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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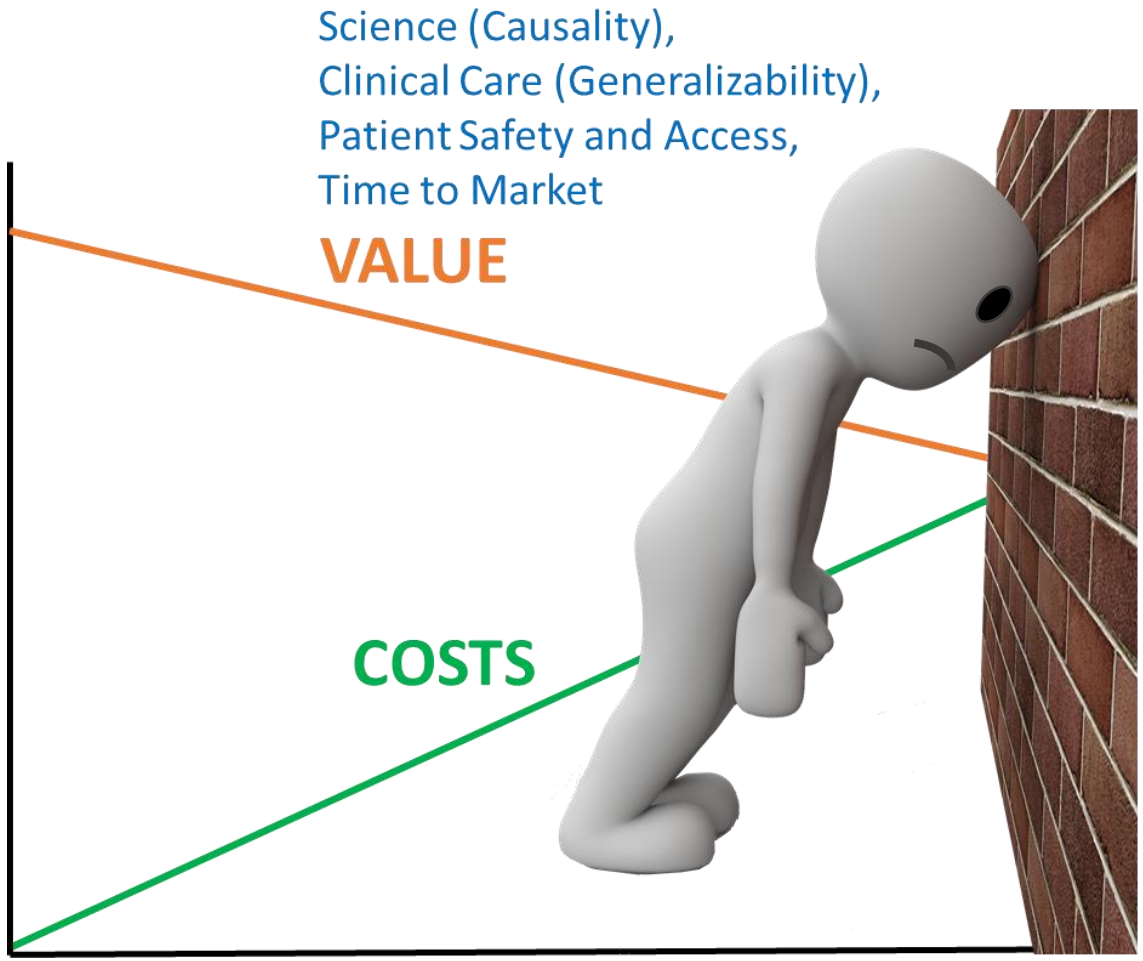
The Clinical Trial Enterprise

Is the Current System for Evidence Generation Sustainable?

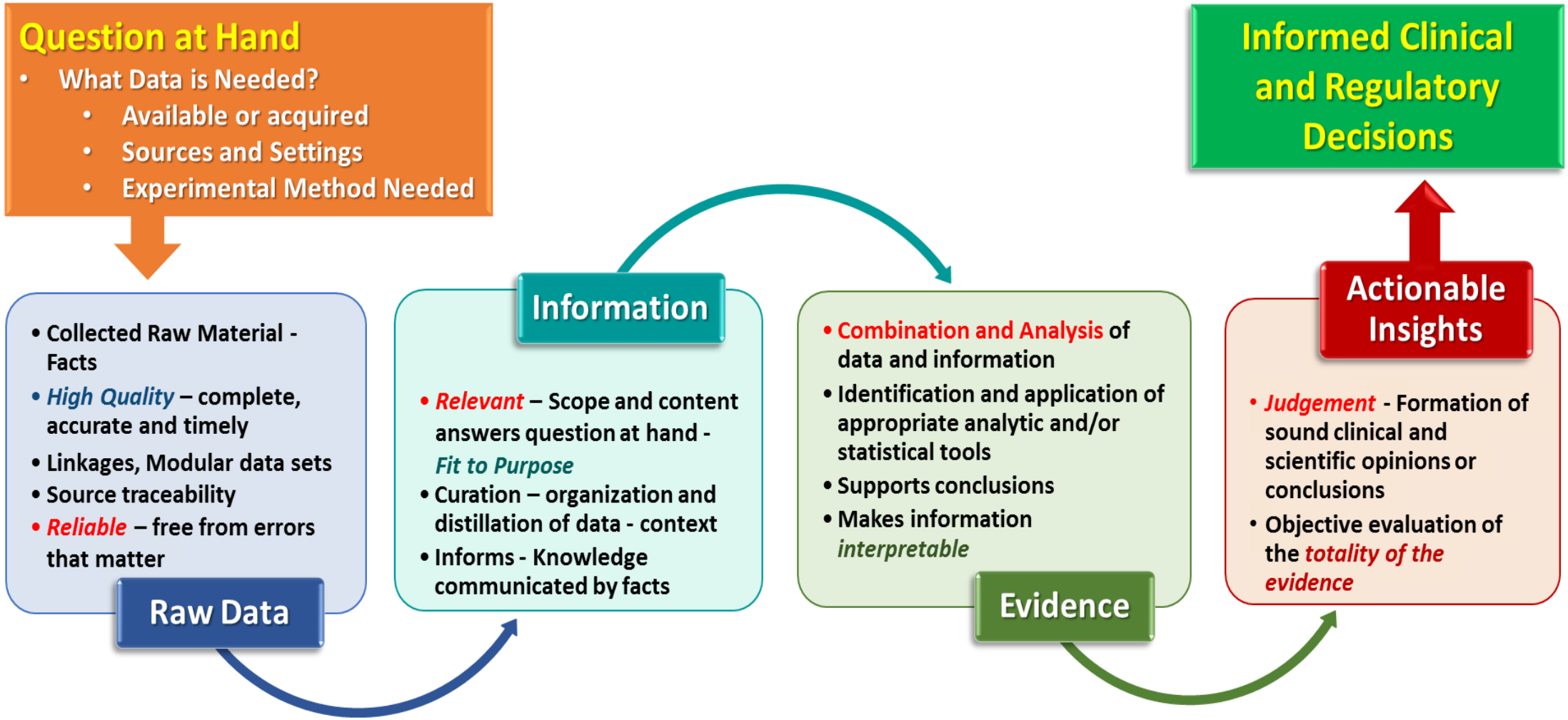


Effective barrier to the generation of clinical and regulatory evidence needed for:

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

Evidence Generation and Evaluation

Actionable Insights for Informed Clinical and Regulatory Decisions

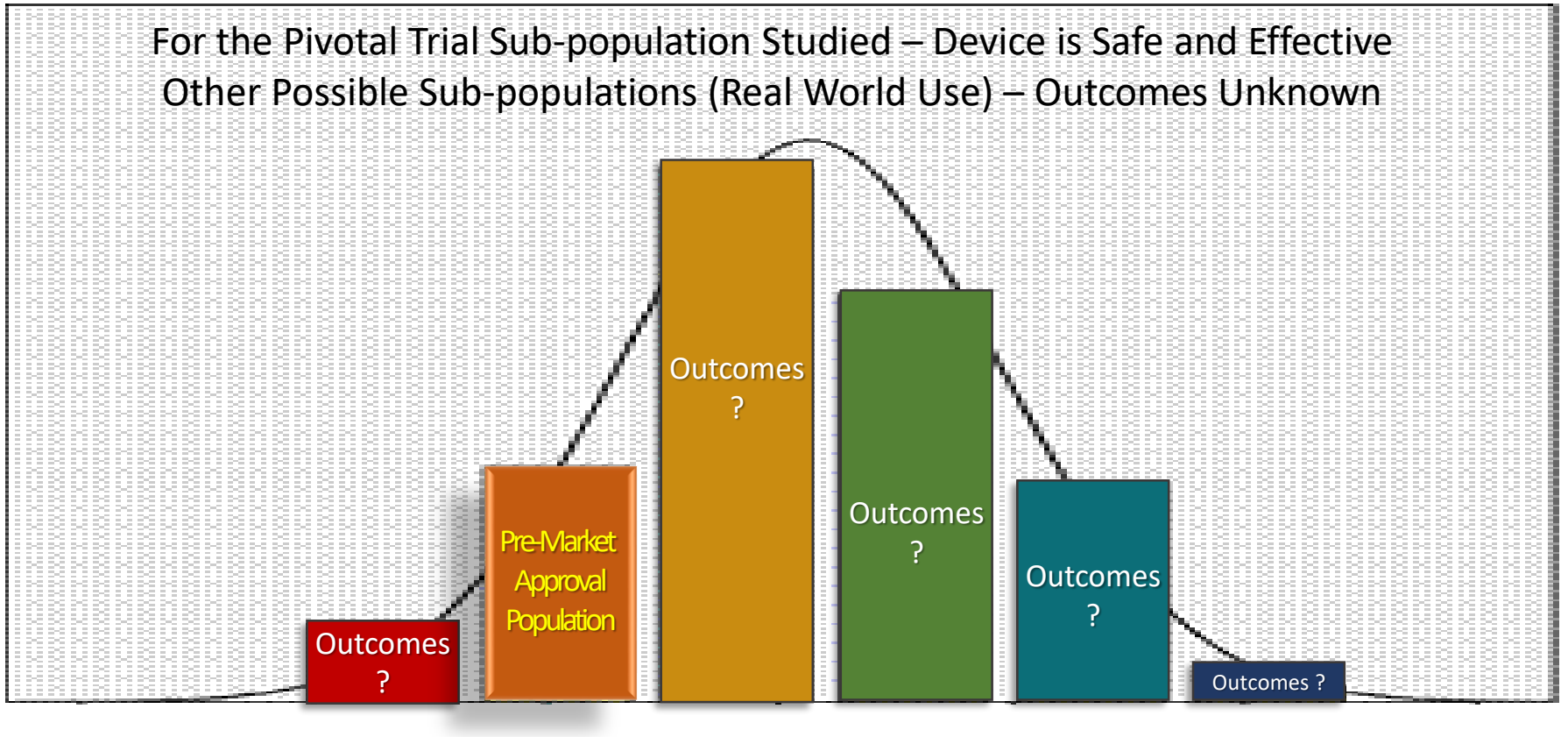


Current Paradigm: Limited Pivotal Trial

Premarket data does not reflect outcomes for post-market uses

Possible Pre-Market Pivotal Trial Populations

Post-Market Real World Population of Use

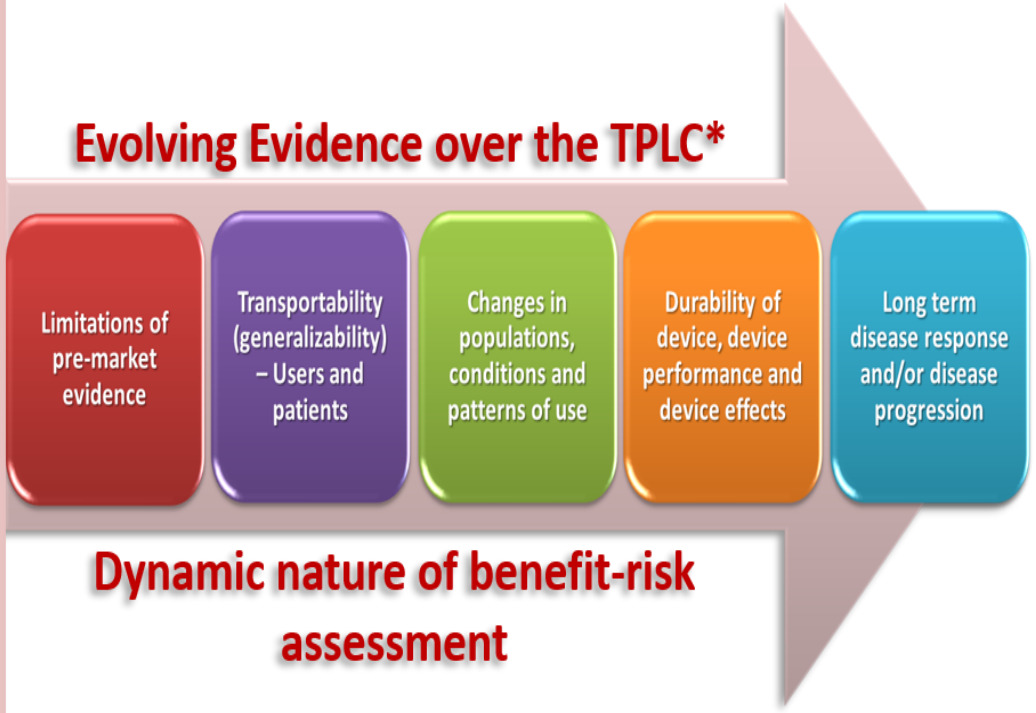


FDA Approval: Is That All There Is?

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



Reasonable Assurance

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

=

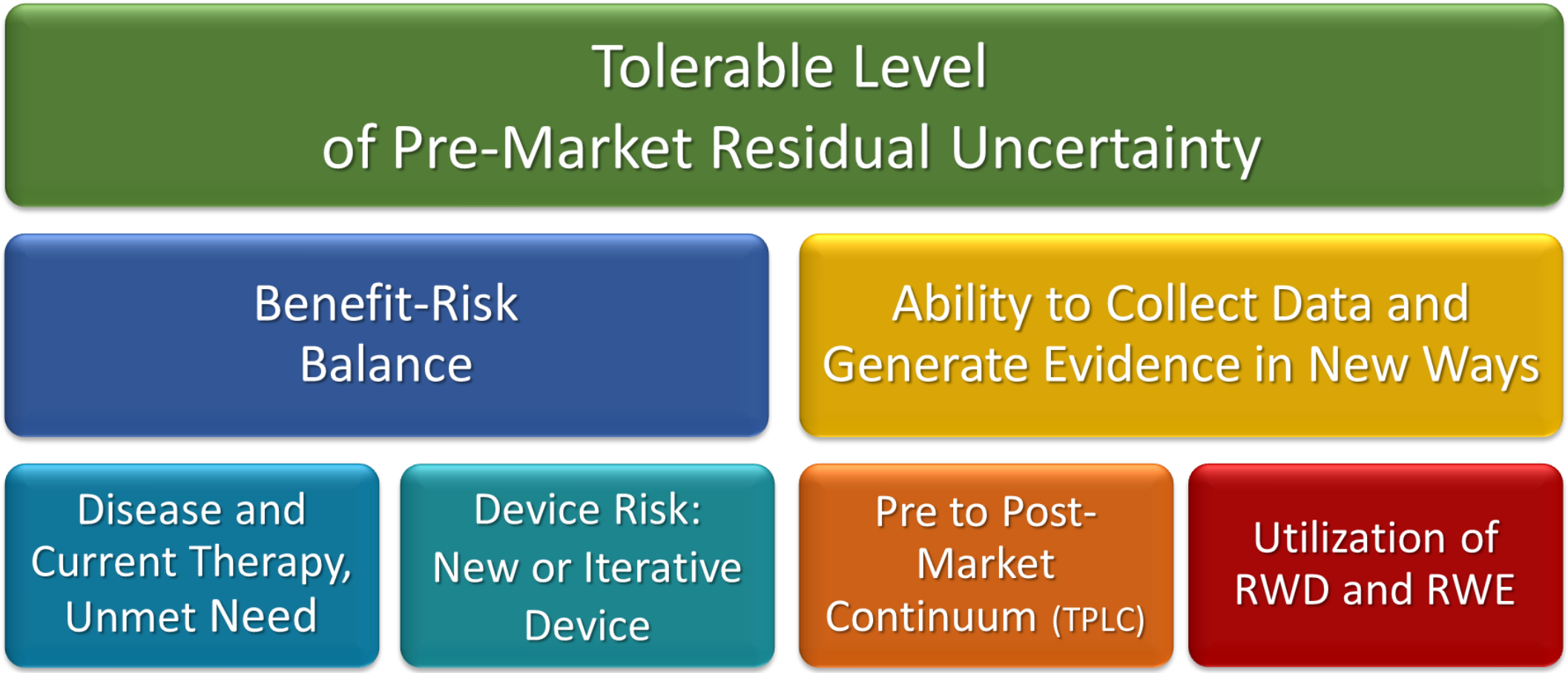
Residual Uncertainty

regarding appropriate and safe device use in the post-market

*Total Product Life Cycle

Reasonable Assurance

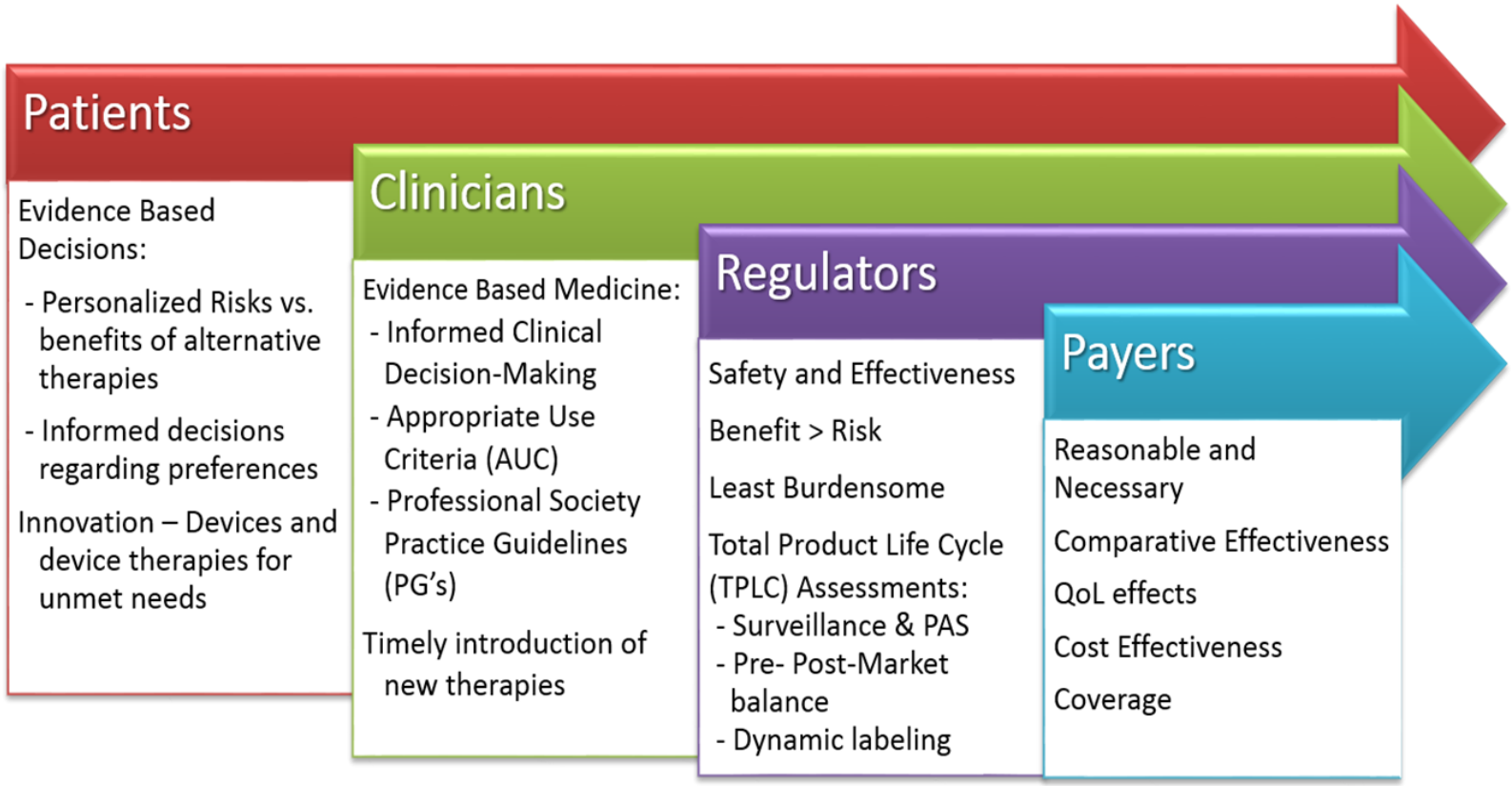
Residual Uncertainty at the Time of Device Approval



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



Produce Continuously Evolving Evidence

↓

Actionable Insights

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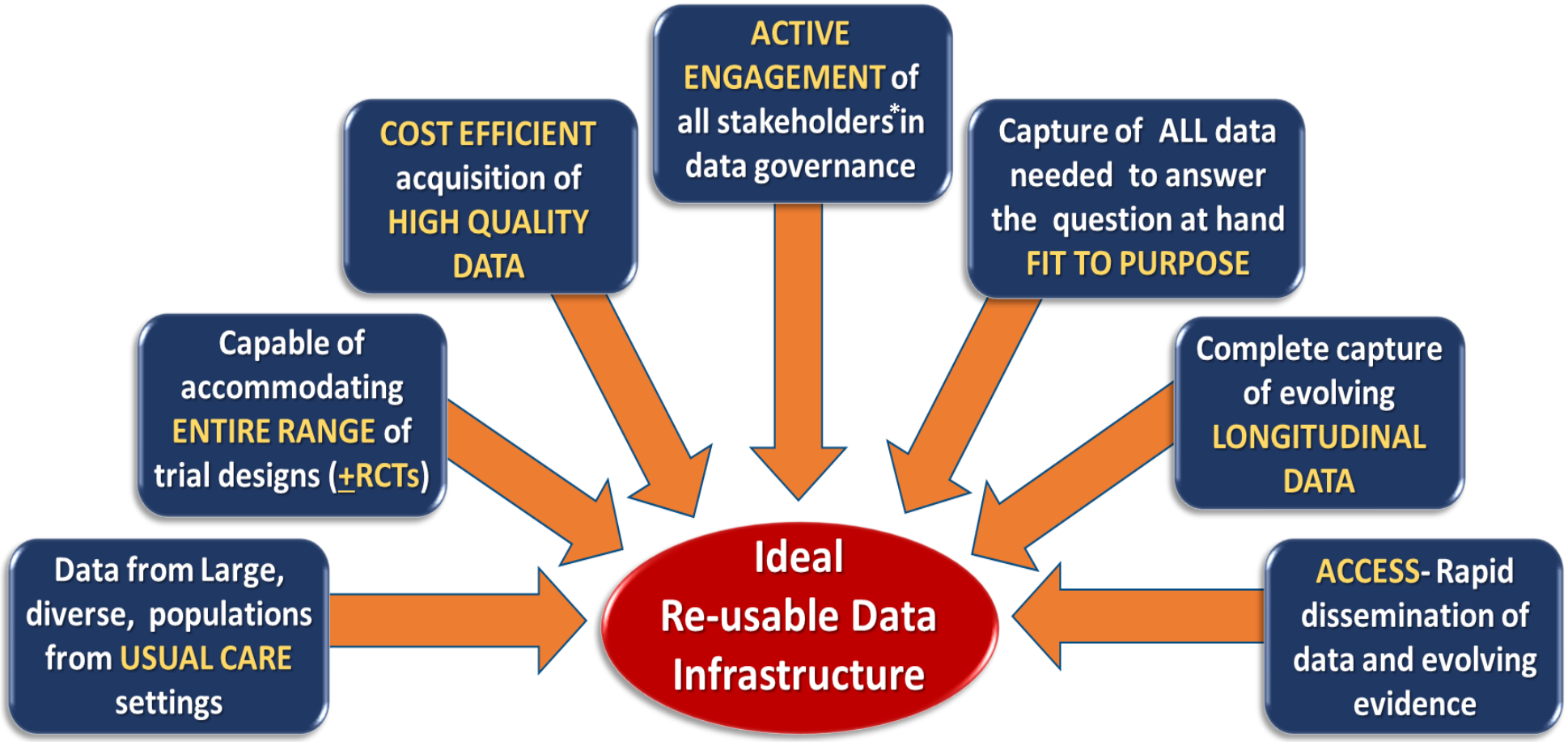
Informed Clinical and Regulatory Decisions

Remaking the Clinical Trial Enterprise

Priorities for Creating a Reusable Clinical Trial Infrastructure



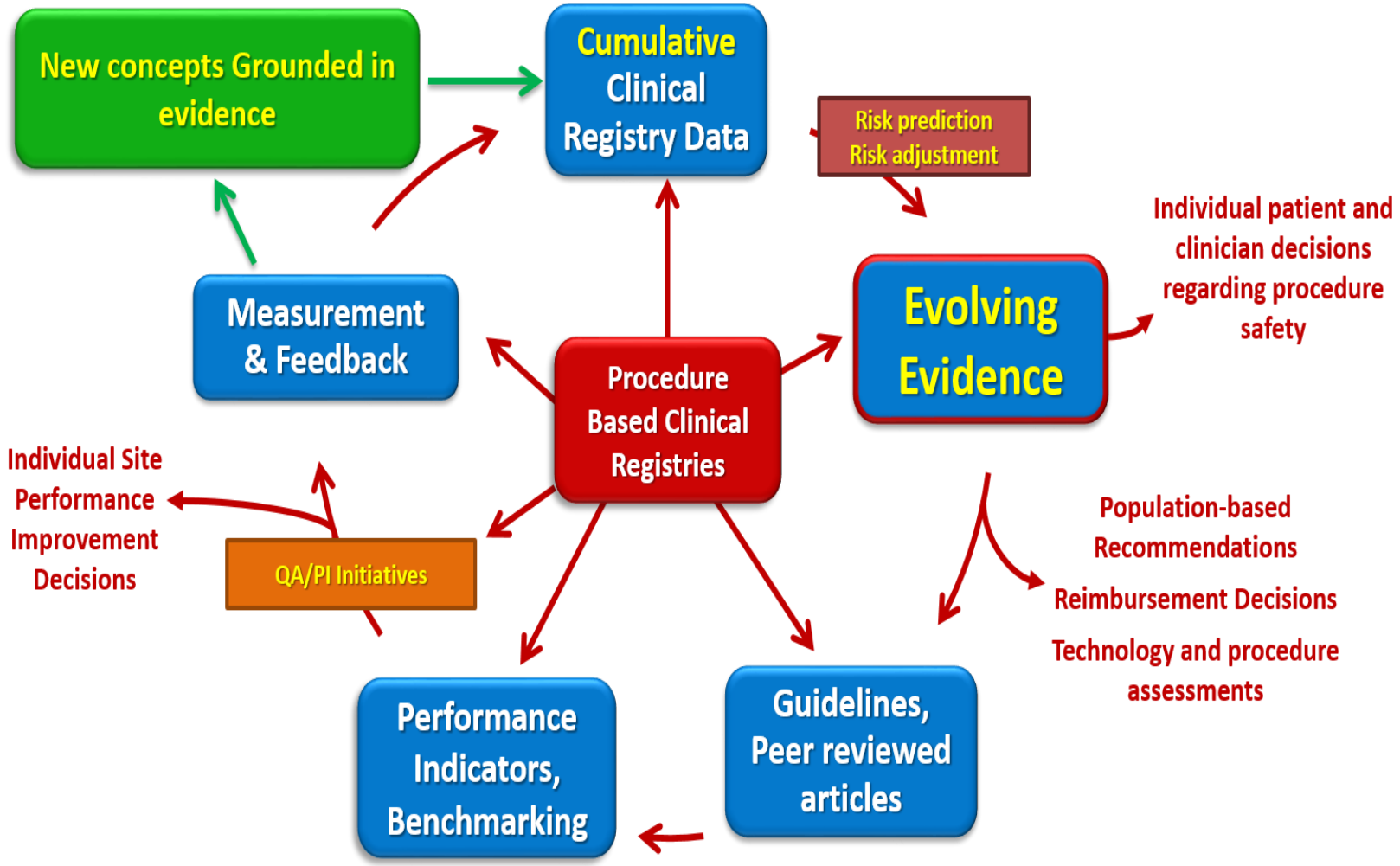
*patients, clinicians, researchers, purchasers, payers, industry, hospitals and health systems, policy makers, and training institutions

Available CV Registries and Datasets

Comprehensive, Valuable and Affordable Real World Evidence

Cardiovascular Procedure-based Registries

Central Roles in the Cycle of Quality

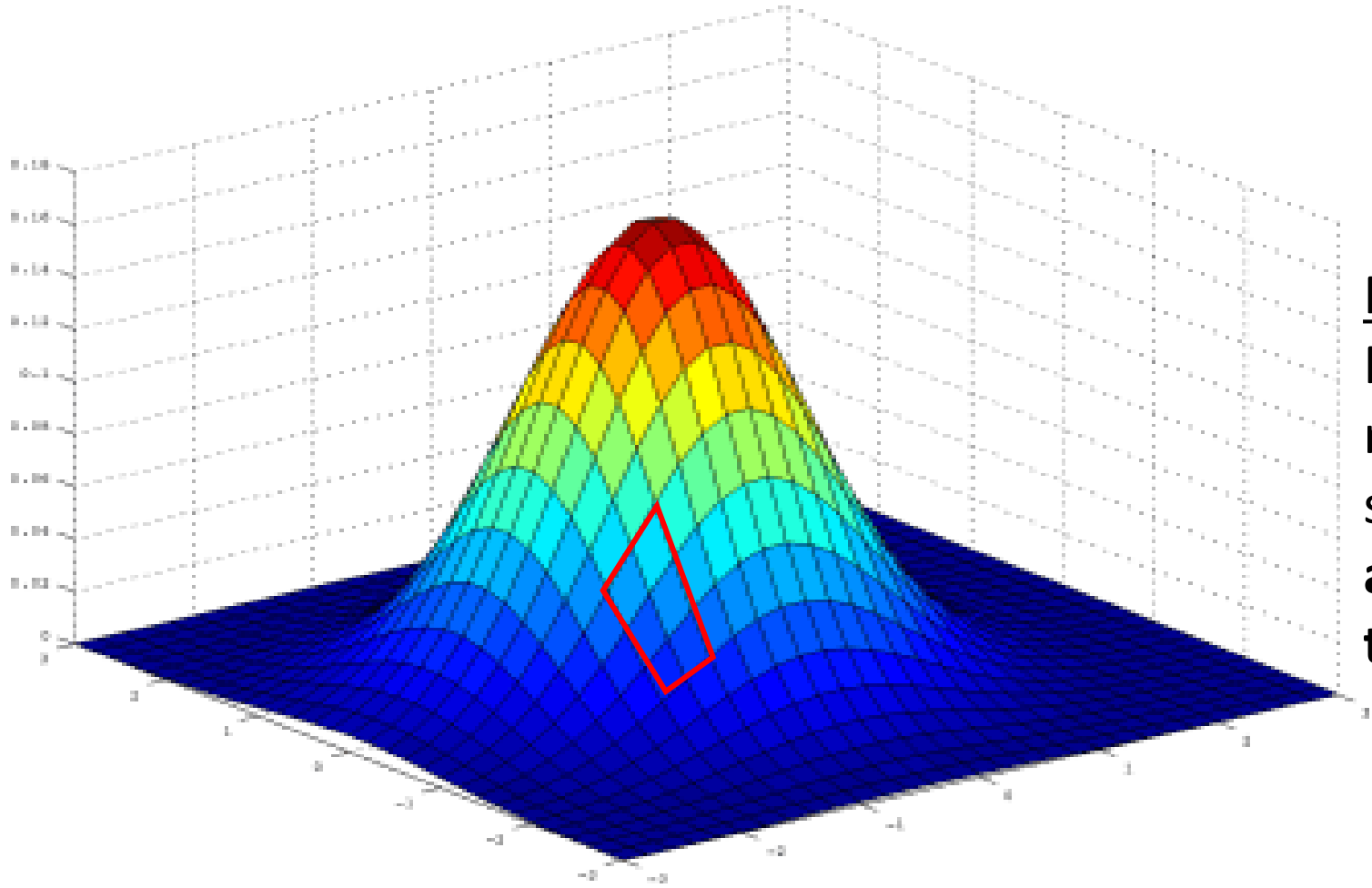


Adapted from: Califf et al. JACC 2002;40:1895–901 and Bhatt et al. JACC 2015;68:2230-2245

Procedure-based Registry Outcomes Data

Continuous capture of a real world use

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



<u>Pre-Specified Analyses</u>

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

Device Approval Population

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?

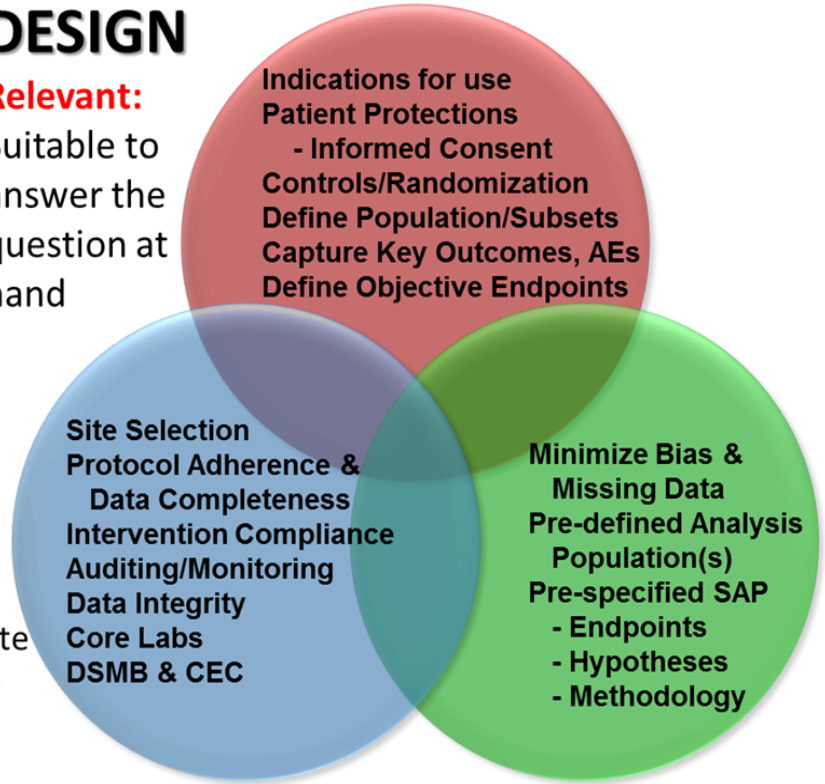
TRIAL DESIGN – Tailored to the Regulatory Need:

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

Registry DCF*
\+ Linkages And Modular Add-ons
Case Report Form

DESIGN

Relevant: Suitable to answer the question at hand



CONDUCT

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

ANALYSIS

Interpretable results providing **Evidence:**

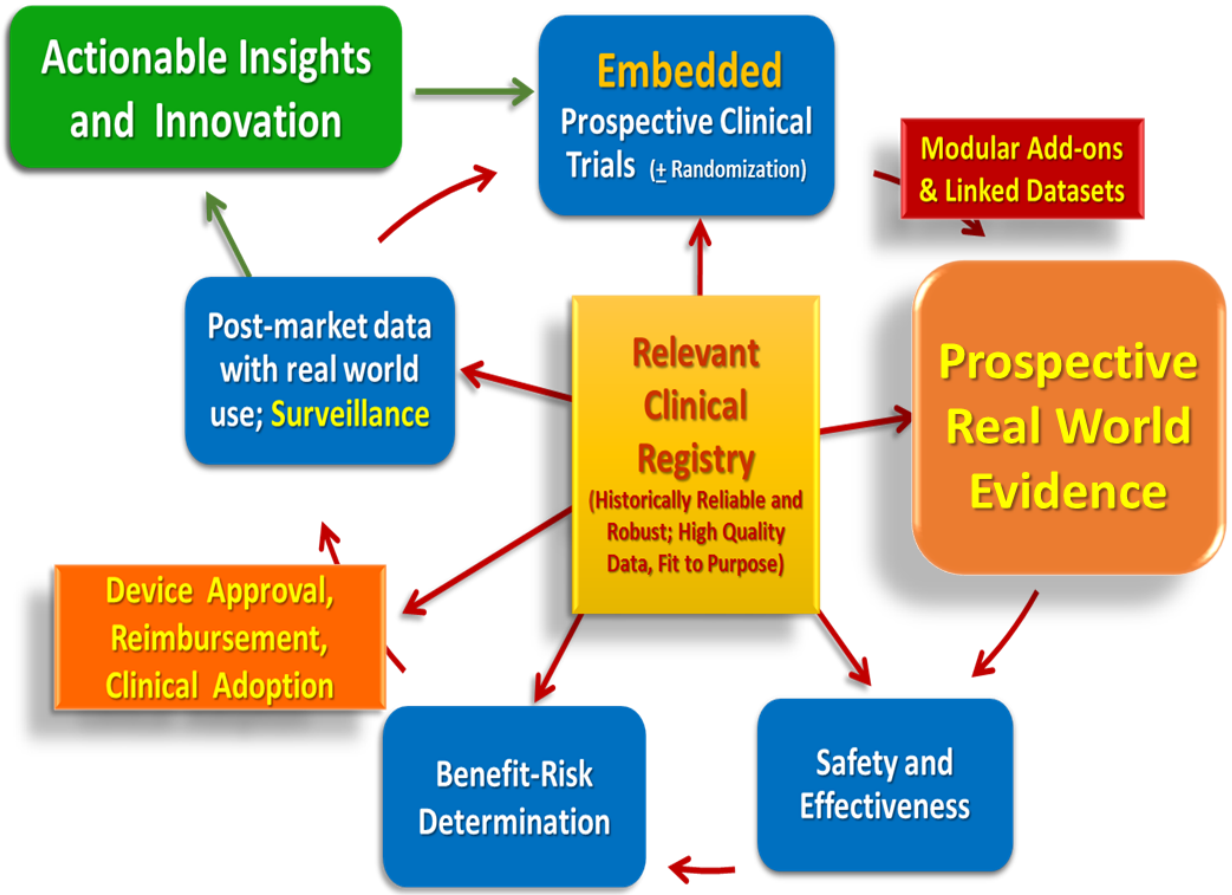
- **Safe and Effective** for proposed uses
- **Benefits outweigh risks**

* DCF = Data Collection Form

Re-engineering the Clinical Trial Enterprise

Registry Embedded Clinical Trials

Lessons from SWEDEHEART*



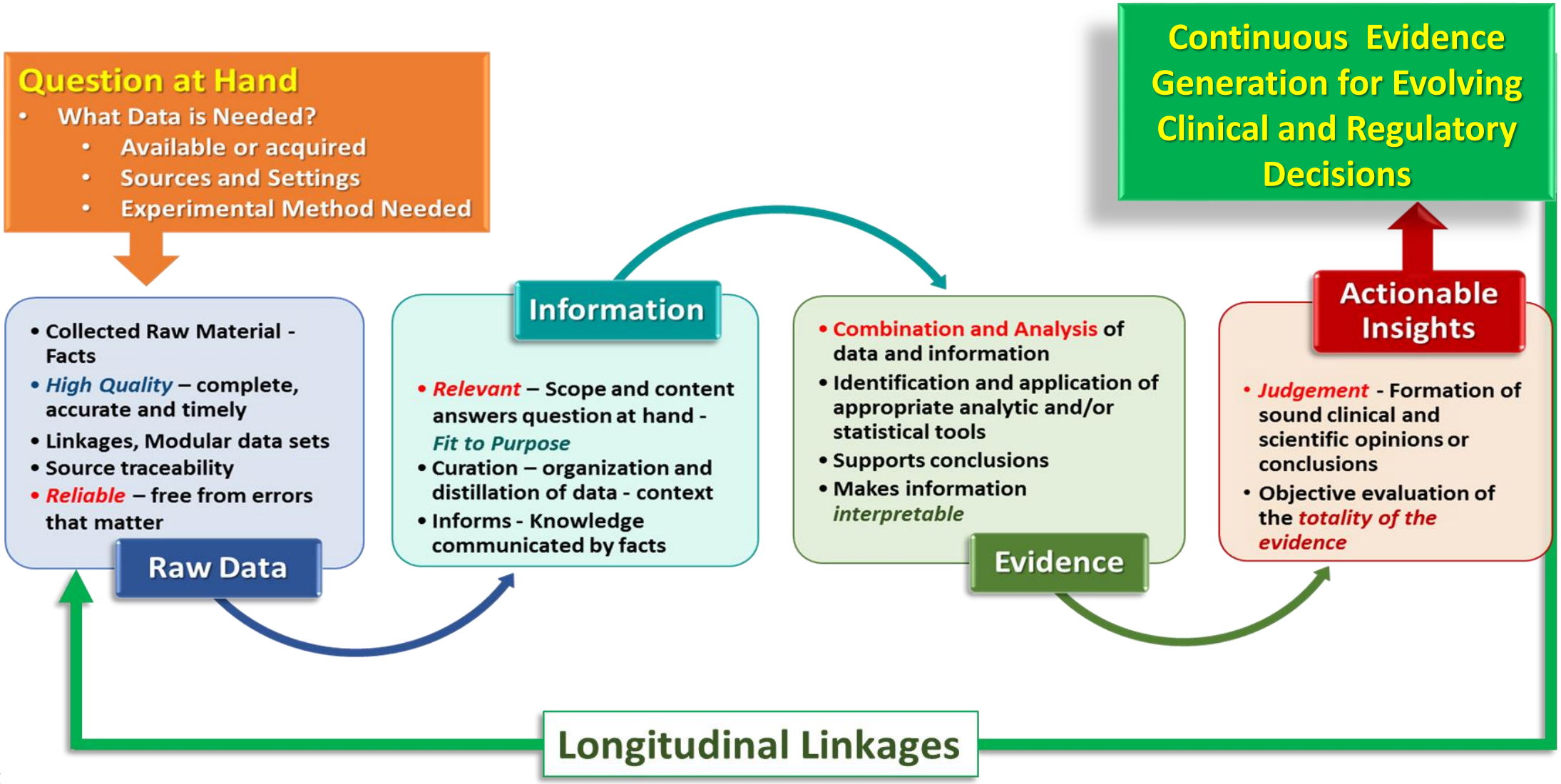
Benefits:

- **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

* http://www.ucr.uu.se/swedeheart/dokument-sh/arsrapporter-sh

Continuous Generation of Longitudinal Evidence

Capturing The Total Product Life Cycle



Re-engineering the Clinical Trial Enterprise

Cardiovascular Device Coordinated Research Network (CDCRN)

Total Product Life Cycle

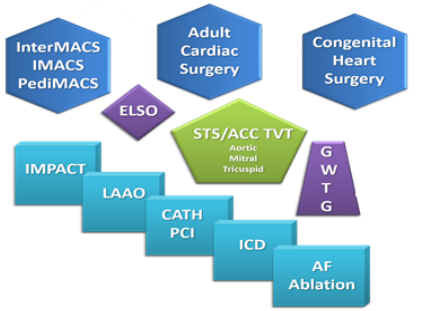
Registry EMBEDDED Trial
1 or more Registries
(Data Collection Forms = CRF)
+
Modular Add-on Data

Linkages

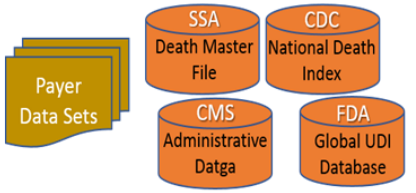
Passive long-term (TPLC) follow-up

- CDCRN provides **Durable linkages** to available CV & Gov't Infrastructure
- Identify **ALL records normally generated over time using direct matching**

Procedure Generated Outcomes



Event Generated Outcomes



(ICD-10 codes) in **Government and Payer datasets**

Primary Trial Data

- **Prospectively collected**
- **Assigned Rx, ± randomization**

Sponsor

Repetitively Harvested data

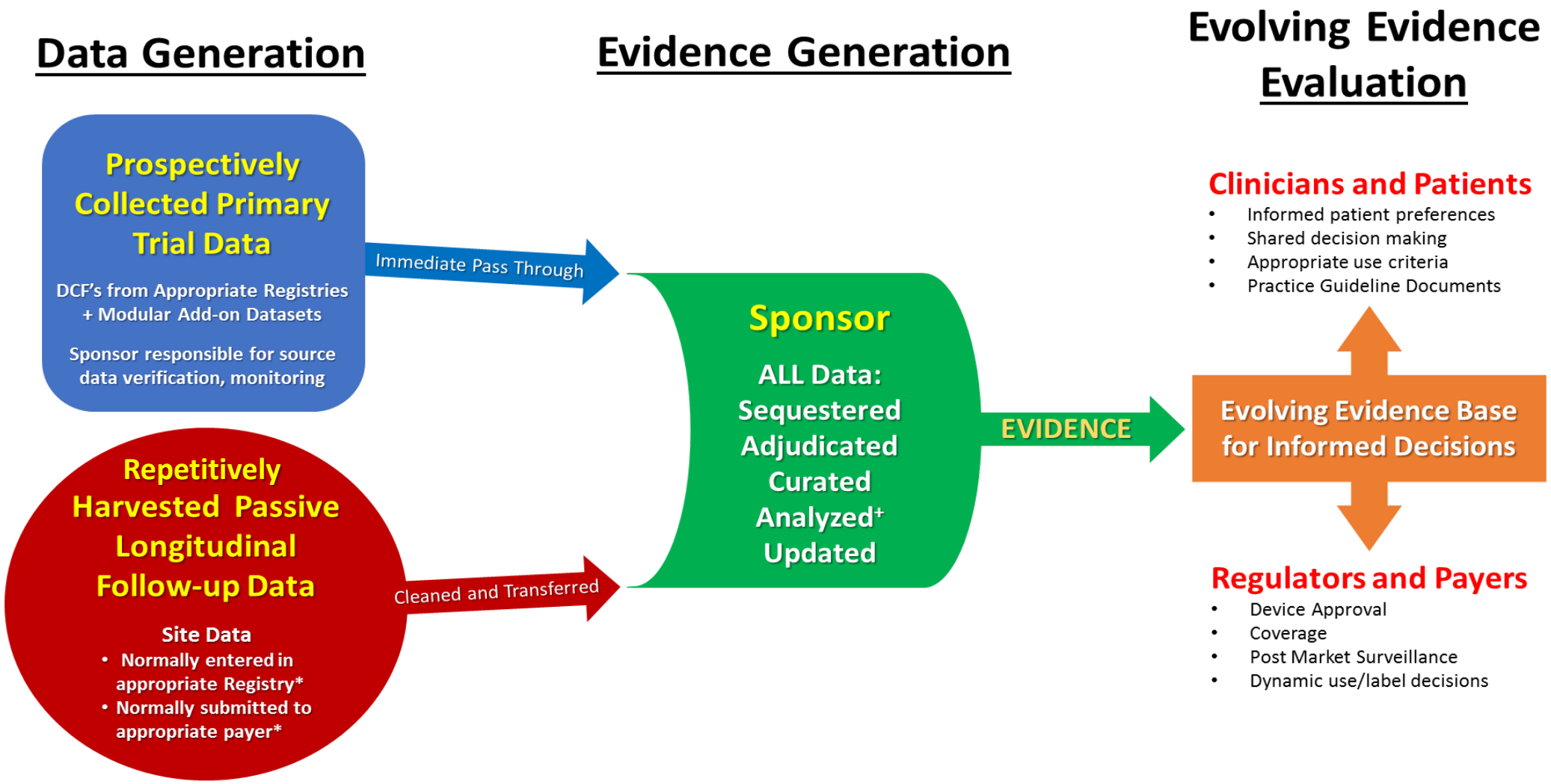
Longitudinal Clinical Outcomes that Matter*

- STS
- ACC
- STS/ACC
- Gov't Datasets
- Others

*(Re)Operation, (Re)Intervention, Death, (Re)Hospitalization, Life Altering Complications - MI, stroke, dialysis

Re-engineering the Clinical Trial Enterprise

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

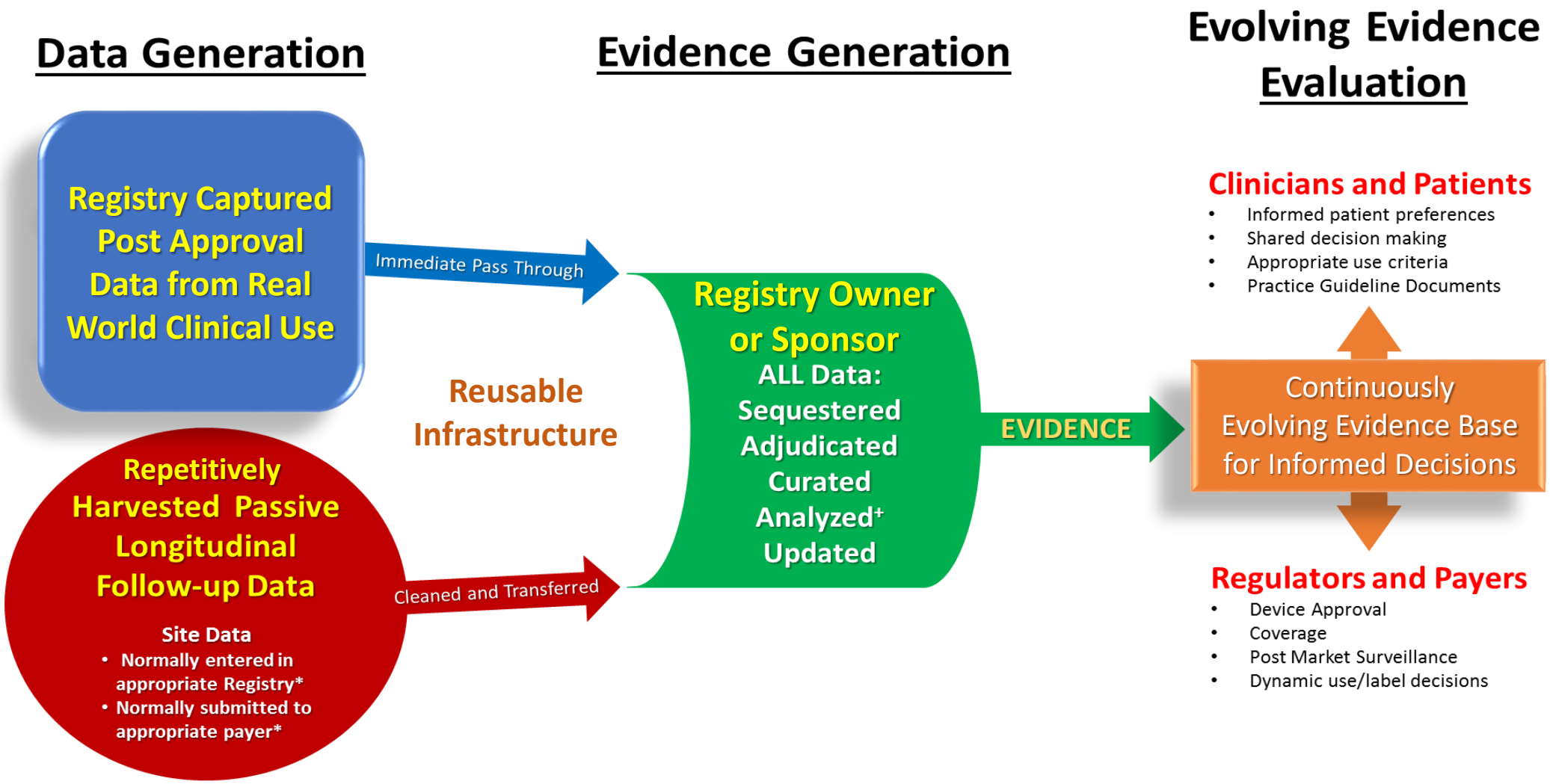


* Anonymized for trial participation

\+ Pre-specified statistical analysis plan

Re-engineering the Clinical Trial Enterprise

Post-Market Data – Going Beyond Procedural Outcomes



* Anonymized for trial participation

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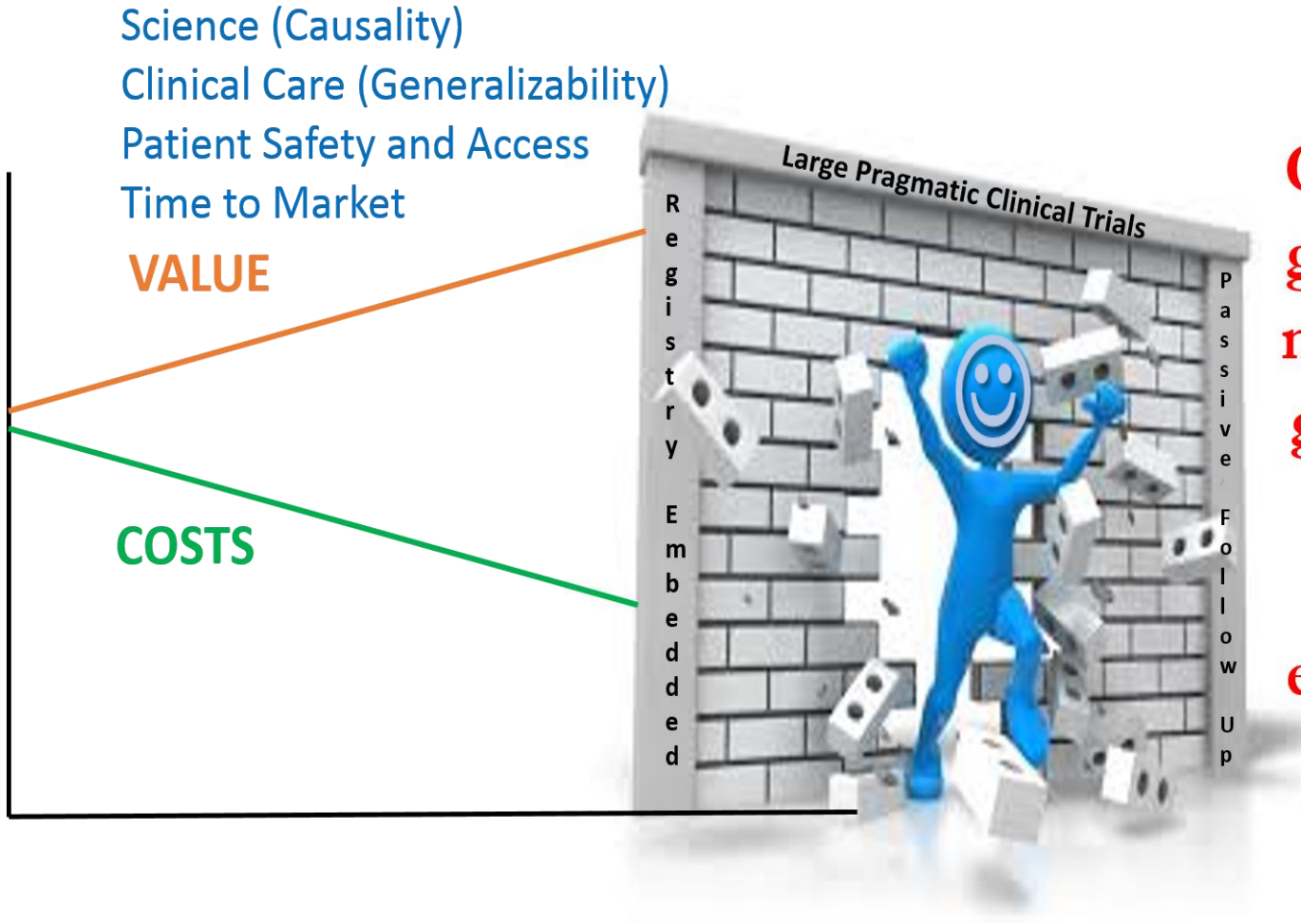
Breaking Down the Barriers

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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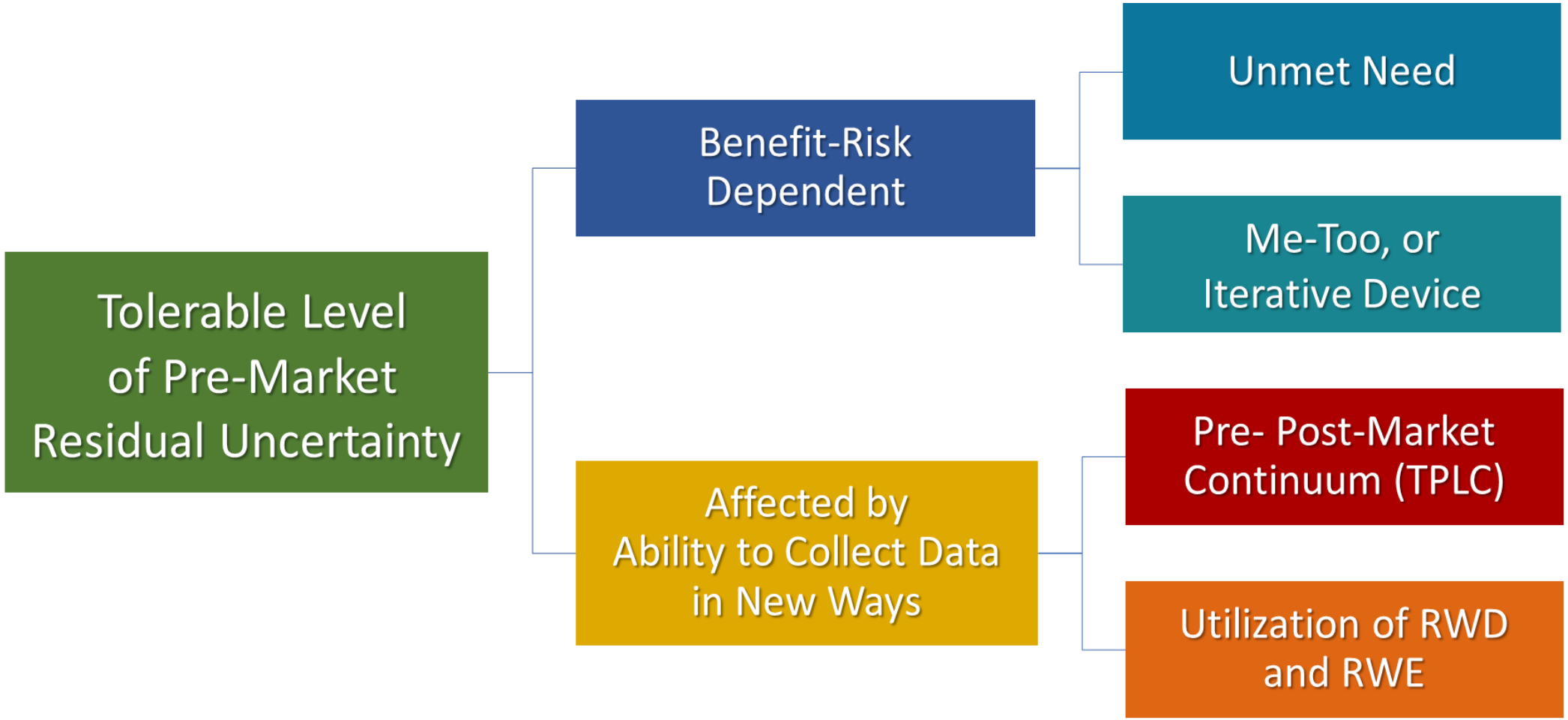
Reasonable Assurance

Residual Uncertainty at the Time of Device Approval



Reasonable Assurance

Residual Uncertainty at the Time of Device Approval

Tolerable Level of Pre-Market Residual Uncertainty

- Benefit-Risk Balance
  - Unmet Need
  - Me-Too, or Iterative Device
- Ability to Collect Data and Generate Evidence in New Ways
  - Pre to Post-Market Continuum (TPLC)
  - Utilization of RWD and RWE

Reasonable Assurance

Residual Uncertainty at the Time of Device Approval

Tolerable Level of Pre-Market Residual Uncertainty

- **Benefit-Risk Balance**
  - Disease and Current Therapy, Unmet Need
  - Device Risk: New or Iterative Device
- **Ability to Collect Data and Generate Evidence in New Ways**
  - Pre to Post-Market Continuum (TPLC)
  - Utilization of RWD and RWE