPTION*** of current clinical uses or utility of registries to end users
- Positions Academic Societies & Registries at the center of the clinical trial enterprise

CDCRN Allows:

- Prospective collection of uniform trial/Rx data
- Programmed passive longitudinal data and evidence acquisition
- Production of Dynamic **CLINICAL/REGULATORY** evidence over TPLC

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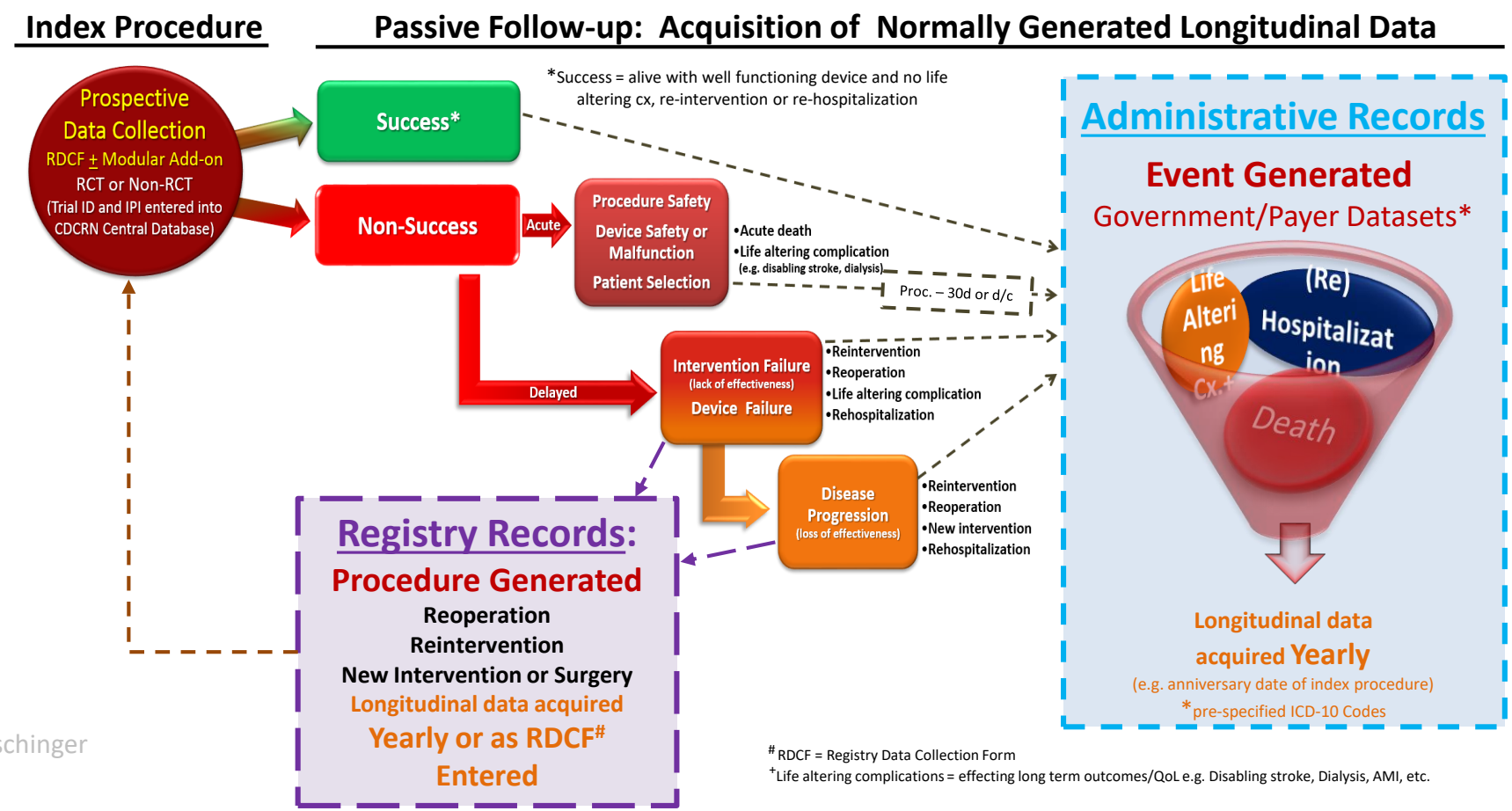
 # Continue to operate independently to fulfill their current individually designed, essential and sustainable missions

Longitudinal Data Generation & Acquisition

Important Hard Outcomes Continuously Tracked Over Time



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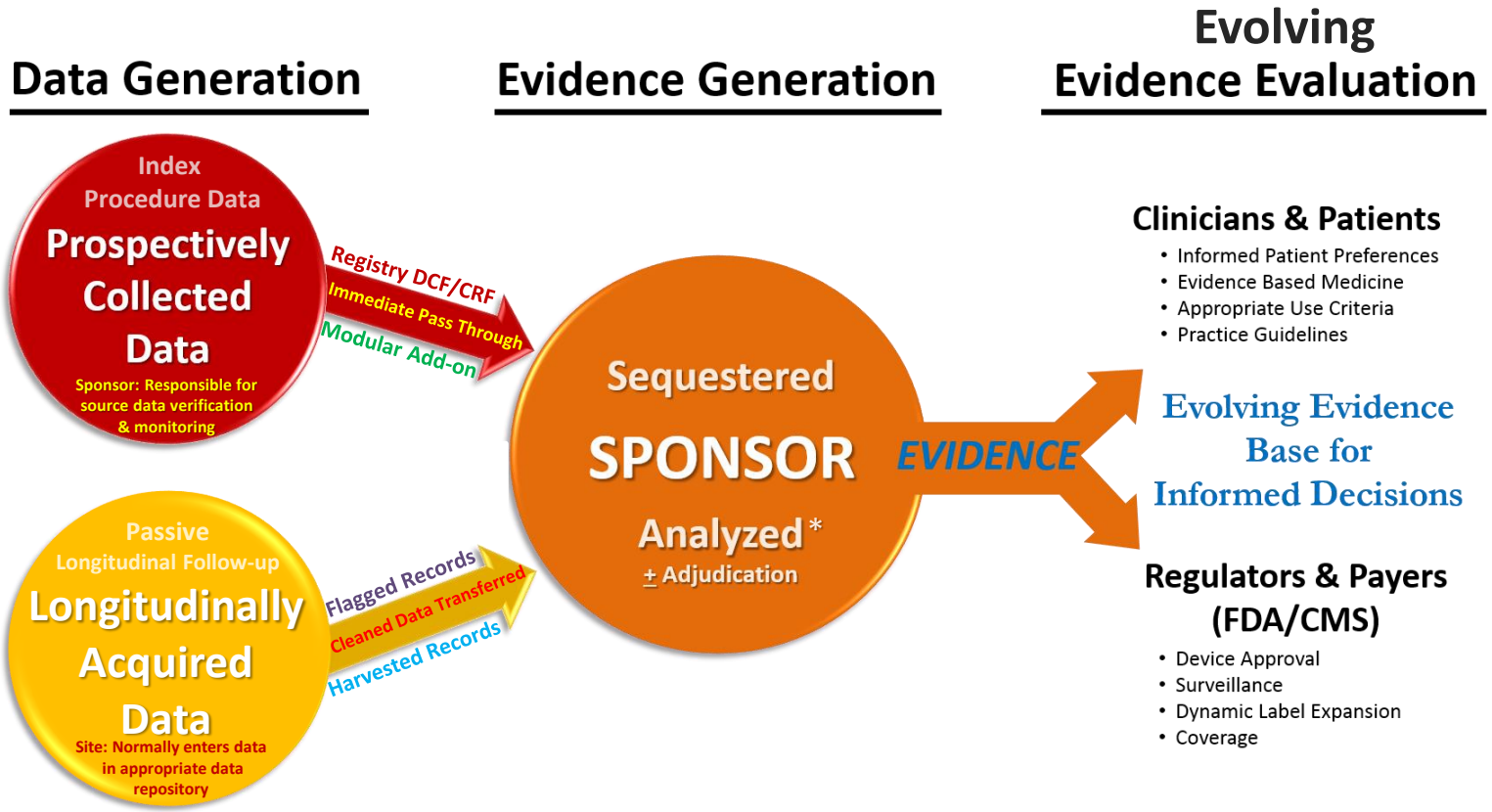
Data Flow and Creation of Evidence



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* Pre-specified statistical analysis plan

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The Common Rule: What's Special about Pragmatic Trials?

Julie Kaneshiro

Office for Human Research Protections (OHRP)

May 16, 2018

OHRP
Office for Human Research Protections

Disclaimer

The opinions expressed are those of the presenter and do not necessarily reflect the policy of the U.S. Department of Health and Human Services.

Topics

- Applicability of the Common Rule to pragmatic trials
- Trial design
- IRB review
- Revised Common Rule
- OHRP initiatives

Determining if the Common Rule Applies

- ✓ The activity is conducted or supported by HHS
- ✓ The activity is non-exempt human subjects research

To determine whether the activity is non-exempt human subjects research, **ask these questions:**

1) Does the activity involve **research**?
2) Does the research involve **human subjects**?
3) Is the human subjects research **exempt**?

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Does the Pragmatic Trial Involve a Research Intervention?

Definition of Research:

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

Who are the Subjects in Pragmatic Trials?

Definition of Human Subject:

- Human subject means a living individual about whom an investigator conducting research:
  - i. Obtains **information or biospecimens** through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
  - ii. Obtains, uses, studies, analyzes, or generates **identifiable private information or identifiable biospecimens**

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Trial Design

- Cluster design and impact on consent – e.g., community, provider, hospital)
- Questions to consider:
  - If a cluster design is proposed, is it necessary?
  - Is the intervention “research”?
  - Who are the subjects?
  - What role, if any, should a patient’s treating physician have in determining whether patients should be asked to enroll?
- Existence of equipoise does not necessarily mean that the study poses minimal risk or that consent can be waived

Which Collaborators Need IRB Review?

- Only institutions engaged in the research need IRB review – *not necessarily all collaborating institutions*

IRB Review: "Engaged"?

- Need to consider the institution's activities
- A few examples of non-engagement:
  - Release to investigators at another institution identifiable private information or identifiable biological specimens
  - Perform commercial services for investigators provided that specified conditions also are met

Pragmatic trials and the Revised Common Rule

- New consent requirements
- IRB review

General Improvements to Informed Consent

- Establishes a new standard to provide the information needed ***to make an informed decision about whether to participate***

- ***Reasonable person*** standard is used to determine what information to include

General Improvements

Information presented in ***sufficient detail***, and ***organized and presented*** in a way that facilitates subject's understanding of why one might or might not want to participate

Not merely a list of isolated facts

General Improvements

- New requirement that certain ***key information*** must be provided ***first***
- **Key information**
  - About ***why one might or might not want to participate***—often include (though not limited to) information about purposes, risks, benefits and alternatives
  - Must be presented in ***concise and focused*** manner

Requirement for Single IRB Review

Applicability

- U.S. institutions engaged in cooperative research for the portion of the research conducted in the U.S.
- Does not apply:
  - When more than single IRB review is required by law (including tribal law)
  - Whenever any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context

Compliance date for sIRB provision: **January 20, 2020**

OHRP Initiatives

- OHRP exploratory workshop on consent
- Public engagement on the regulation of certain types of health services research