

FDA and Pragmatic Trials

Robert M Califf MD

Collaboratory Grand Rounds

March 31st, 2017

FDA and Pragmatic Trials

- The FDA's role with medical products
- Pragmatic trials and "real world evidence"
- What do patients/consumers ("people") want?
- How can we (the spirit of the NIH Collaboratory and PCORnet/PCRF) help?

Pragmatic Trials

- An intent to inform decision makers (patients, clinicians, administrators and policy makers) as opposed to elucidating a biological or social mechanism
- An intent to enroll a patient population relevant to the decision in practice and representative of the patients/populations and clinical setting for whom the decision is relevant
- Either an intent to:
 - Streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial or
 - Measure a broad range of outcomes
 - Califf and Sugarman; Clinical Trials 2015; 12: 436-441

Lessons from FDA

1. The FDA affects us all. Appreciate it and work with it.
2. We should not forget about tobacco and nicotine delivery products.
3. Biomedical science, engineering and information technology are affecting food as much as medical products
4. Technology is at a major inflection point. Put to good use, it will dramatically improve health in the US and around the world.
5. We need higher quality evidence across the spectrum of products pertinent to health and healthcare.
6. At its core almost every FDA decision involves a balance of benefits and risks

Lessons from FDA

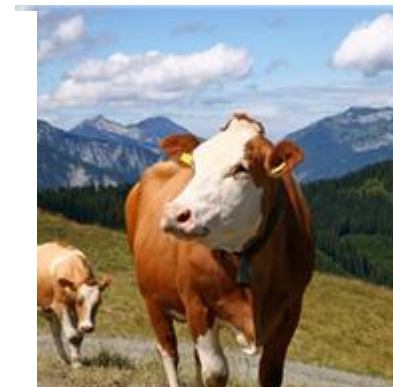
7. FDA regulated products exist in a global environment
8. There is much more to a medical product than the clinical trial results
9. The most positive outcomes will come from an ecosystem focused on defining benefits and risks:
 - Academic health and science systems
 - Health care providers
 - Medical products companies
 - Regulators
 - Patients and consumers
10. You can make the system better if you identify flaws, design improvements and work with the ecosystem

FDA Regulates a Spectrum of Health Products : 20-25 cents of every GDP dollar

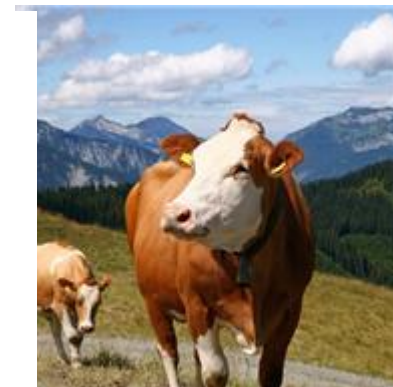
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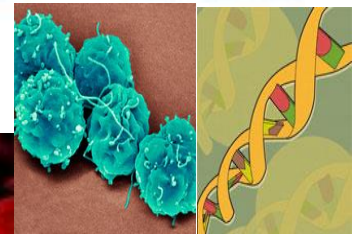
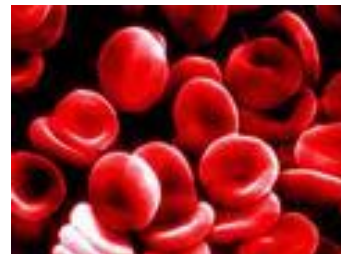
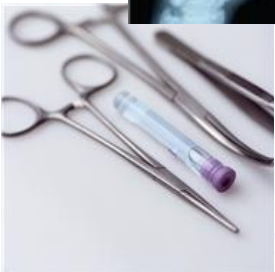
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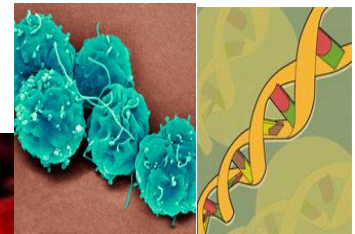
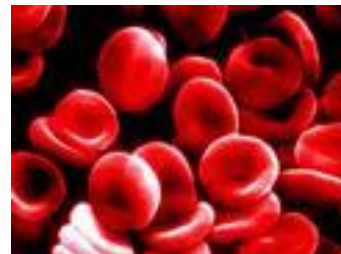
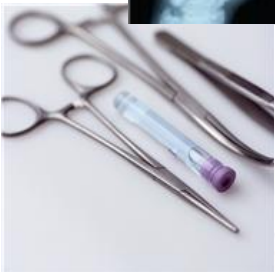
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FDA Mission

FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

FDA Mission

FDA also has responsibility for regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors

FDA Mission

- FDA is also responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.

FDA Mission

Finally, FDA plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

The Core FDA Issue in Medical Products

- Do the benefits outweigh the risks for the condition of use for which the product is labeled?
 - Adequate and well controlled clinical studies
- Is the device safe and effective for its intended use?
 - Valid scientific evidence

Substantial Evidence

- “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, **on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use** prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

Adequate and Well Controlled

- To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency, and detailed patient records are made available at the clinical sites. **From a scientific standpoint, however, it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim.** Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured.
 - Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

Valid Scientific Evidence

- 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. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable.

Good Clinical Practice

- An international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials. It also serves to protect the rights, integrity and confidentiality of trial subjects.
- Instantiated in ICH documents
 - The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

ICH Guidelines

- International Council for Harmonisation - Efficacy
- International Council for Harmonisation - Joint Safety/Efficacy (Multidisciplinary)
- International Council for Harmonisation - Quality
- International Council for Harmonisation - Safety

Good Clinical Practices (GCPs)

- Factors that influence whether studies with limited or no monitoring may be relied on include the following:
 - The existence of a prospective plan to assure data quality.
 - Studies that have features that make them inherently less susceptible to bias, such as those with relatively simple procedures, noncritical entry criteria, and readily assessed outcomes.
 - The ability to sample critical data and make comparisons to supporting records (e.g., hospital records).
 - Conduct of the study by a group with established operating procedures and a history of implementing such procedures effectively

Cost of Developing A Drug

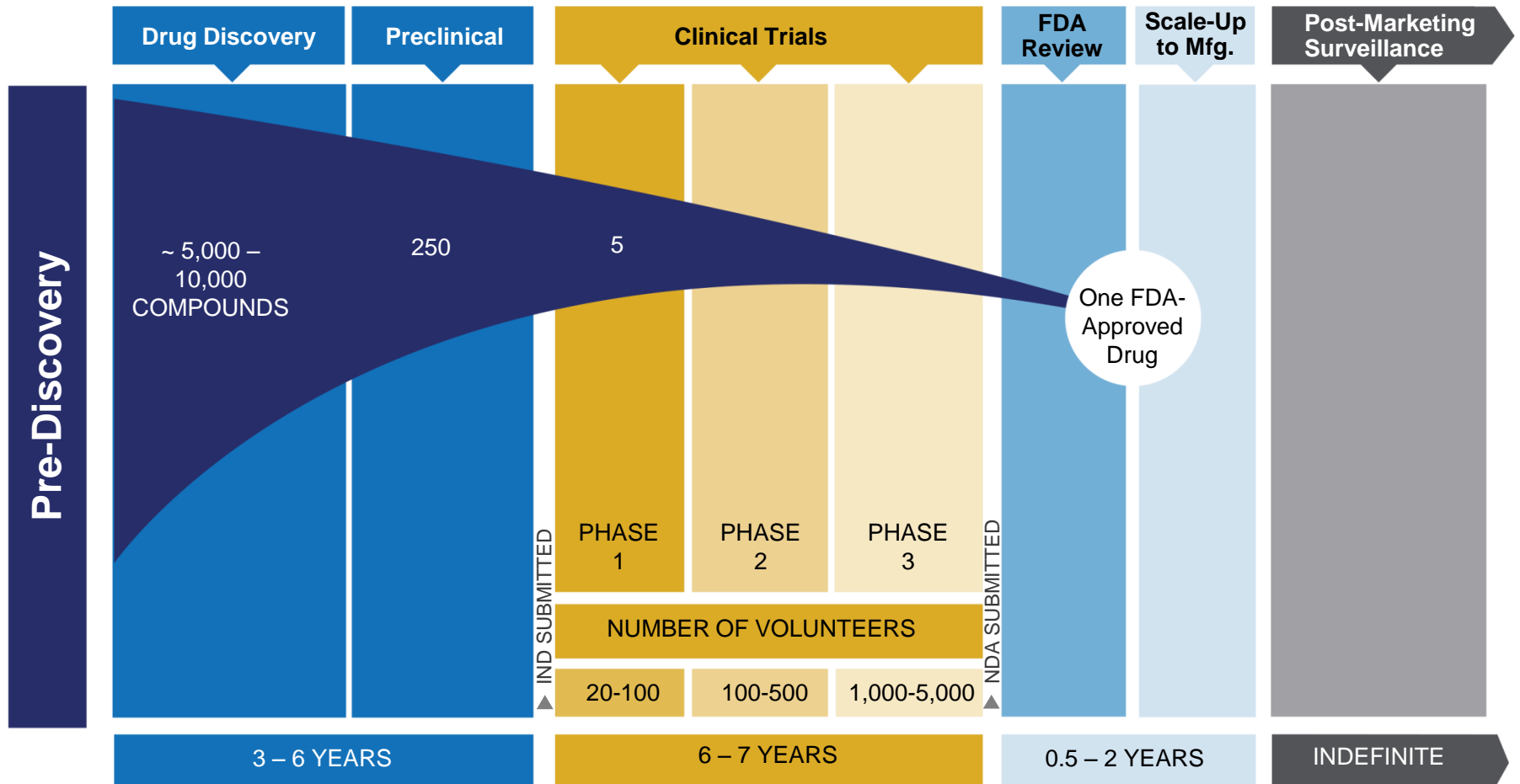
March 10, 2016

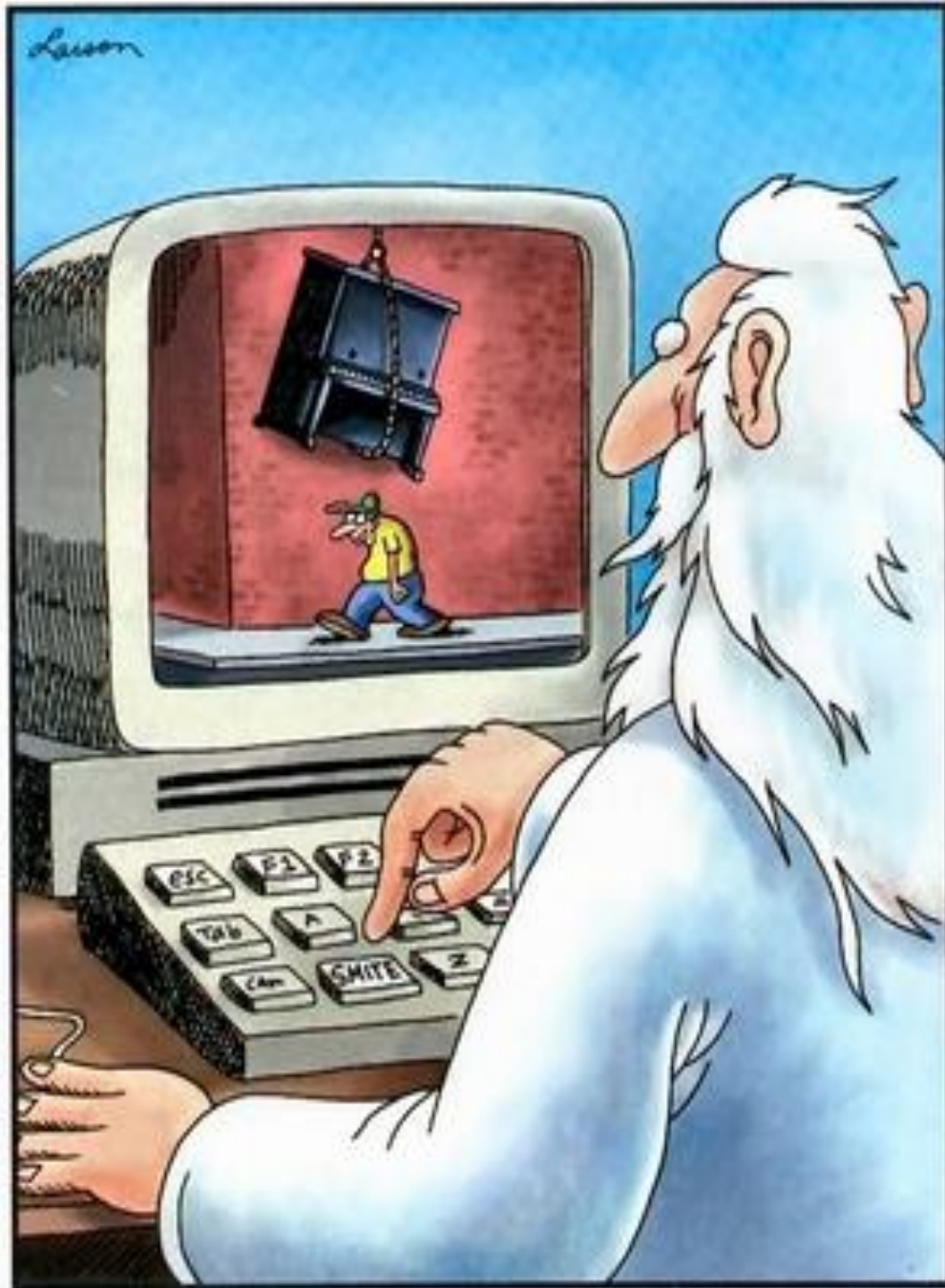
Tufts CSDD Assessment of Cost to Develop and Win Marketing Approval for a New Drug Now Published

BOSTON – March 10, 2016 – The most recent analysis by the Tufts Center for the Study of Drug Development of the average cost to develop and gain marketing approval for a new drug—pegged at \$2.558 billion—has been published in the *Journal of Health Economics*, it was announced today.

(Includes cost of failure and cost of capital)

DRUG DISCOVERY AND DEVELOPMENT TIMELINE





God at His computer

Our National Clinical Research System is Well-intentioned But Flawed

- High percentage of decisions not supported by evidence*
- Health outcomes and disparities are not improving
- Current system is great **except**:
 - Too slow, too expensive, and not reliable
 - Doesn't answer questions that matter most to patients
 - Unattractive to clinicians & administrators

We are not generating the evidence we need to support the healthcare decisions that patients and their doctors have to make every day.

Which Treatment is Best for Whom?

High-Quality Evidence is Scarce

< 15% of Guideline Recommendations Supported by
High Quality Evidence

 ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD

Joseph M. Allen, MA

Judith M. Kramer, MD, MS

Robert M. Califf, MD

Sidney C. Smith Jr, MD

CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for spe-

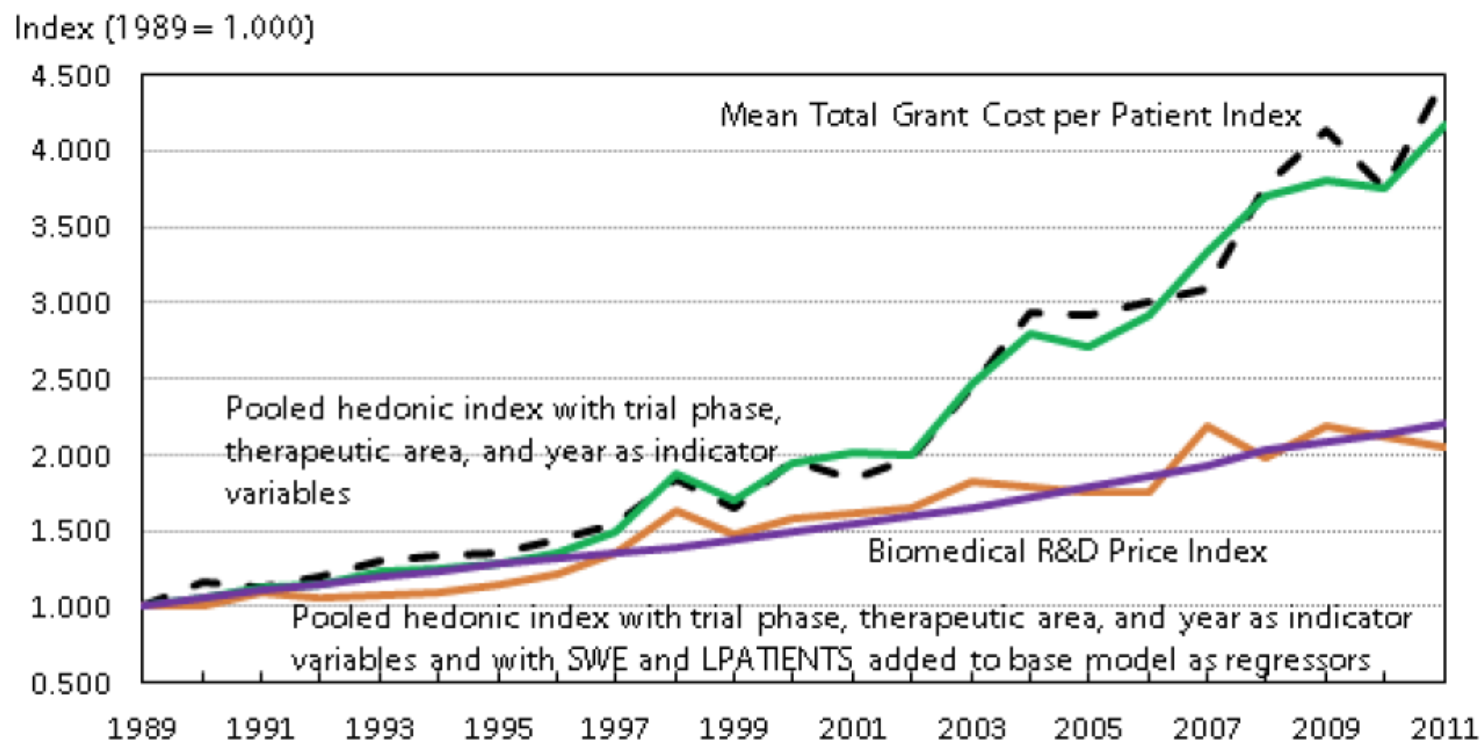
Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

Trial Hyperinflation

Figure 3. Mean Total Grant Cost per Patient Index, Biomedical R&D Price Index, and pooled hedonic indexes, 1989–2011



Source: Authors' calculations based on Medidata Solutions, Inc.'s, PICAS[®] database.

What Do Patients/Consumers Want?

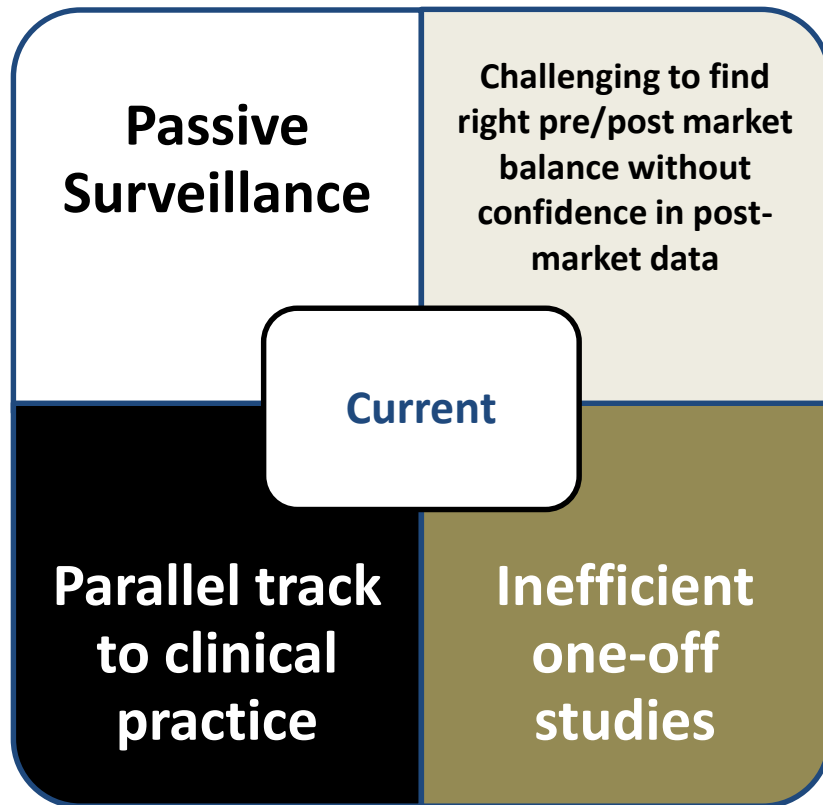
(my distilled and perhaps incorrect summary)

- Better diagnostic and therapeutic technologies
- Assurance of the safety and effectiveness of these technologies
- Which treatment is best and how should it be used?
- Studies that answer the questions relevant to their lives

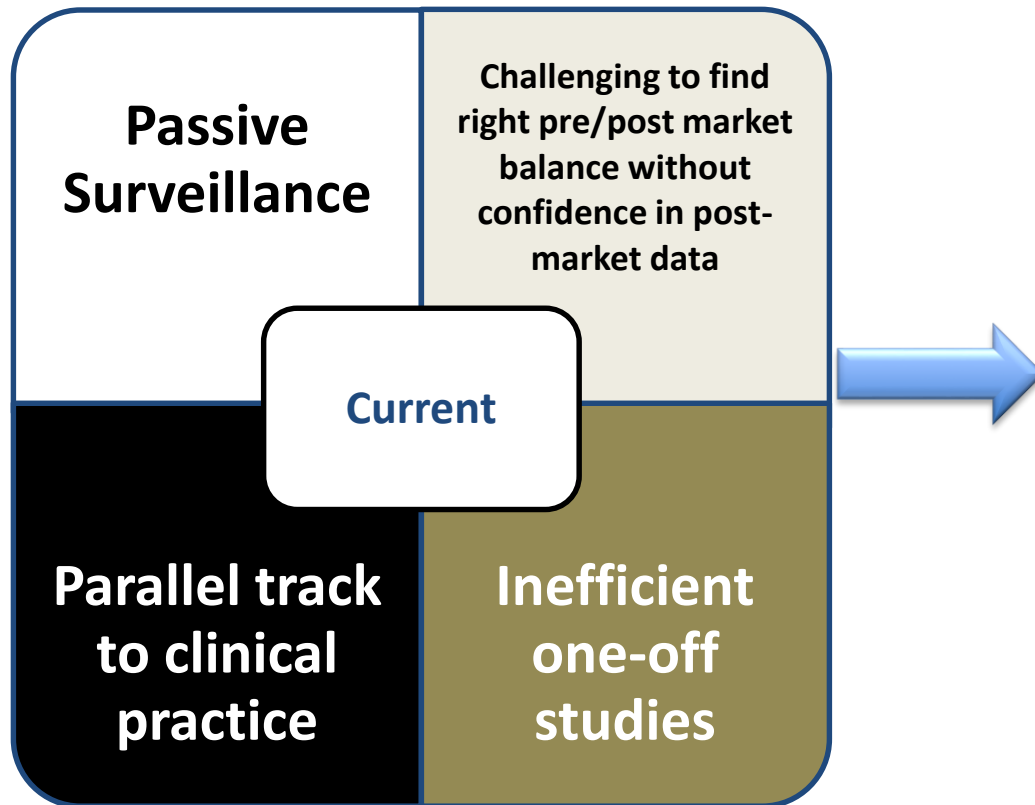


National System Paradigm Shift

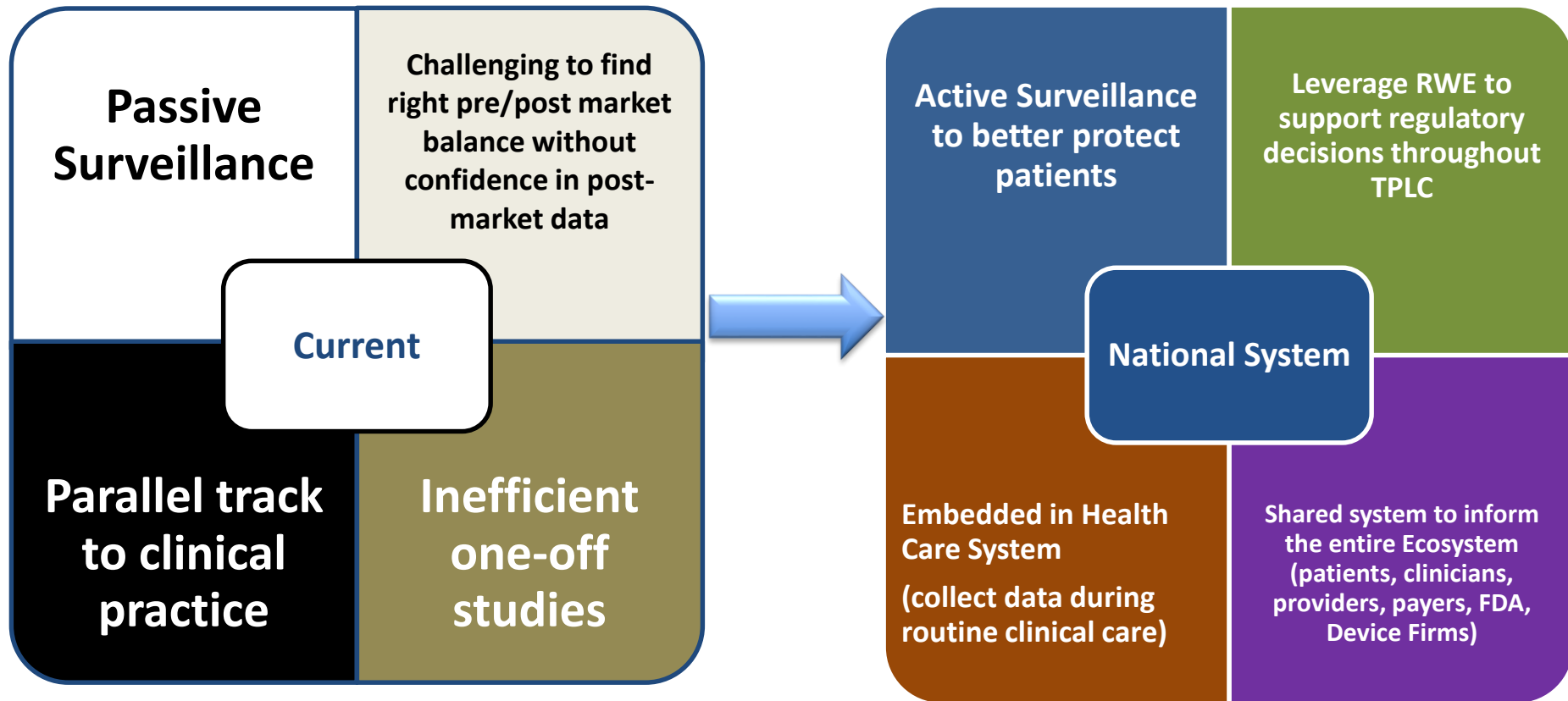
National System Paradigm Shift



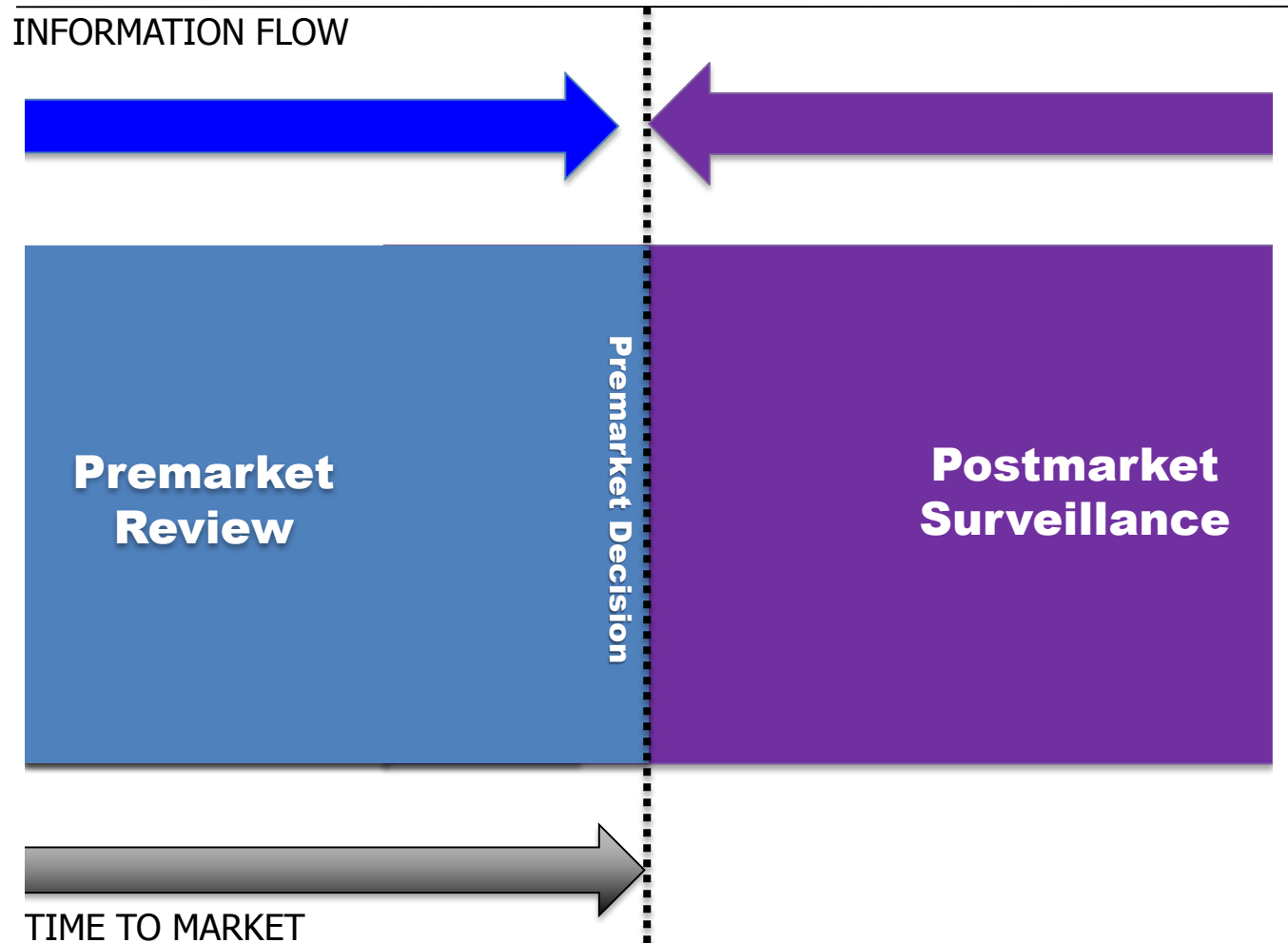
National System Paradigm Shift



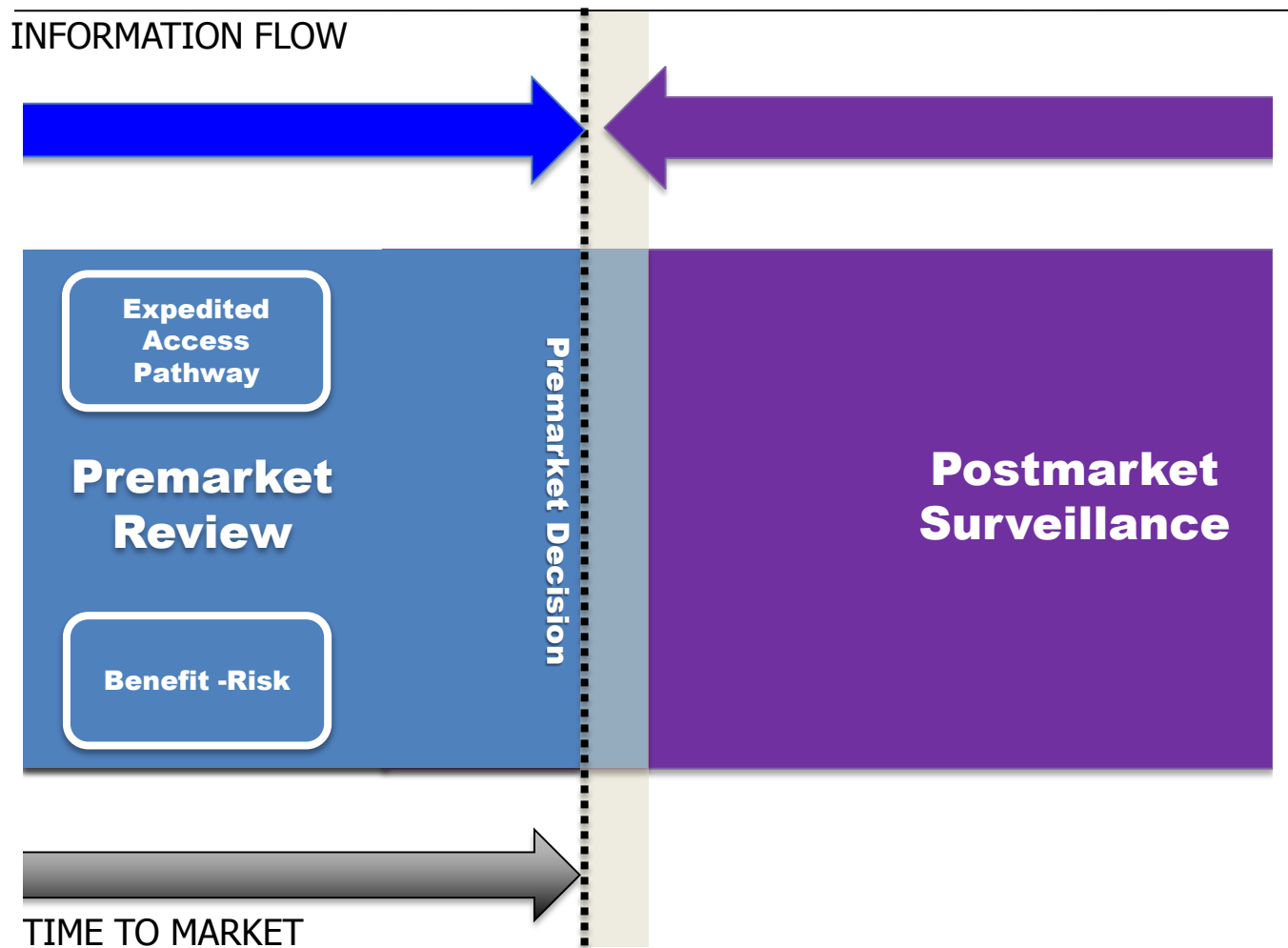
National System Paradigm Shift



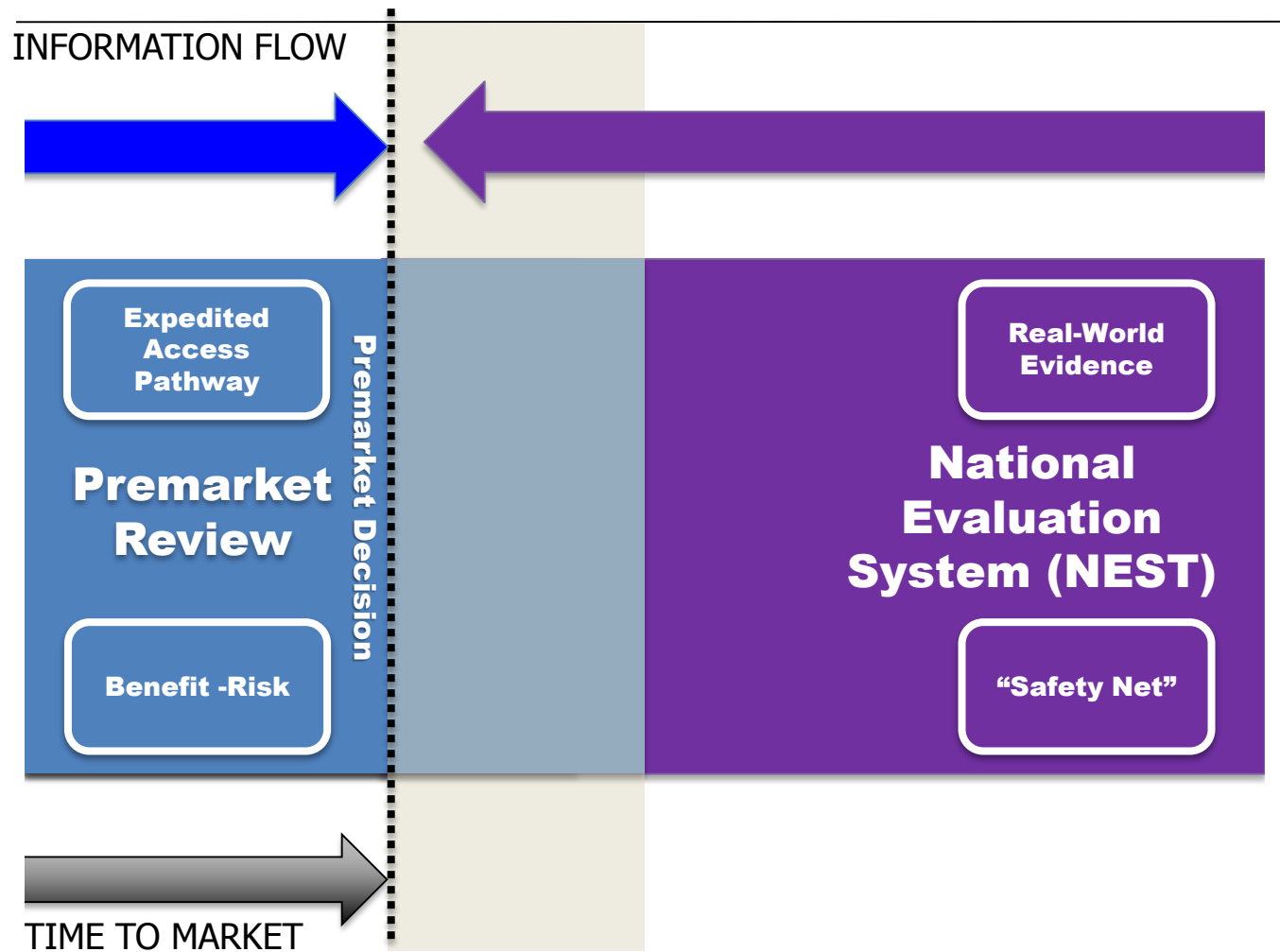
Learning Medical Device Ecosystem



Learning Medical Device Ecosystem



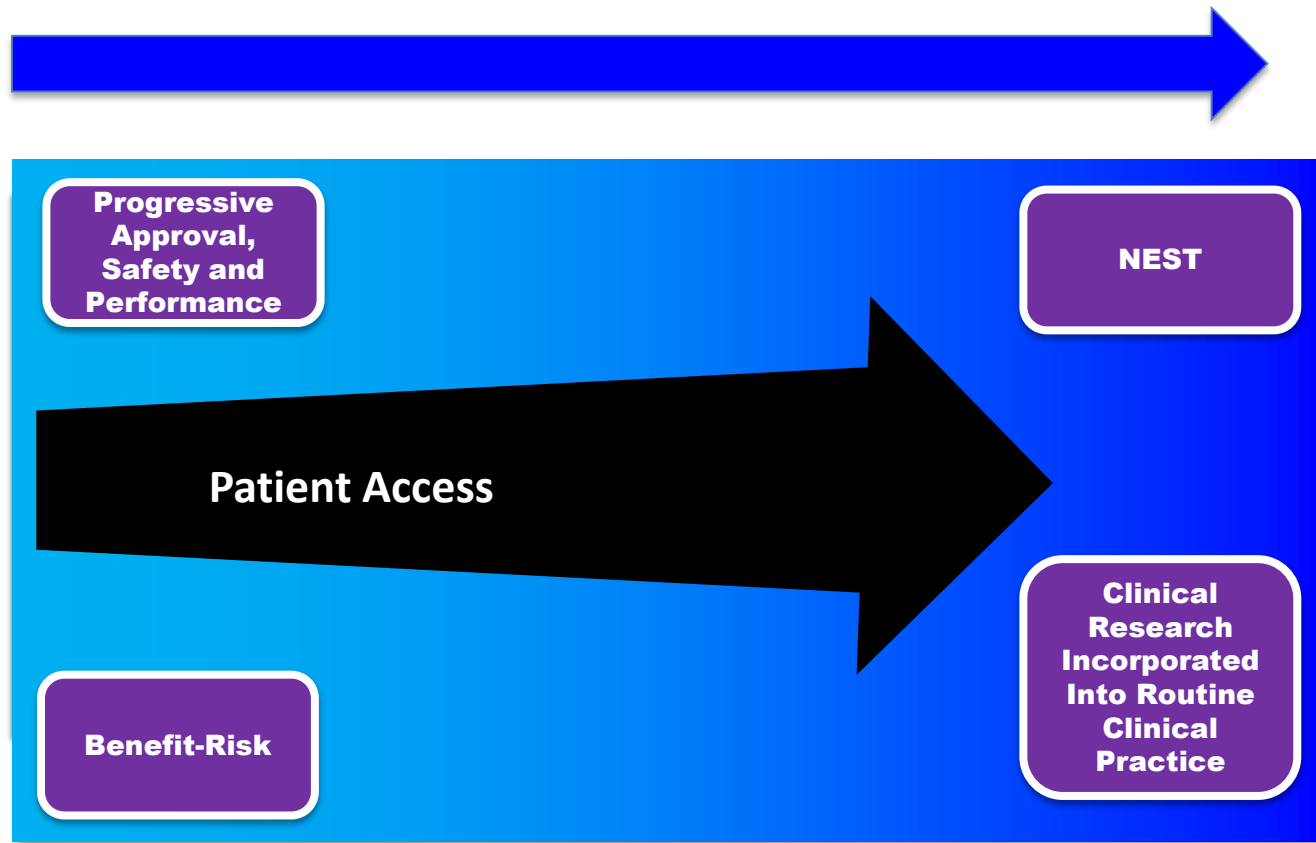
Learning Medical Device Ecosystem



Learning Medical Device Ecosystem

Total Product Life Cycle (TPLC) Framework

EVOLUTION OF BENEFIT–RISK EVIDENCE



The Evidence Continuum

- Step 1: Regulatory approval for marketing
- Step 2: Health Technology Assessment
- Step 3: Payor Decisions
- Step 4: Individual provider/patient decisions
- **PREMISE: THIS SHOULD BE A CONTINUUM, NOT DISCRETE STEPS**

Real World Evidence and FDA

- The term “real-world evidence” is widely used by those who develop medical products or who study, deliver, or pay for health care, but its specific meaning is elusive. We believe it refers to information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health applications. Key to understanding the usefulness of real-world evidence is an appreciation of its potential for complementing the knowledge gained from traditional clinical trials, whose well-known limitations make it difficult to generalize findings to larger, more inclusive populations of patients, providers, and health care delivery systems or settings that reflect actual use in practice.

» N Engl J Med 2016; 375:2293-2297

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W.

Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L.

Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-

Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa

A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert

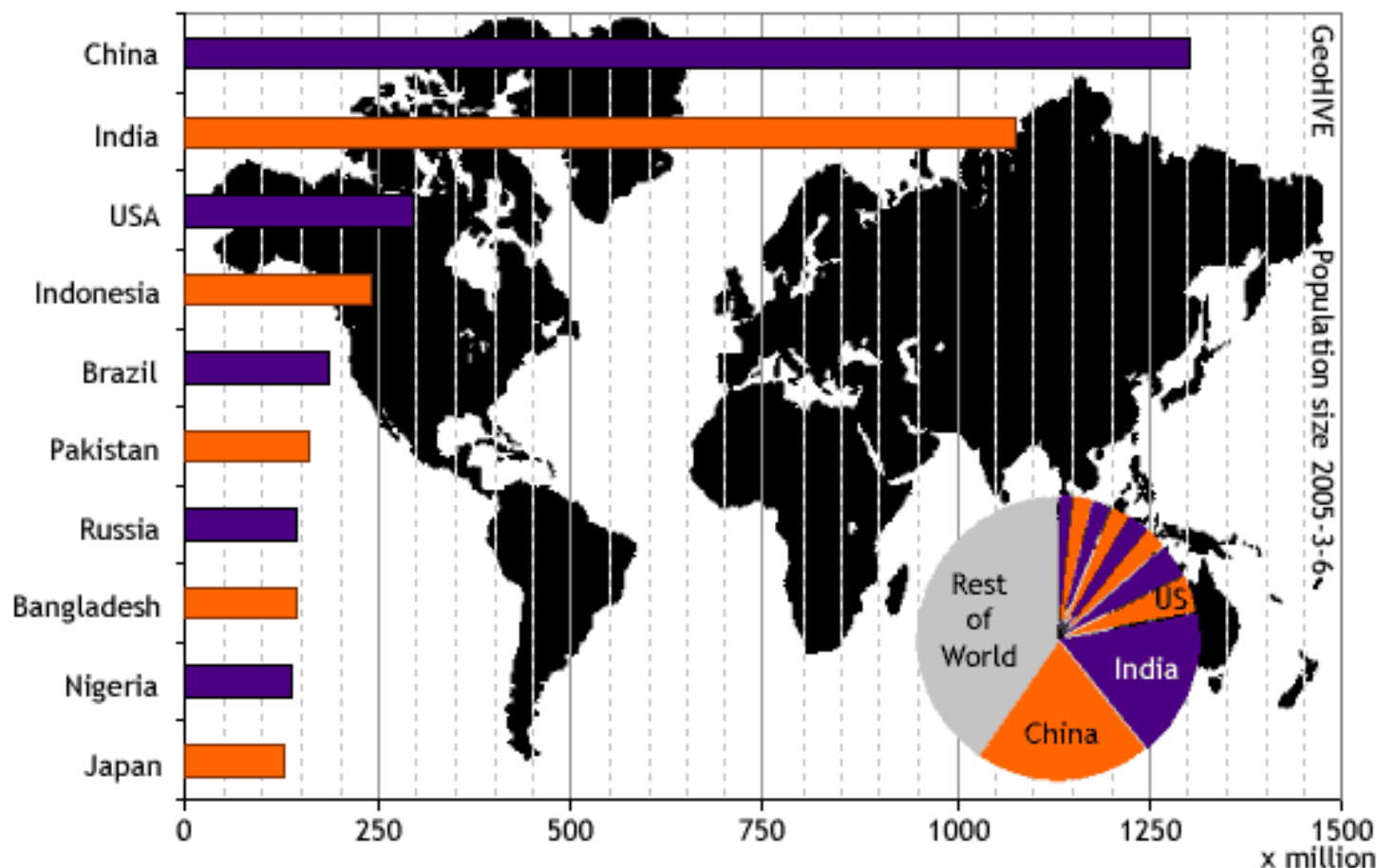
Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue,

Ph.D., and Robert M. Califf, M.D.

N Engl J Med 2016; 375:2293-2297 December 8,

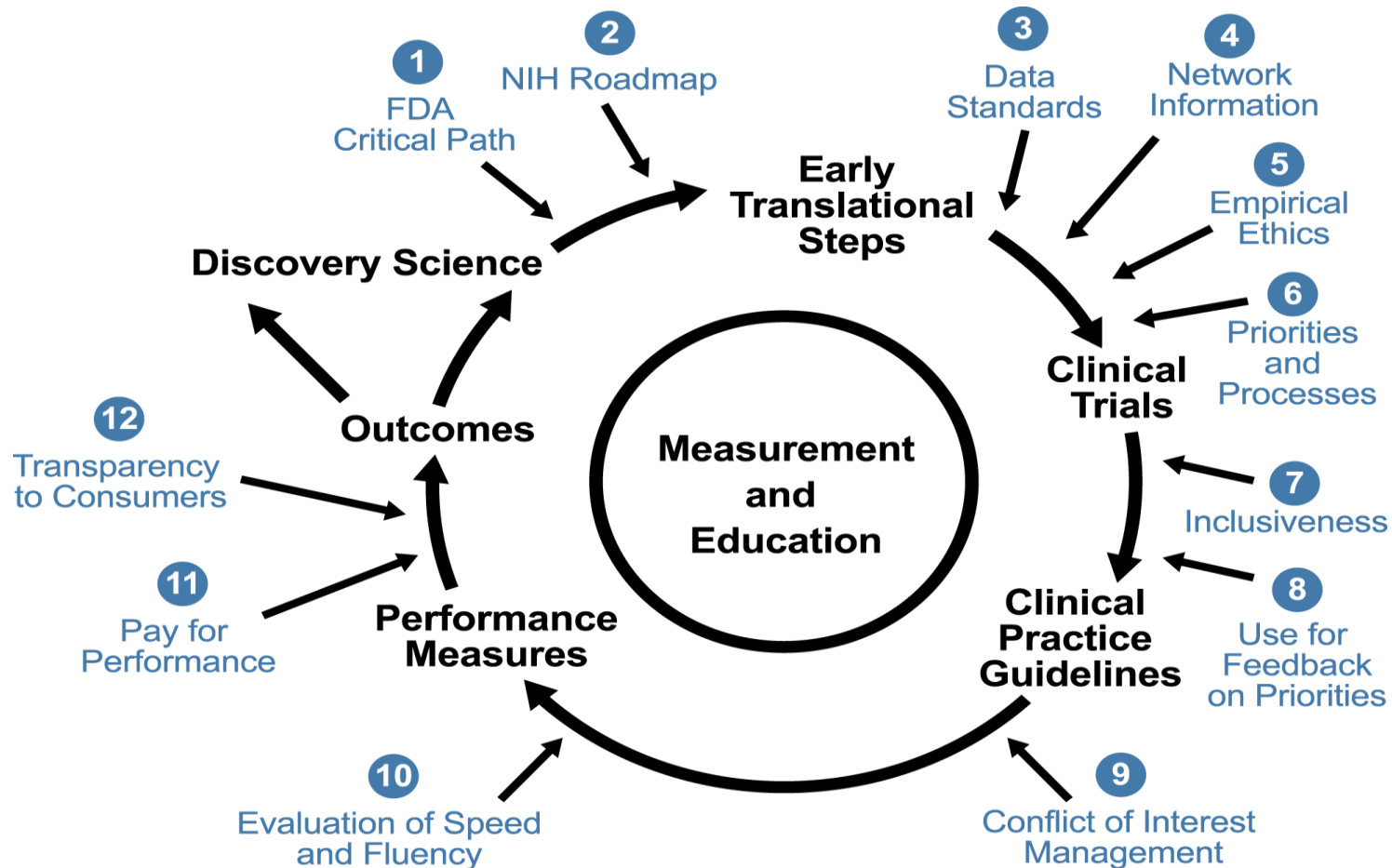
2016DOI: 10.1056/NEJMs1609216

World Population Dominated by Asia

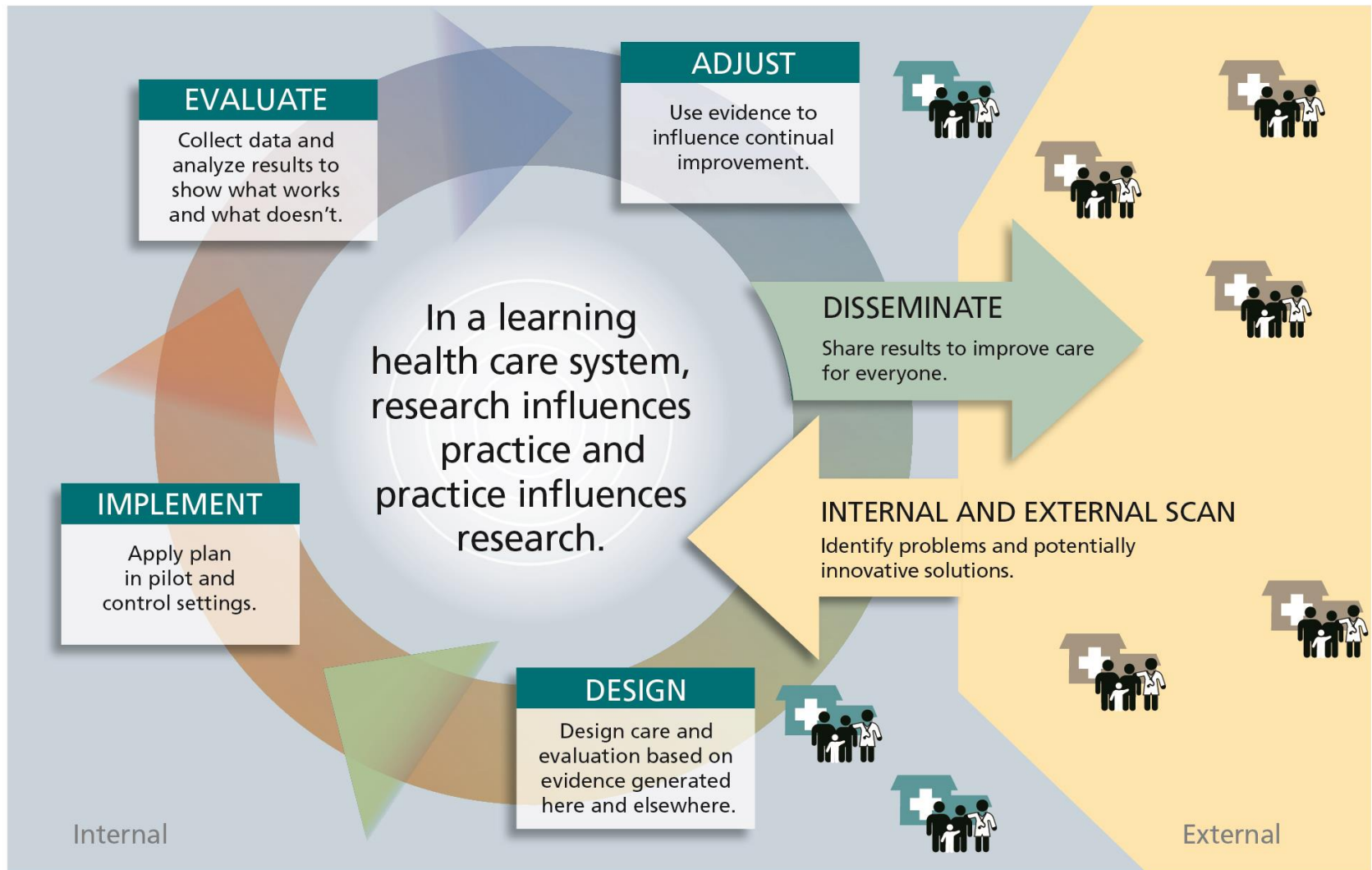


•Source: GeoHive

Generating Evidence to Inform Decisions



Learning health care systems

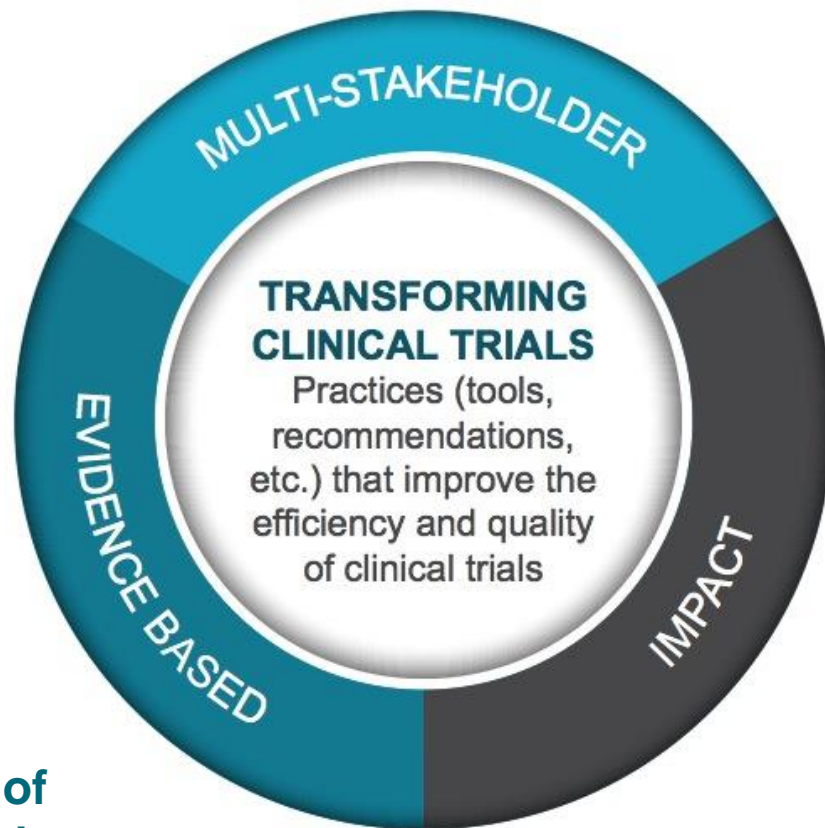


CTTI



Public-Private Partnership
co-founded by Academia & FDA
involves multiple stakeholders
90+ members

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials



PROJECT PORTFOLIO <i>November 2016</i>	Systematic Evidence Generation	Patients as Equal Partners	Efficient & Quality Trials	Public Health Concern	Safe & Ethical Trials
Complete Projects	Large Simple Trials		GCP Training Monitoring Quality by Design Recruitment Site Metrics	ABDD Streamlining HABP/VABP Trials ABDD Unmet Need Long-Term Opioid Data	Central IRB Central IRB Advancement DMCs Informed Consent IND Safety SAE Reporting
Active Projects	MCT Legal & Regulatory MCT Mobile Devices MCT Novel Endpoints MCT Stakeholder Perceptions Real World Evidence Registry Trials State of Clinical Trials	Patient Groups & Clinical Trials	GCP Follow On Investigator Community	ABDD HABP/VABP Studies ABDD Peds Trials	IND Safety Advancement Pregnancy Testing

**COLLABORATIONS
PORTFOLIO**
November 2016

**Systematic
Evidence
Generation**

**Patients as
Equal Partners**

**Efficient &
Quality Trials**

**Public Health
Concern**

**Safe &
Ethical Trials**

Completed Collaborations

Clinical Trials for
Comparative
Effectiveness

Electronic
Healthcare Data

Patient
Engagement
Survey

Clinical Trials Poll

FDA Training
Course

Patient
Engagement
Survey

Cardiovascular
Endpoints

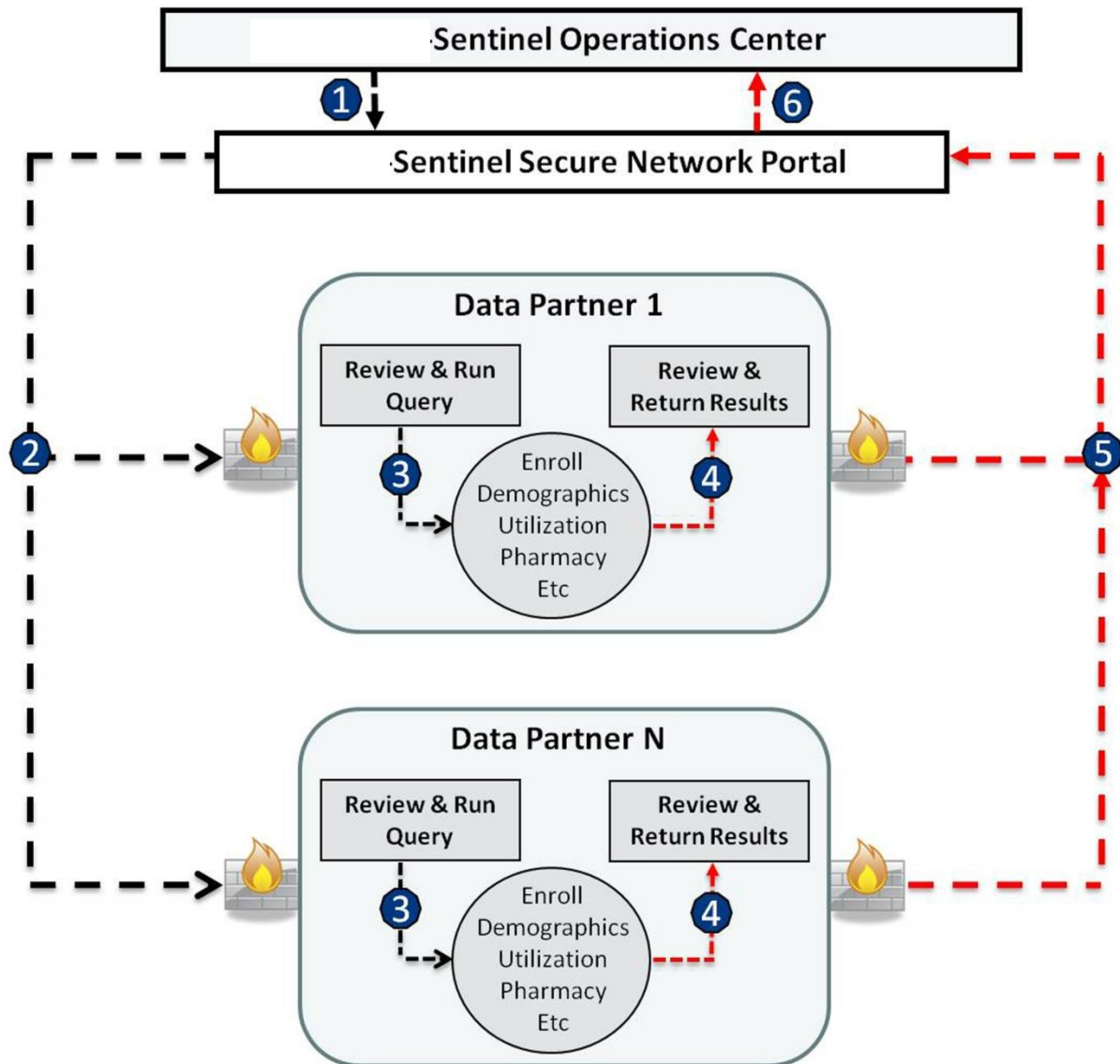
Active Collaborations

Sentinel IMPACT-
AFib

Patient
Engagement
Collaborative

ABDD PTN

Sentinel Distributed Analysis



1- User creates and submits query (a computer program)

2- Data partners retrieve query

3- Data partners review and run query against their local data

4- Data partners review results

5- Data partners return results via secure network

6 Results are aggregated

Demonstration Project Overview-NIH Healthcare Systems Research Collaboratory

10 Demonstration Projects
spanning 12 NIH institutes
and centers

Major clinical outcome trials

1-year planning phase (UH2)

Implementation phase (UH3)

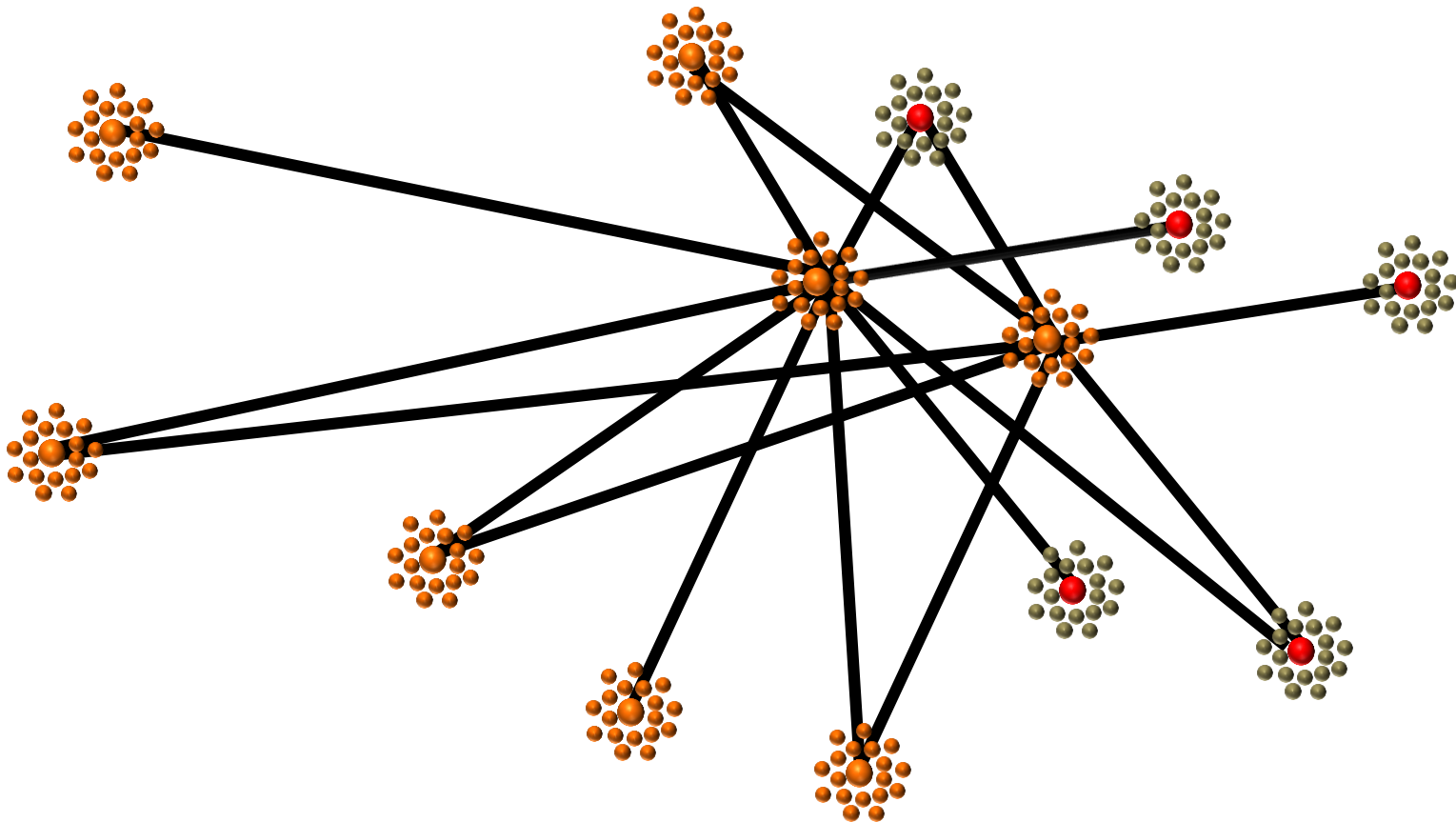
Using EHRs and minimal
additional data collection

Log order reduction in cost



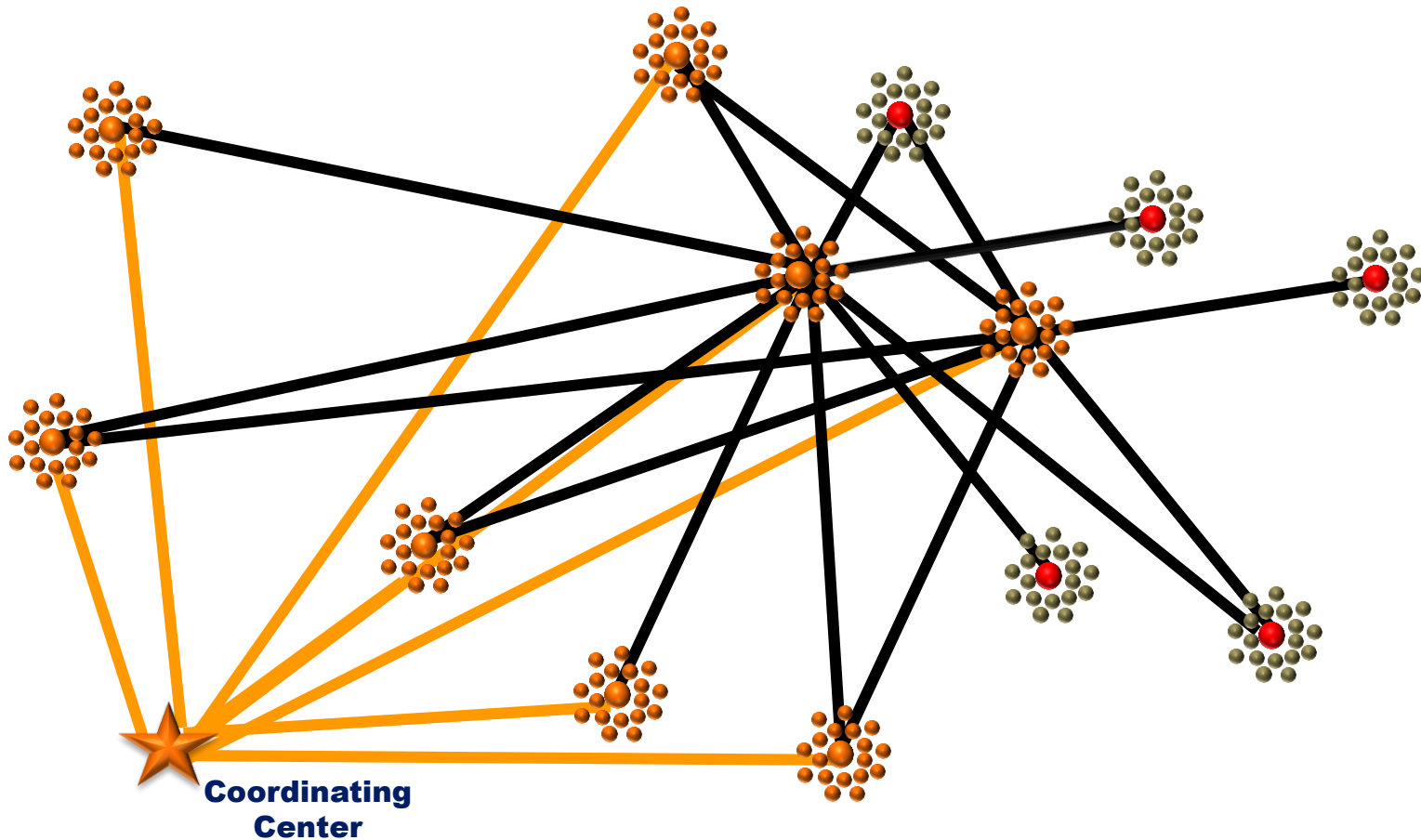
Device Surveillance and Trials

NEST

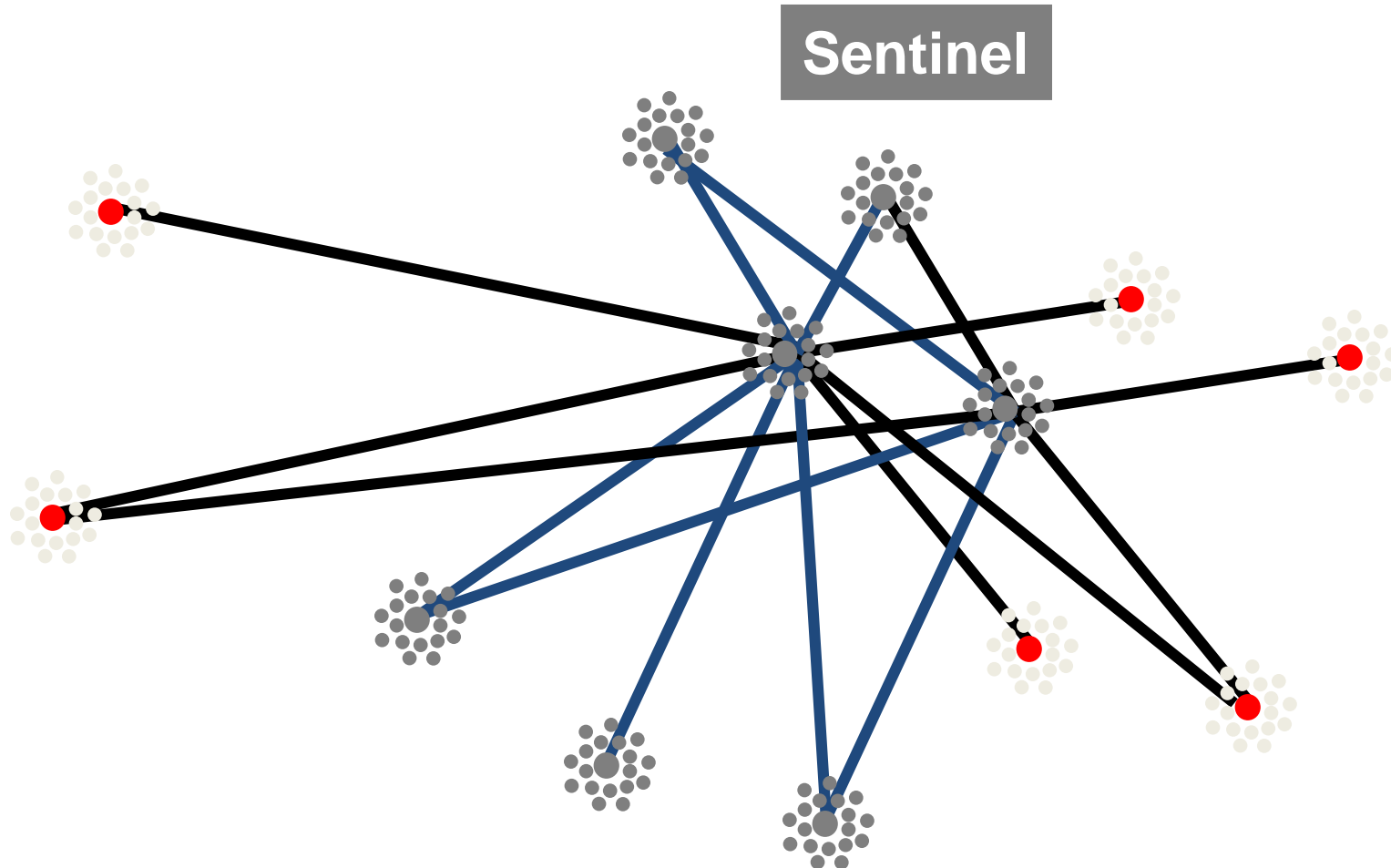


Device Surveillance and Trials

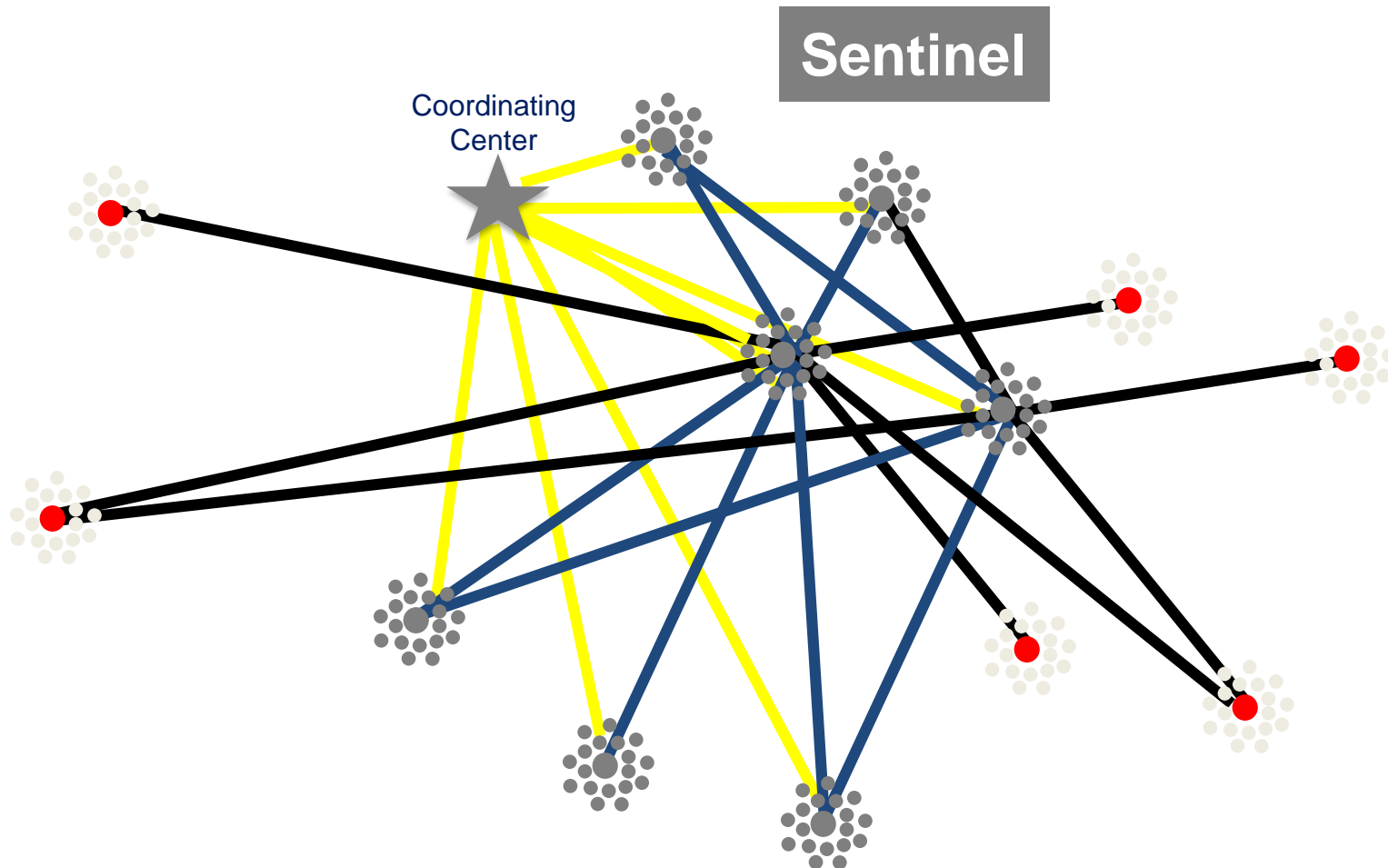
NEST



Drug Surveillance and Trials

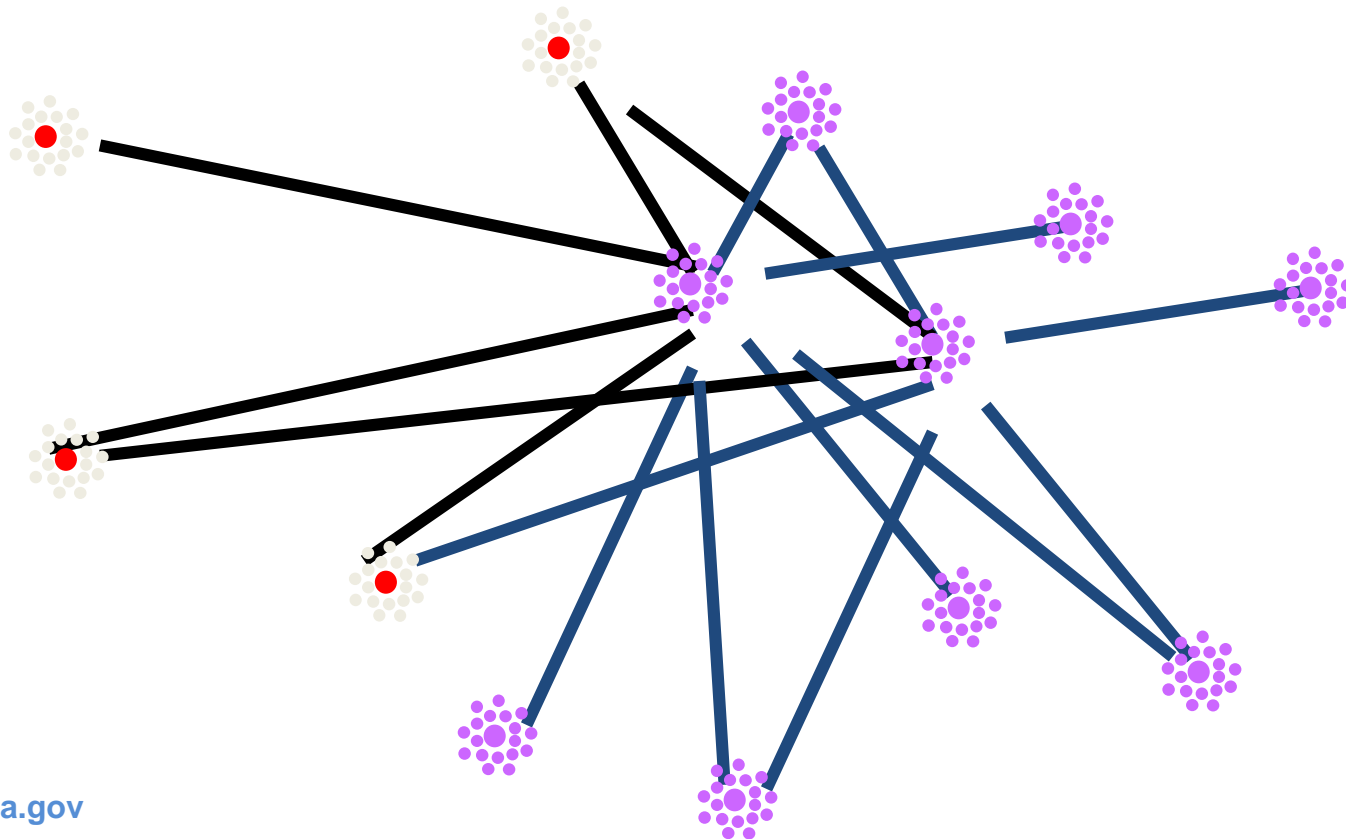


Drug Surveillance and Trials



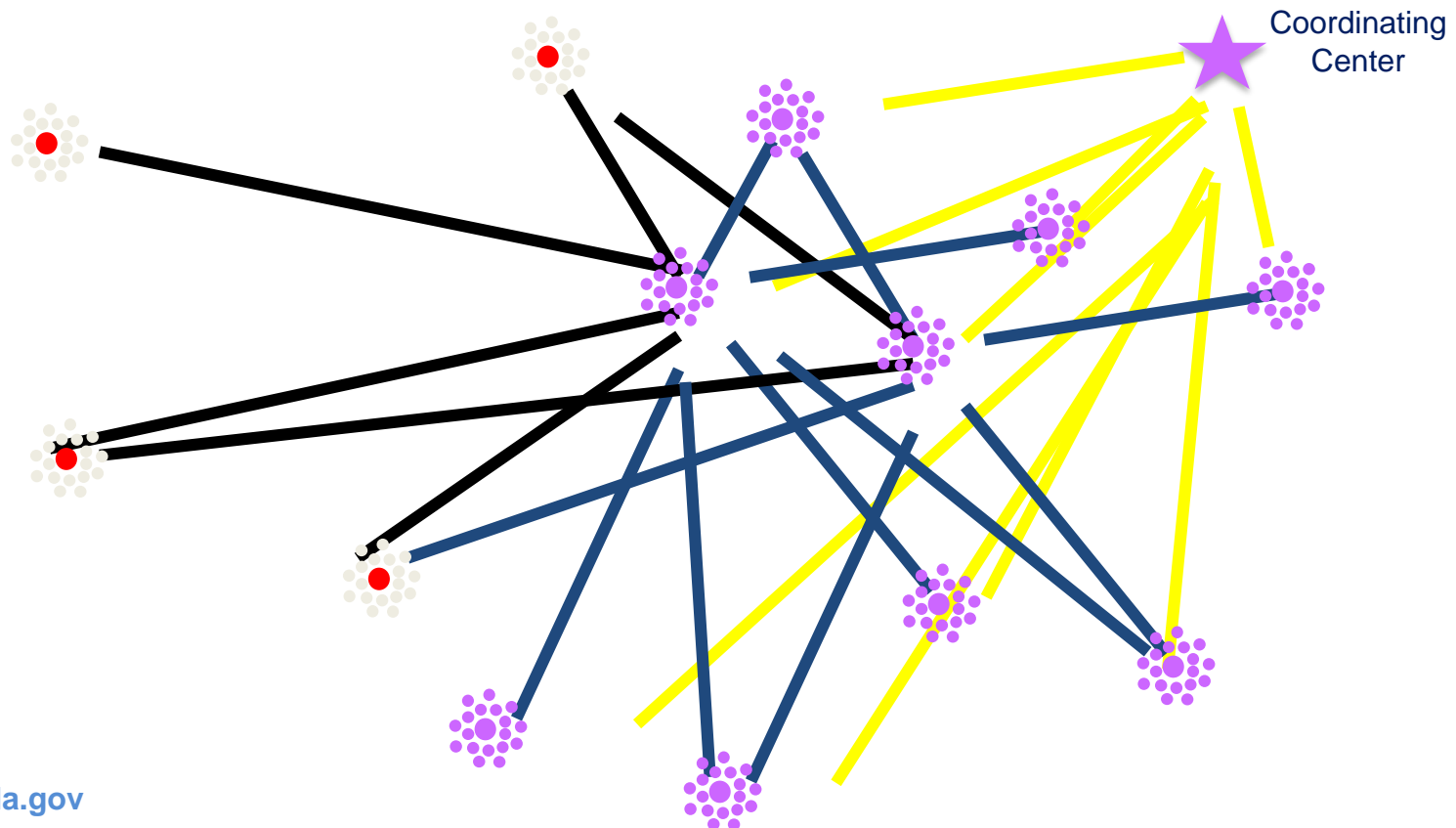
Post Market Studies, including comparative effectiveness

PCORnet



Post Market Studies, including comparative effectiveness

PCORnet



Call to Action

- **Organize operational systems that bring together research networks embedded in practice**
 - to enable patients, consumers, clinicians, industry, government, and health care systems to participate in prospective trials and observational studies
 - Develop operational/regulatory approaches to facilitate practice-based systems for therapeutic research, safety surveillance, public health, and quality improvement.
 - Support adequate time commitment for clinicians to engage with patients to ensure mutual understanding and appropriate consent
 - Efficient systems for contracting and liability
 - Clinical care and research closely aligned in “learning health system” supported by education and training
 - **How can delivery systems with their evolving power create a system that encourages participation in an efficient system?**

Call to Action

- **Establish a robust framework for privacy, confidentiality, and security**
 - endorsed by patients and consumers to ensure the trust a learning health system will require,
 - Robust procedures that ensure data security and protect confidentiality
 - Efficient and thorough digital system of education and research permissions for patients
 - Balance of individual autonomy and public health needs
 - Great start: Precision Medicine Initiative: Privacy and Trust Principles
 - **How can delivery systems take on a more constructive role to move the system to a participatory learning system?**

Call to Action

- **Adopt a common approach to configuring, storing, and re-using digital health care data to enable use in care, research, safety surveillance, and public health**
 - As called for in the Nationwide Interoperability Roadmap published by the Office of the National Coordinator for Health Information Technology.
 - Common standards and terminology for prospective data collection
 - Continuous effort to curate data to produce high quality data sets for analysis using common data models
 - Leverage existing digital health/healthcare data to create efficiencies (registries, claims data, EHR data, personal devices)
 - **Can delivery systems figure out how to share data at the scale needed now that we understand the needed sample sizes?**

Call to Action

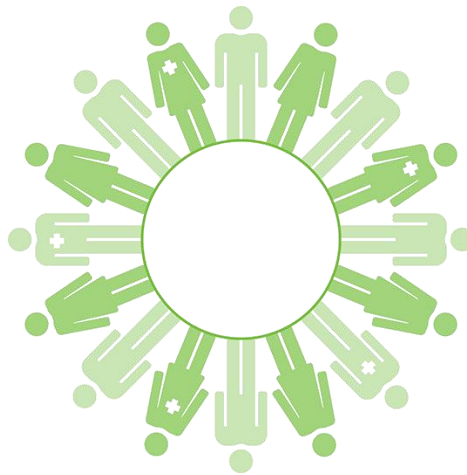
- **Develop and test new methods to reliably answer research questions**
 - more efficient RCTs,
 - Novel designs such as cluster-randomized trials, basket trials
 - And more reliable observational studies aimed at assessment of interventions
 - “Meta-knowledge” on which methods are best for which types of questions
 - By leveraging data already collected by health information technology and other electronic sources to answer research questions or facilitate the conduct of new trials.
 - **Will delivery systems value clinical science enough to create the needed work force and reward scholarly activity in this arena?**

Call to Action

- **Ensure the development of novel approaches focusing on streamlining and harmonizing processes in ways that eliminate barriers that promote unnecessary complexity, while ensuring safeguards that are truly needed.**
 - Streamlined and harmonized processes eliminate barriers to efficient research while ensuring needed safeguards
 - Systems for high quality and efficient ethics review and contracting
 - Development of approaches to assuring quality systems through better use of analytics
 - **Can AMCs regard efficiency in research with the same seriousness as they have addressed efficiency in clinical care?**

PCORnet embodies a “community of research”
by uniting people, clinicians & systems

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20

Patient-Powered Research
Networks (**PPRNs**)

PCORnet embodies a “community of research”
by uniting people, clinicians & systems



20
Patient-Powered Research
Networks (**PPRNs**)

+

13
Clinical Data
Research Networks
(**CDRNs**)

PCORnet embodies a “community of research”
by uniting people, clinicians & systems



20
Patient-Powered Research
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+

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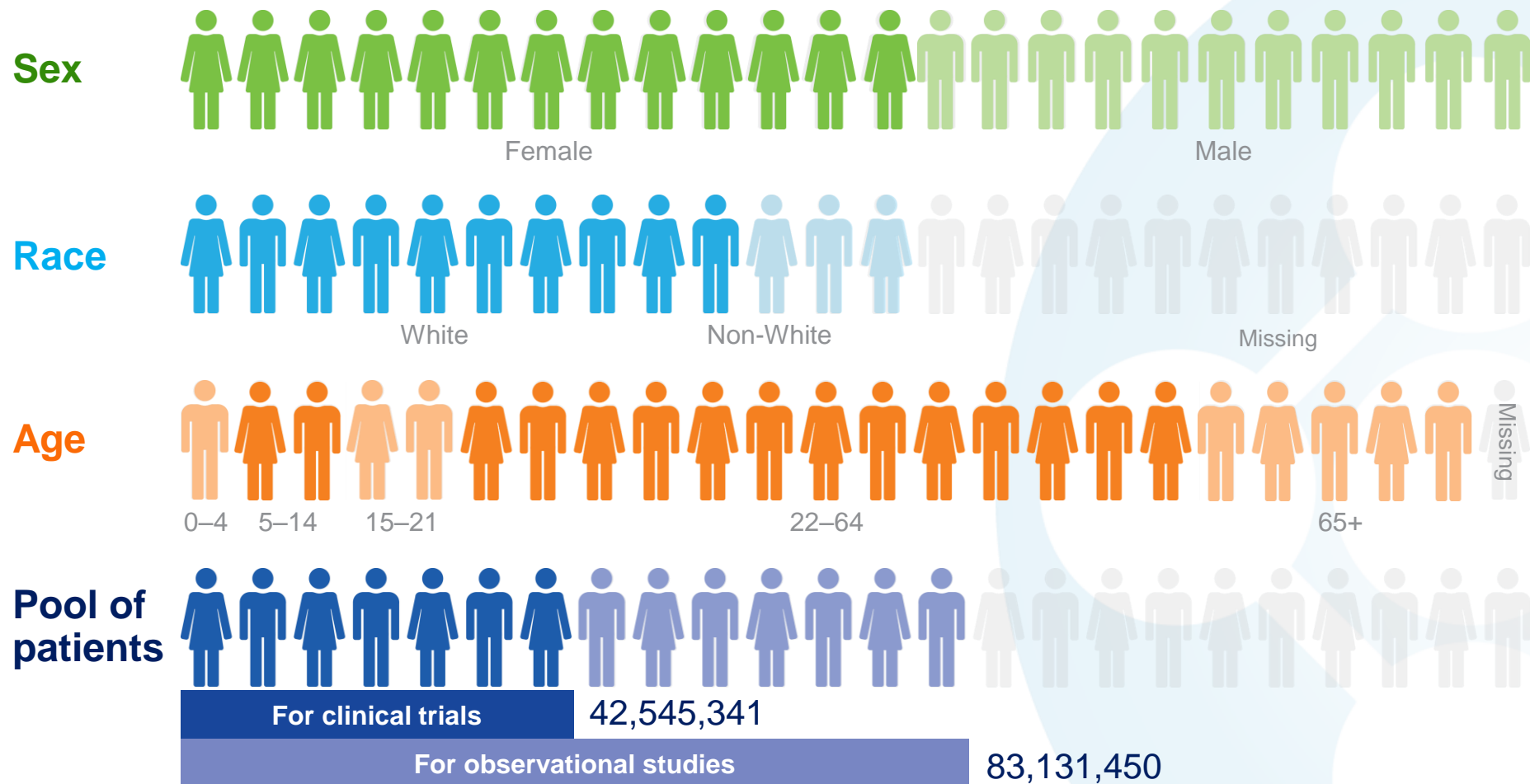
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PCORnet
A national infrastructure
for people-centered
clinical research

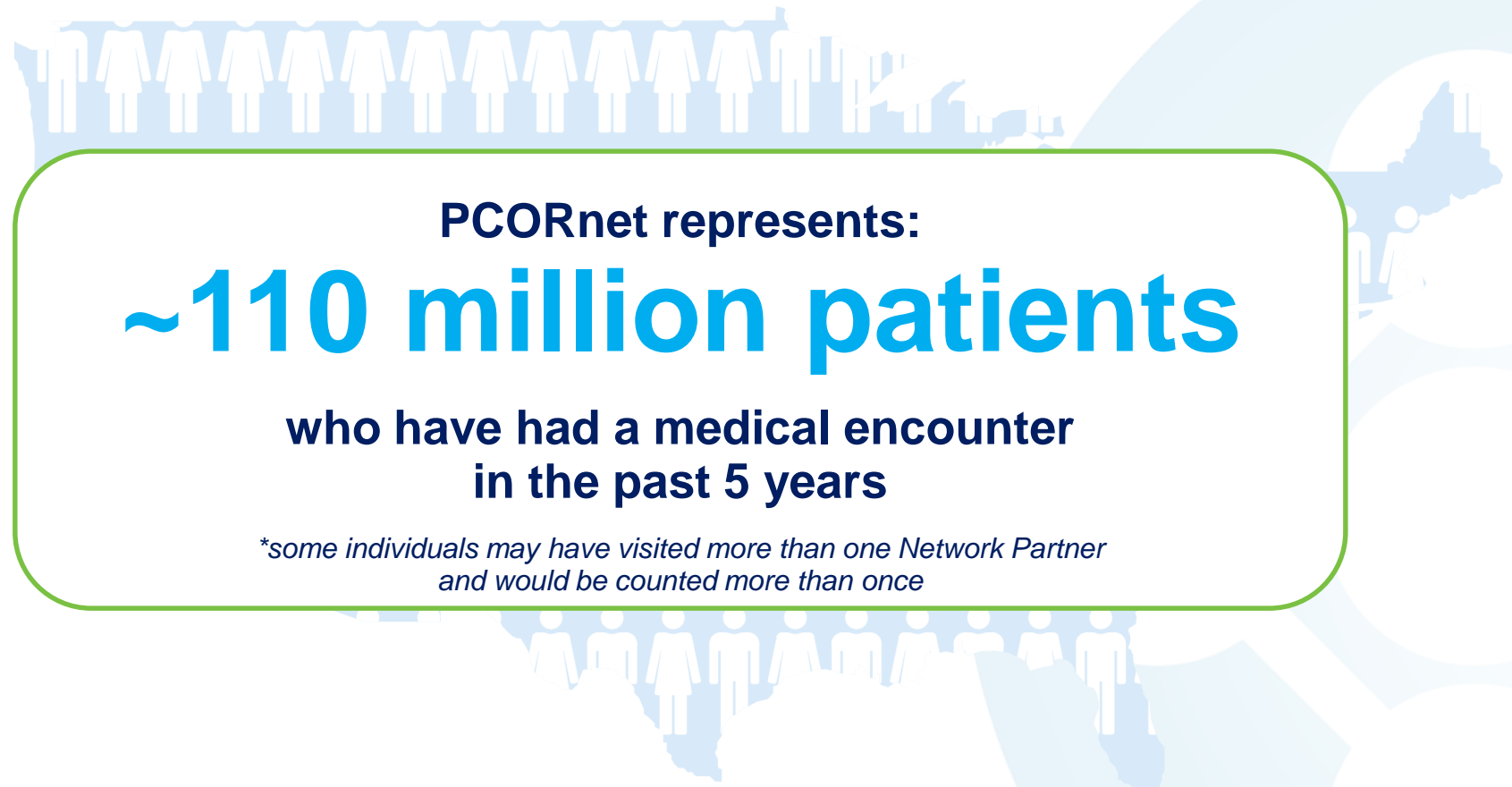
Resulting in a national evidence system with unparalleled research readiness



Resulting in a national evidence system with unparalleled research readiness



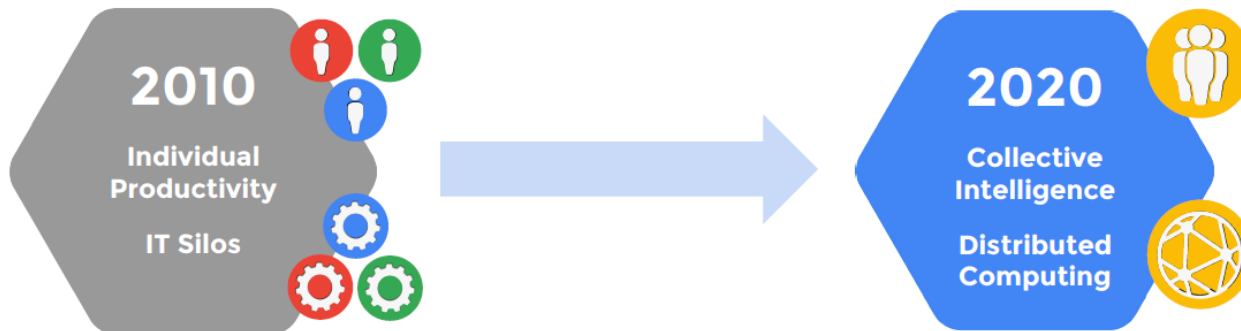
Resulting in a national evidence system with unparalleled research readiness



PCORnet represents:
~110 million patients
who have had a medical encounter
in the past 5 years

**some individuals may have visited more than one Network Partner
and would be counted more than once*

Digital Transformation



- Data on premise, hard to access, analyze and use
- Productivity tools built for individual, local usage
- IT focusing on **where** it computes

- Data stored in cloud, simple to query
- Collaborative, cloud based productivity applications
- Machine learning drives deep, actionable insights
- IT changing **how** it computes

What Can we Do?

- Do pragmatic trials that clearly answer meaningful questions to patients and providers
- Do better trials
 - at a lower cost,
 - more quickly
 - efficiently
 - with more centrality on the patient (and the provider)
- Develop standards and systems that are efficient, streamlined and augment clinical care rather than creating burdens or “parallel universes”