# The Future of Randomized Trials: The Use of Registries

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# Disclosure

I am a full time employee of the FDA.

I have no conflicts of interest to report

# Disclaimer

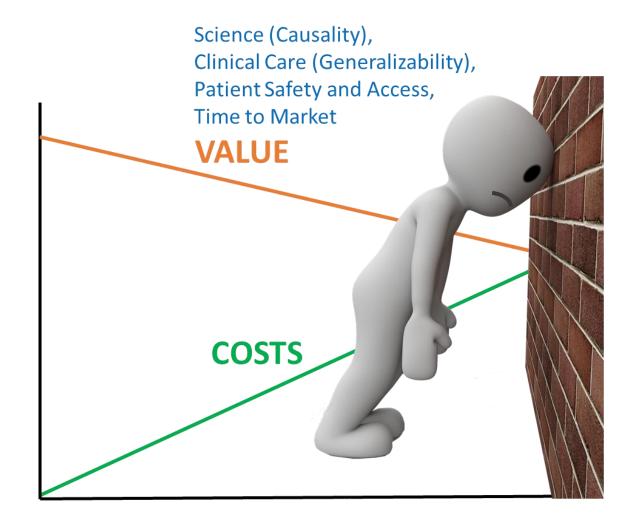
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John Laschinger, MD

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# The Clinical Trial Enterprise

Is the Current System for Evidence Generation Sustainable?



Effective barrier to the generation of clinical and regulatory evidence needed for:

- Innovation & Access
- Informed clinical use throughout the Total Product Life Cycle (TPLC)

# Evidence Generation and Evaluation

Actionable Insights for Informed Clinical and Regulatory Decisions

#### **Question at Hand**

- What Data is Needed?
  - Available or acquired
  - Sources and Settings
  - Experimental Method Needed



- High Quality complete, accurate and timely
- Linkages, Modular data sets
- Source traceability
- Reliable free from errors that matter

**Raw Data** 

#### Information

- Relevant Scope and content answers question at hand -Fit to Purpose
- Curation organization and distillation of data - context
- Informs Knowledge communicated by facts

- Combination and Analysis of data and information
- Identification and application of appropriate analytic and/or statistical tools
- Supports conclusions
- Makes information interpretable

Evidence

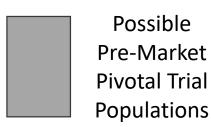
Informed Clinical and Regulatory Decisions



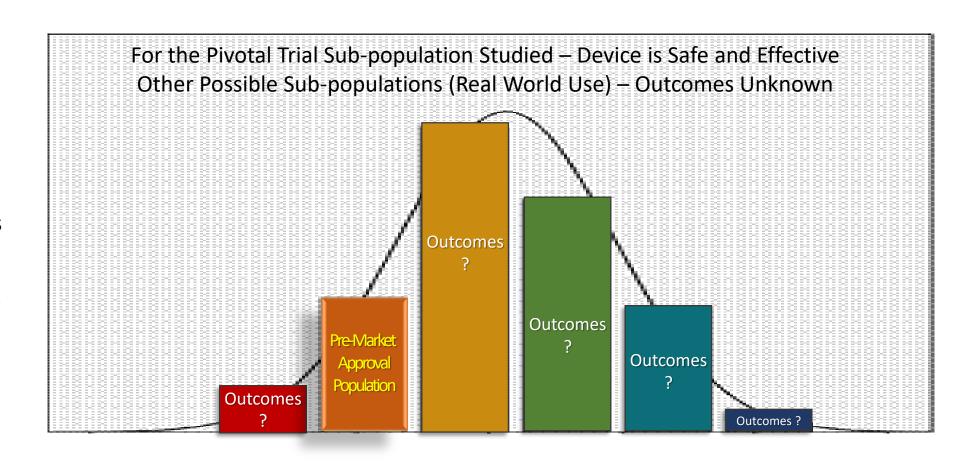
- Judgement Formation of sound clinical and scientific opinions or conclusions
- Objective evaluation of the totality of the evidence

# Current Paradigm: Limited Pivotal Trial

Premarket data does not reflect outcomes for post-market uses



Post-Market
Real World
Population
of Use



# FDA Approval: Is That All There Is?

What happens post-approval?

# Pre-Market Clinical Evidence Limitations:

- Non-Generalizable:
   Narrow indications,
   populations, users and
   conditions of use,
   relatively small study sizes
- Compromises in trial design and endpoints
- Finite: Limited Follow-up
- Many Unanswered & unanswerable questions

# Evolving Evidence over the TPLC\* Transportability Changes in Durability of

populations,

conditions and

patterns of use

Dynamic nature of benefit-risk assessment

(generalizability)

- Users and

patients

pre-market

evidence

## Reasonable Assurance

of safety and effectiveness at the time of device Approval/Clearance

Long term

disease response

and/or disease

progression

device, device

performance and

device effects



# Residual Uncertainty

regarding appropriate and safe device use in the post-market

Residual Uncertainty at the Time of Device Approval

Tolerable Level of Pre-Market Residual Uncertainty

Benefit-Risk Balance Ability to Collect Data and Generate Evidence in New Ways

Disease and Current Therapy, Unmet Need

Device Risk: New or Iterative Device

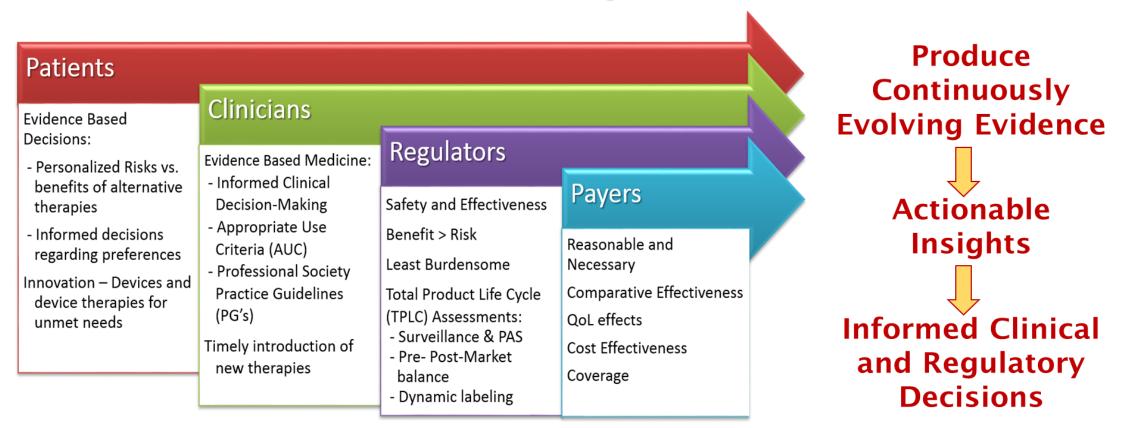
Pre to Post-Market Continuum (TPLC)

Utilization of RWD and RWE

# The Clinical Trial Enterprise

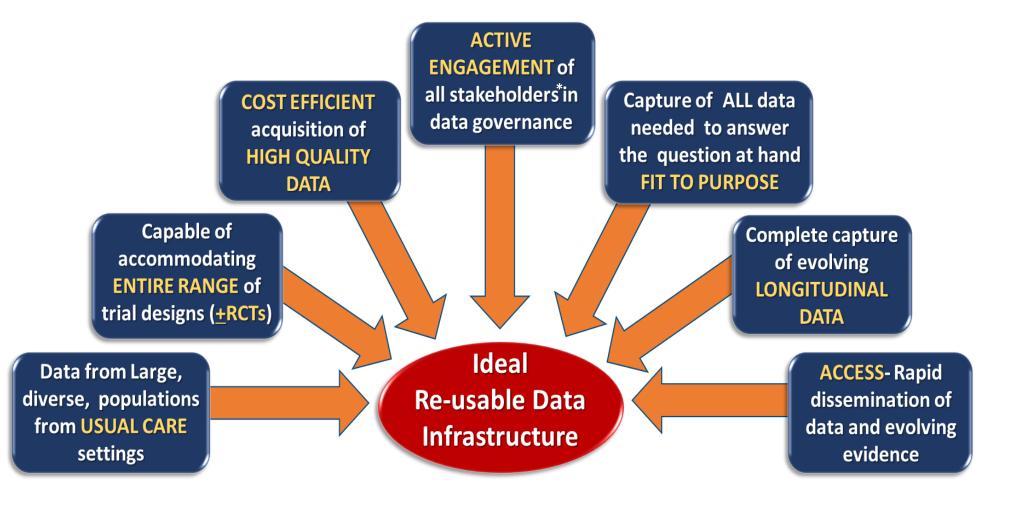
Keeping Up in Times of Rapid Change

Can it be Remade to Satisfy the Needs of Patients, Clinicians, Regulators and Payers



# Remaking the Clinical Trial Enterprise

Priorities for Creating a Reusable Clinical Trial Infrastructure



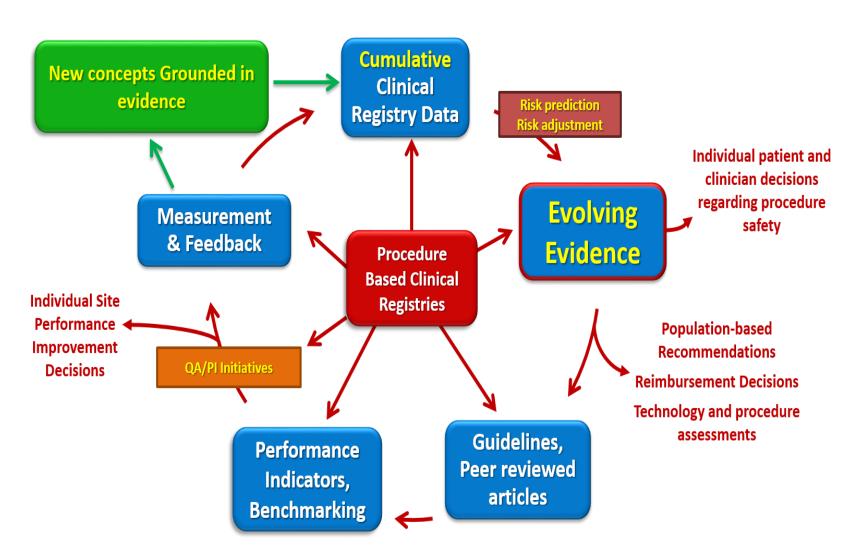
Laschinger JC \* patients, clinicians, researchers, purchasers, payers, industry, hospitals and health systems, policy makers, and training institutions

# Available CV Registries and Datasets

Comprehensive, Valuable and Affordable Real World Evidence

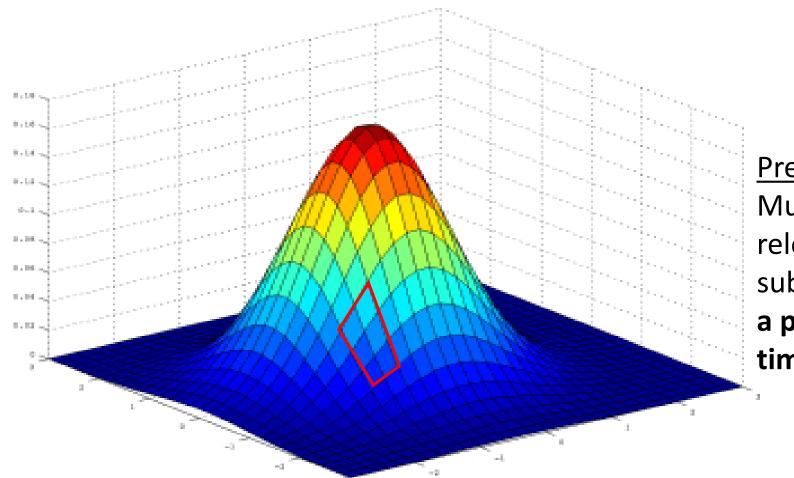
Cardiovascular Procedure-based Registries

Central Roles in the Cycle of Quality



# Procedure-based Registry Outcomes Data Continuous capture of a real world use

Risk Adjusted Outcomes for Entire Population (Real World Data and Evidence)



**Pre-Specified Analyses** Multiple clinically relevant, risk adjusted sub-group outcomes at a pre-defined point in time



# The Registry Embedded Pivotal IDE Clinical Trial

Using Existing Registry Platforms for Prospective Evidence Acquisition

#### **Preliminary Questions:**

- Is it a good platform Reliable, Robust and Relevant based on historical use?
- Can patient protections; data governance, access, and data privacy be maintained?

#### **TRIAL DESIGN** – Tailored to the Regulatory Need:

- Least burdensome
- Appropriate Controls
- + Randomization
- Pre/post-market balance



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#### DESIGN

Registry DCF\*

Linkages And Modular Add-ons

Case Report Form

Relevant:

Suitable to answer the question at hand

Indications for use **Patient Protections** 

- Informed Consent Controls/Randomization **Define Population/Subsets Capture Key Outcomes, AEs Define Objective Endpoints** 

# CONDUCT

**Quality Data** is acquired - complete and accurate - free from errors that

matter

Site Selection **Protocol Adherence & Data Completeness Intervention Compliance Auditing/Monitoring Data Integrity Core Labs DSMB & CEC** 

Minimize Bias & **Missing Data Pre-defined Analysis** Population(s) **Pre-specified SAP** 

- Endpoints
- Hypotheses
- Methodology

#### **ANALYSIS**

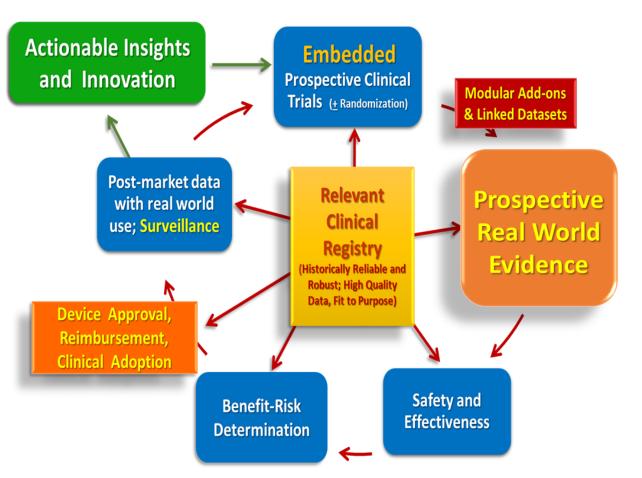
**Interpretable** results providing **Evidence:** 

- Safe and **Effective** for proposed uses
- **Benefits** outweigh risks

\* DCF = Data Collection Form

Registry Embedded Clinical Trials

#### **Lessons from SWEDEHEART**\*



### **Benefits:**

#### Cost-effective

- Existing re-usable platform
- Standardized datasets and endpoints

#### Flexible

- Single arm or randomized trials
- Modular add-ons

#### Familiarity with dataset

- Easier source verification
- Consolidation of site personnel

#### Generalizable and Individualized

- Wider site participation
- Broader patient populations
- Robust sub-population analyses

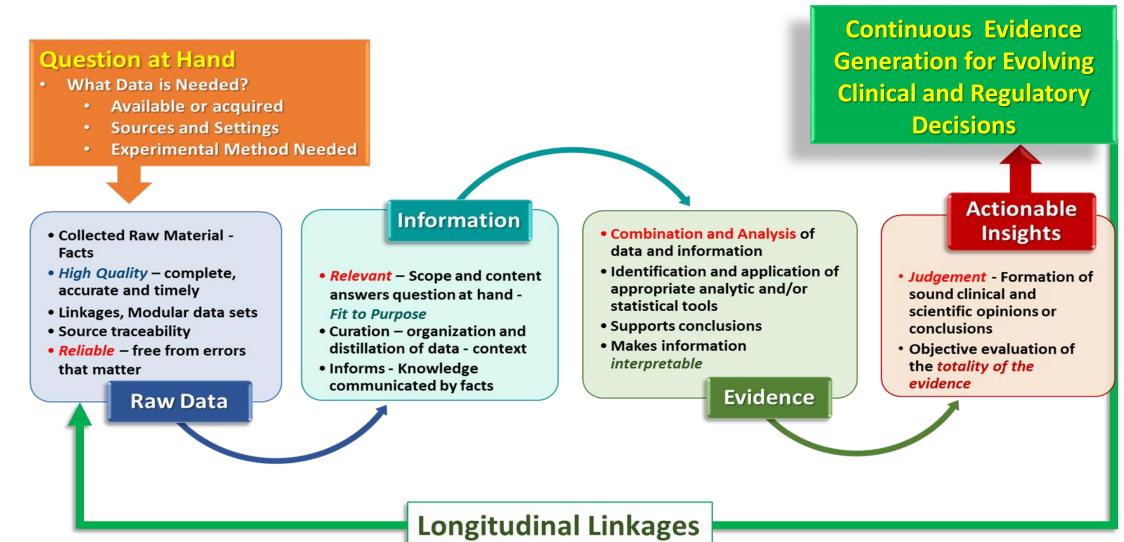
#### Connective

Linkages to administrative data sources for late outcomes

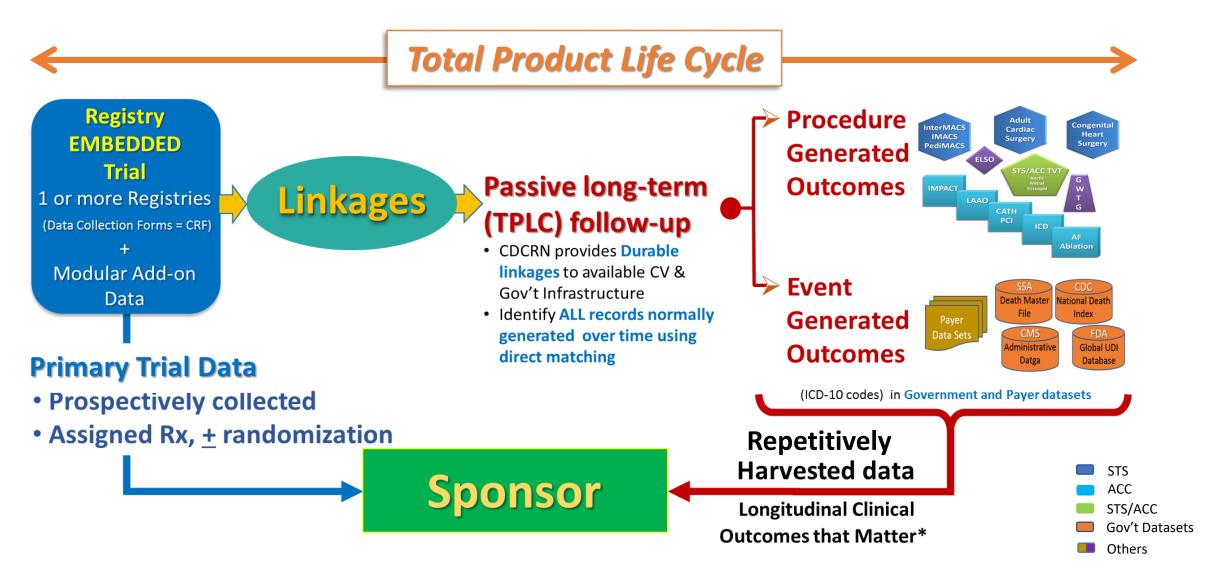
<sup>\*</sup> http://www.ucr.uu.se/swedeheart/dokument-sh/arsrapporter-sh

# Continuous Generation of Longitudinal Evidence

Capturing The Total Product Life Cycle



Cardiovascular Device Coordinated Research Network (CDCRN)



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Prospective Trial - Data Flow and Creation of Evidence (CDCRN)

#### **Evolving Evidence Data Generation Evidence Generation Evaluation Prospectively Clinicians and Patients Collected Primary** Informed patient preferences Shared decision making **Trial Data** Immediate Pass Through Appropriate use criteria Practice Guideline Documents DCF's from Appropriate Registries + Modular Add-on Datasets **Sponsor** Sponsor responsible for source **ALL Data:** data verification, monitoring **Evolving Evidence Base** Sequestered **EVIDENCE Adjudicated** for Informed Decisions Repetitively Curated **Harvested Passive** Analyzed+ Longitudinal **Updated Regulators and Payers** Follow-up Data Cleaned and Transferred Device Approval Site Data Coverage Post Market Surveillance · Normally entered in Dynamic use/label decisions appropriate Registry\* · Normally submitted to

appropriate payer\*

<sup>\*</sup> Anonymized for trial participation 

Pre-specified statistical analysis plan

Post-Market Data - Going Beyond Procedural Outcomes

# **Data Generation**

#### **Evidence Generation**

# **Evolving Evidence Evaluation**

Registry Captured
Post Approval
Data from Real
World Clinical Use

Immediate Pass Through

Reusable Infrastructure

Cleaned and Transferred

Registry Owner or Sponsor

ALL Data:
Sequestered
Adjudicated
Curated
Analyzed+
Updated

#### **Clinicians and Patients**

- Informed patient preferences
- · Shared decision making
- Appropriate use criteria
- Practice Guideline Documents

Continuously
Evolving Evidence Base
for Informed Decisions

#### **Regulators and Payers**

- Device Approval
- Coverage
- Post Market Surveillance
- Dynamic use/label decisions

Harvested Passive Longitudinal Follow-up Data

#### Site Data

Repetitively

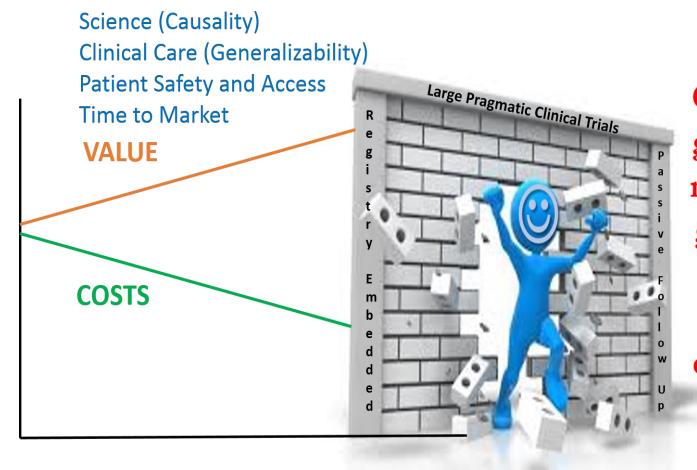
- Normally entered in appropriate Registry\*
- Normally submitted to appropriate payer\*

**EVIDENCE** 

<sup>\*</sup> Anonymized for trial participation

# Breaking Down the Barriers

CDCRN:
Harnessing
Existing
Infrastructure
to Create Value
While Reducing
Costs



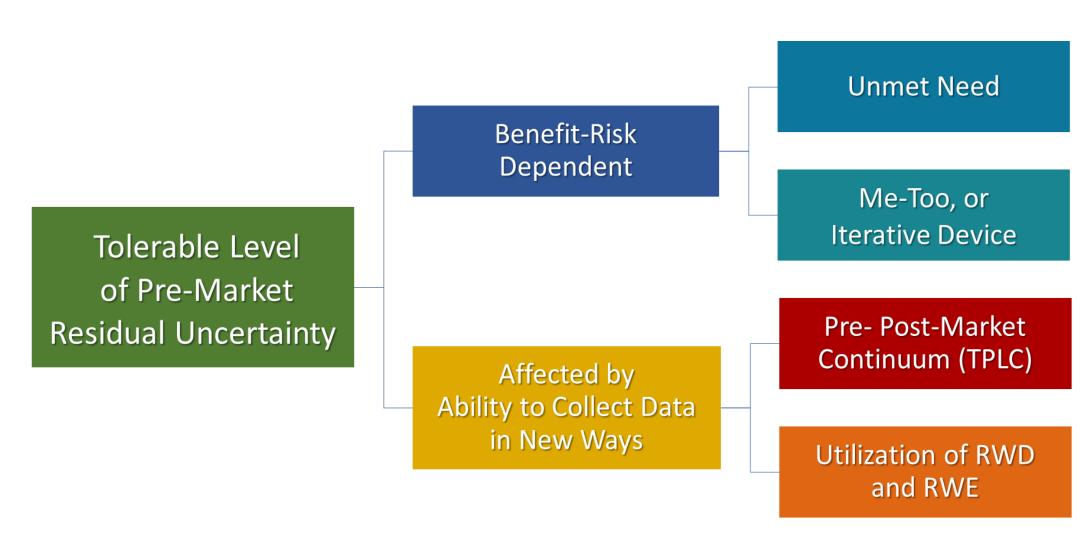
Cost-effective generation of meaningful & generalizable clinical and regulatory evidence over the TPLC

# Thank You!

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Residual Uncertainty at the Time of Device Approval



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Tolerable Level of Pre-Market Residual Uncertainty

Benefit-Risk Balance Ability to Collect Data and Generate Evidence in New Ways

Unmet Need Me-Too, or Iterative Device

Pre to Post-Market Continuum (TPLC)

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