

Evidence Generation: Moving into the Modern Era

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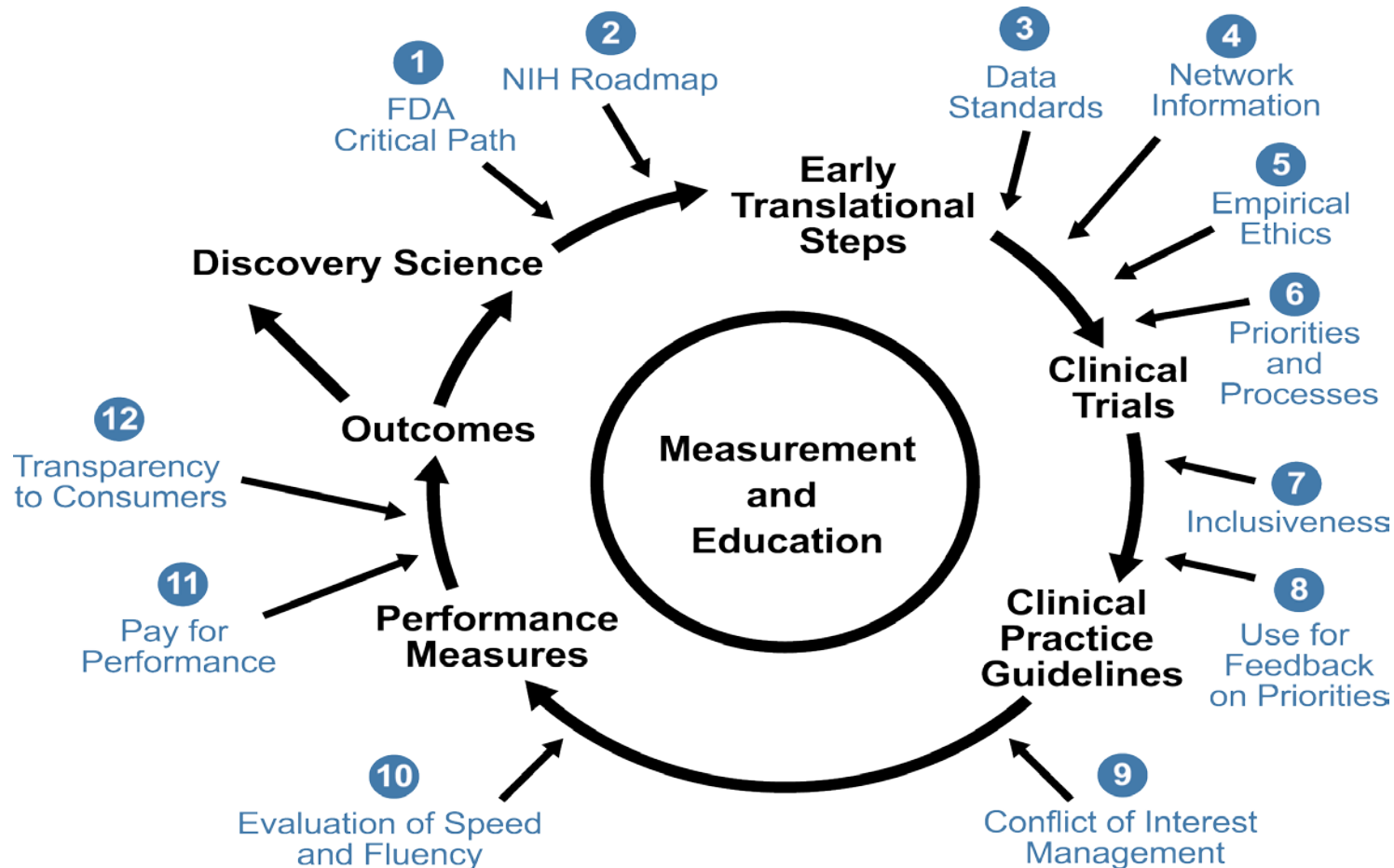
The Problem

- I know nothing about opera, but I do know that ...
- FDA needs more evidence
 - To make better decisions
 - To improve labels to provide clinicians and patients with accurate and useful information for safe and effective use of drugs, devices and biologics in practice
- CMS and other payers need evidence to calculate the value of medical products as used in practice
- The current system is not delivering adequate evidence in the face of an explosion of new medical products and increased understanding of how to evaluate products already in clinical use

But it's a good problem to have

- Current system producing highly effective medical products
- Pipelines are in good shape
- Life expectancy continues to increase every year
- We are doing very well compared with the past
- Now it's a matter of going to the next level

Generating Evidence to Inform Decisions



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

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

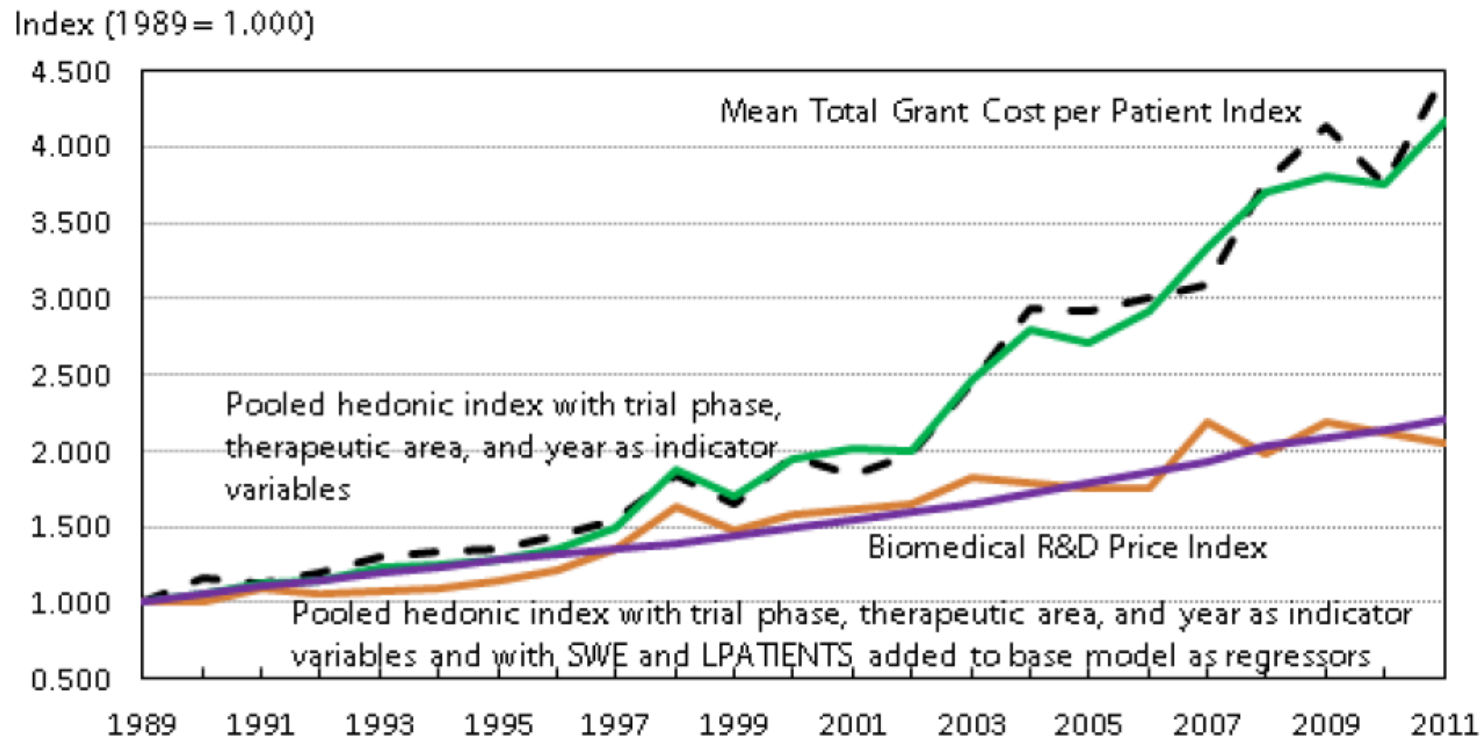
Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

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.

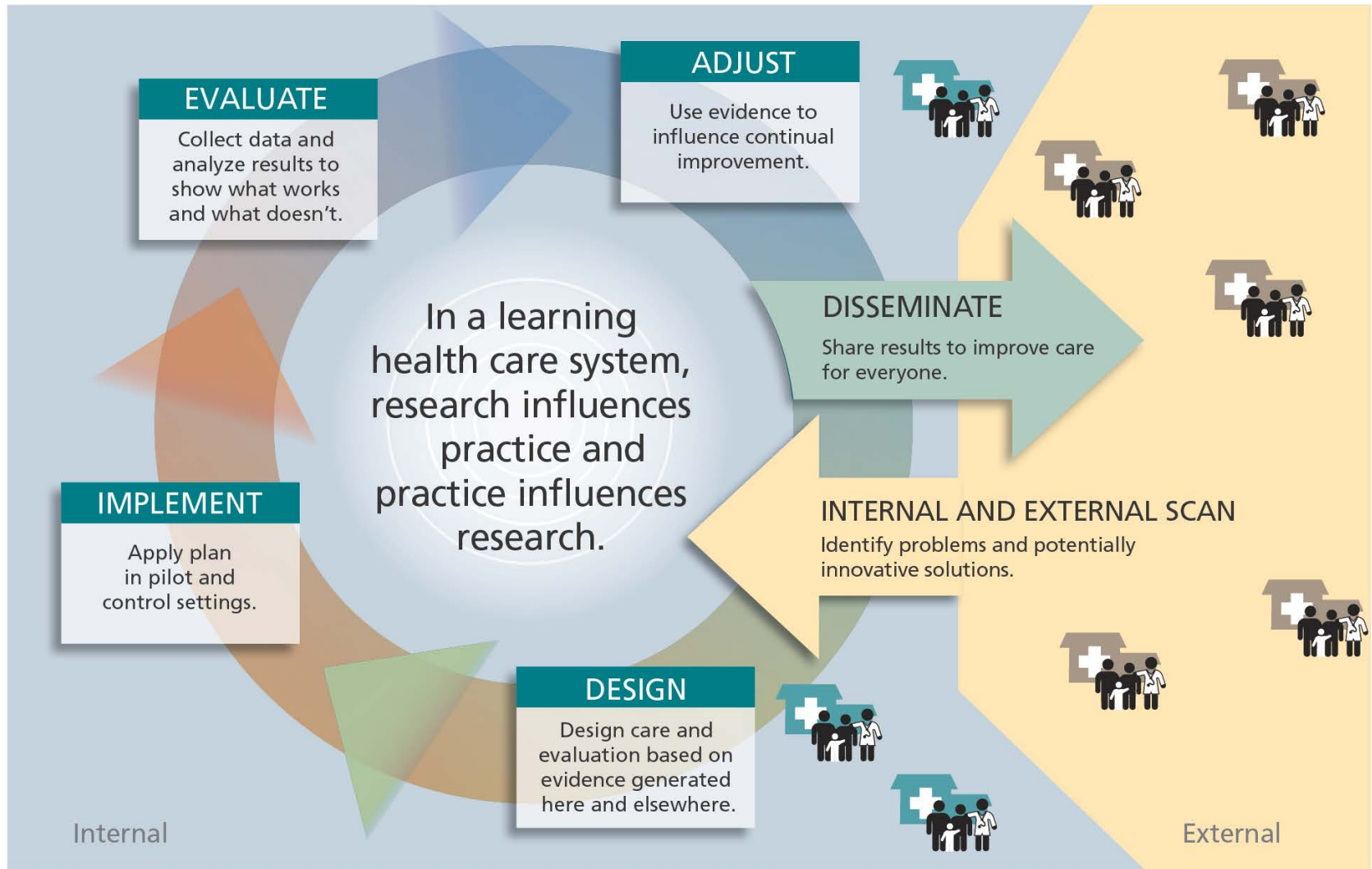
Trial Hyperinflation

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



Berndt E, Cockburn I. Monthly Labor Review, June 2014

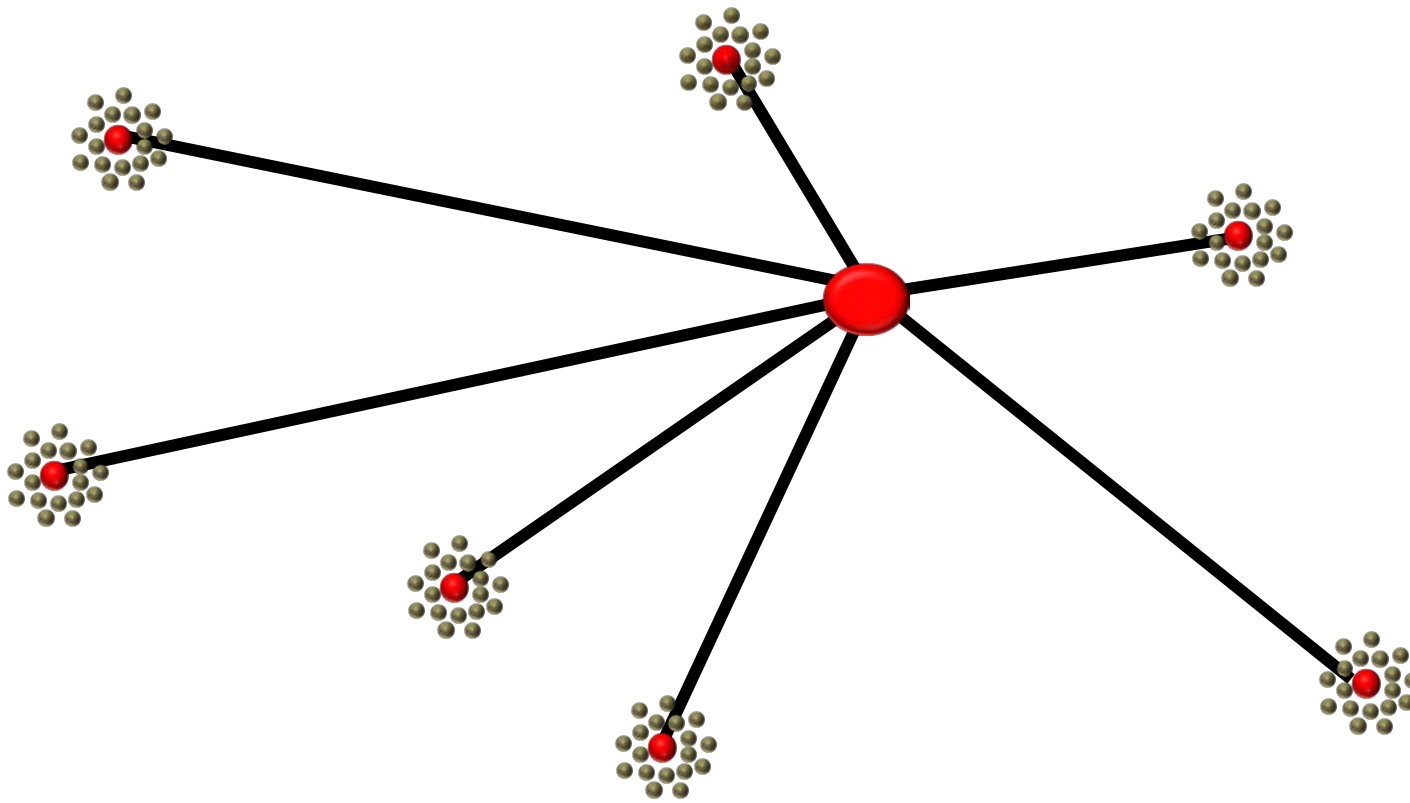
Learning health care systems



Historical model of clinical research: Many recruitment sites and a coordinating center

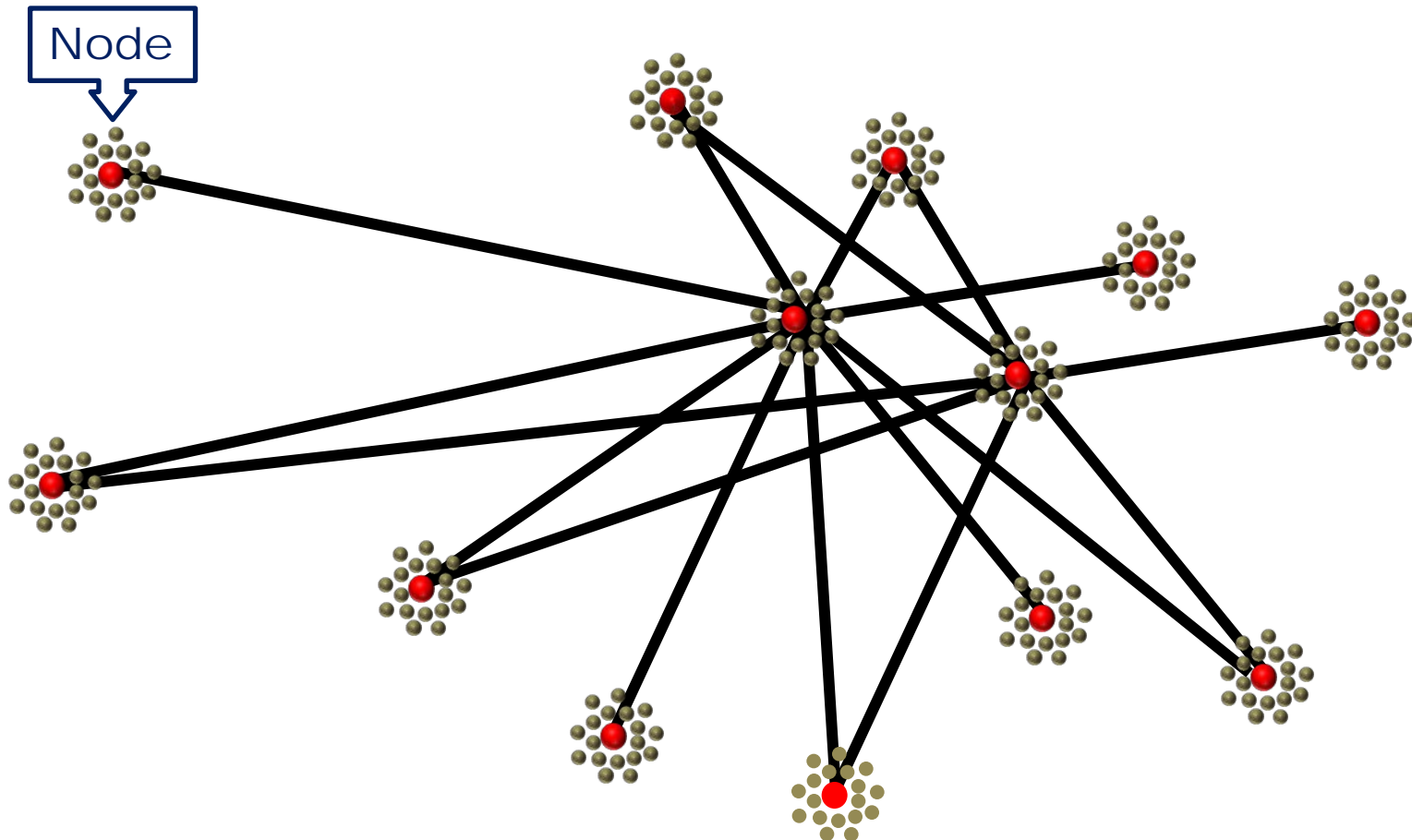


- Hub & spoke model
- Top-down decision-making
- Sites operated independently

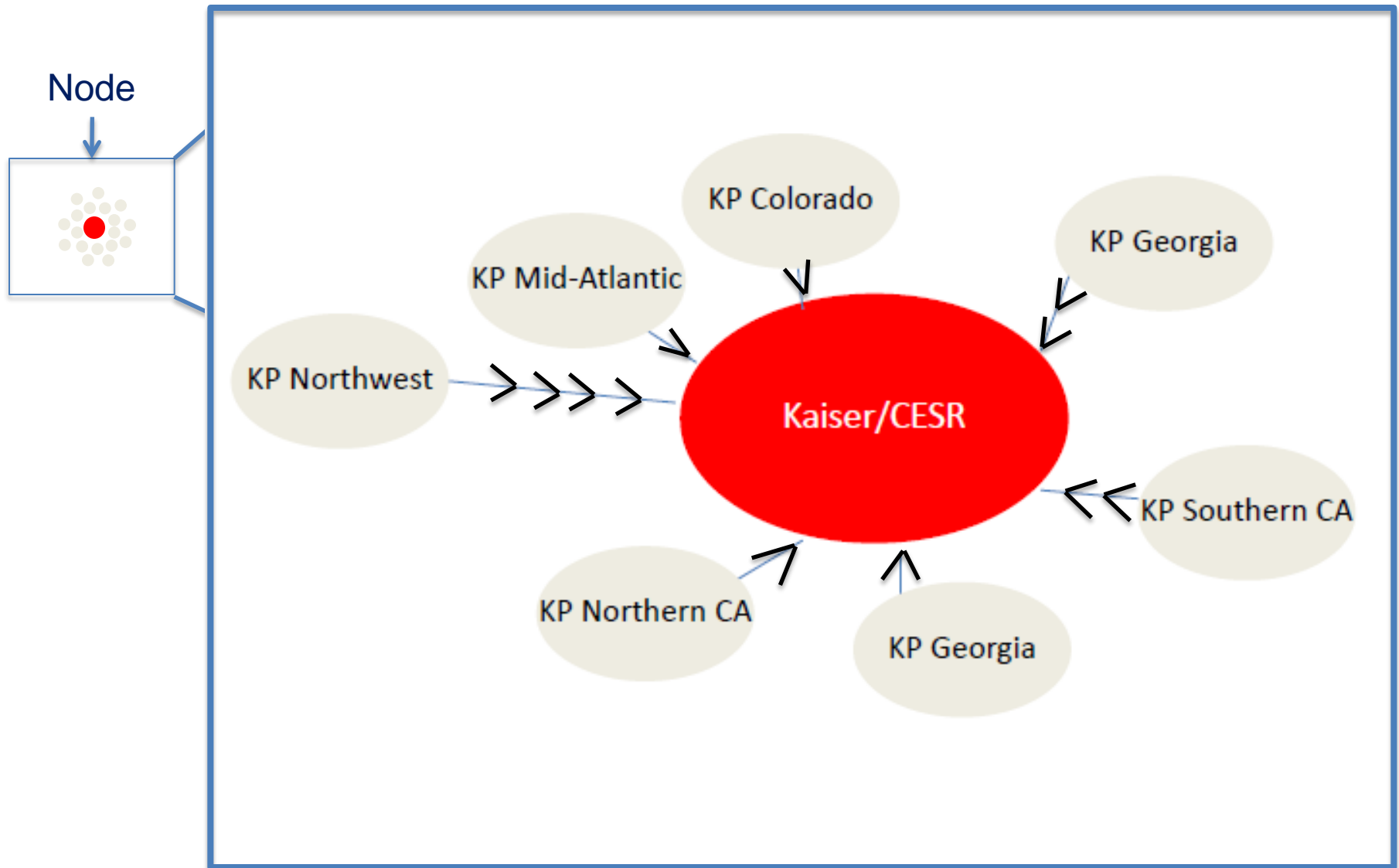


Modified Model

Data Shared, Sites owned by Health Systems

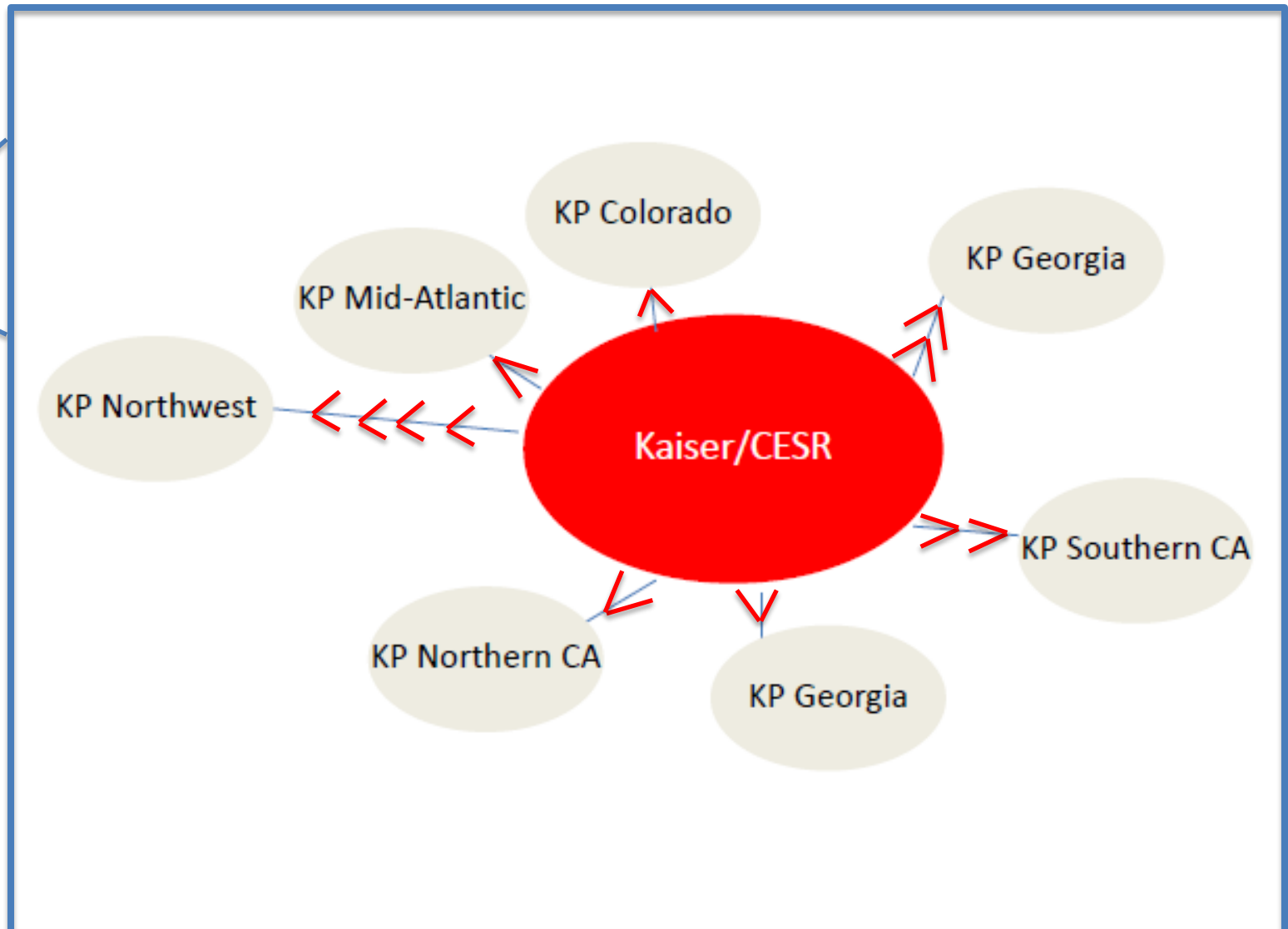


Previously Independent Sites now part of
large integrated health systems
increasingly sophisticated data warehouses



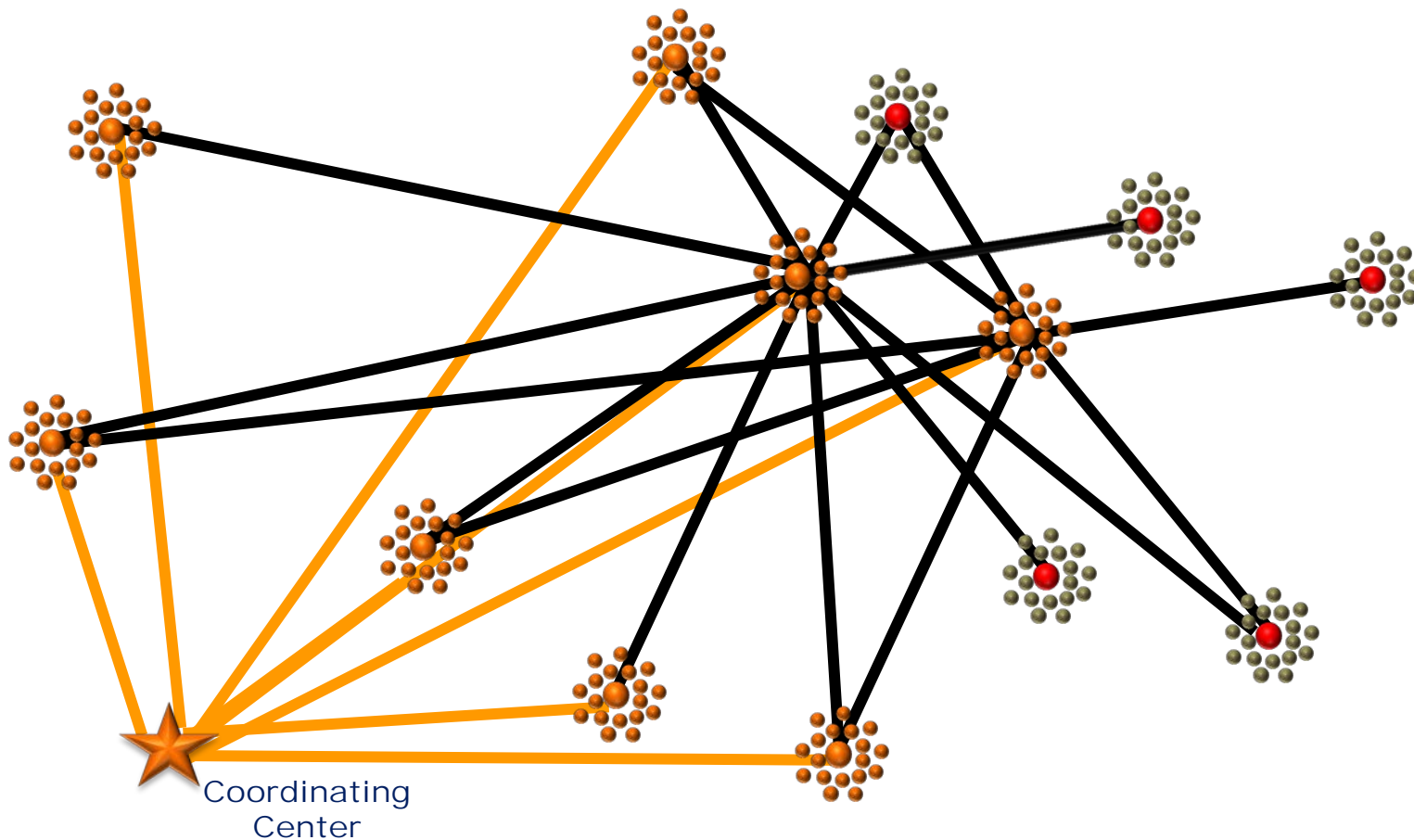
Nodes are Operational Clusters Using Common Data

Node

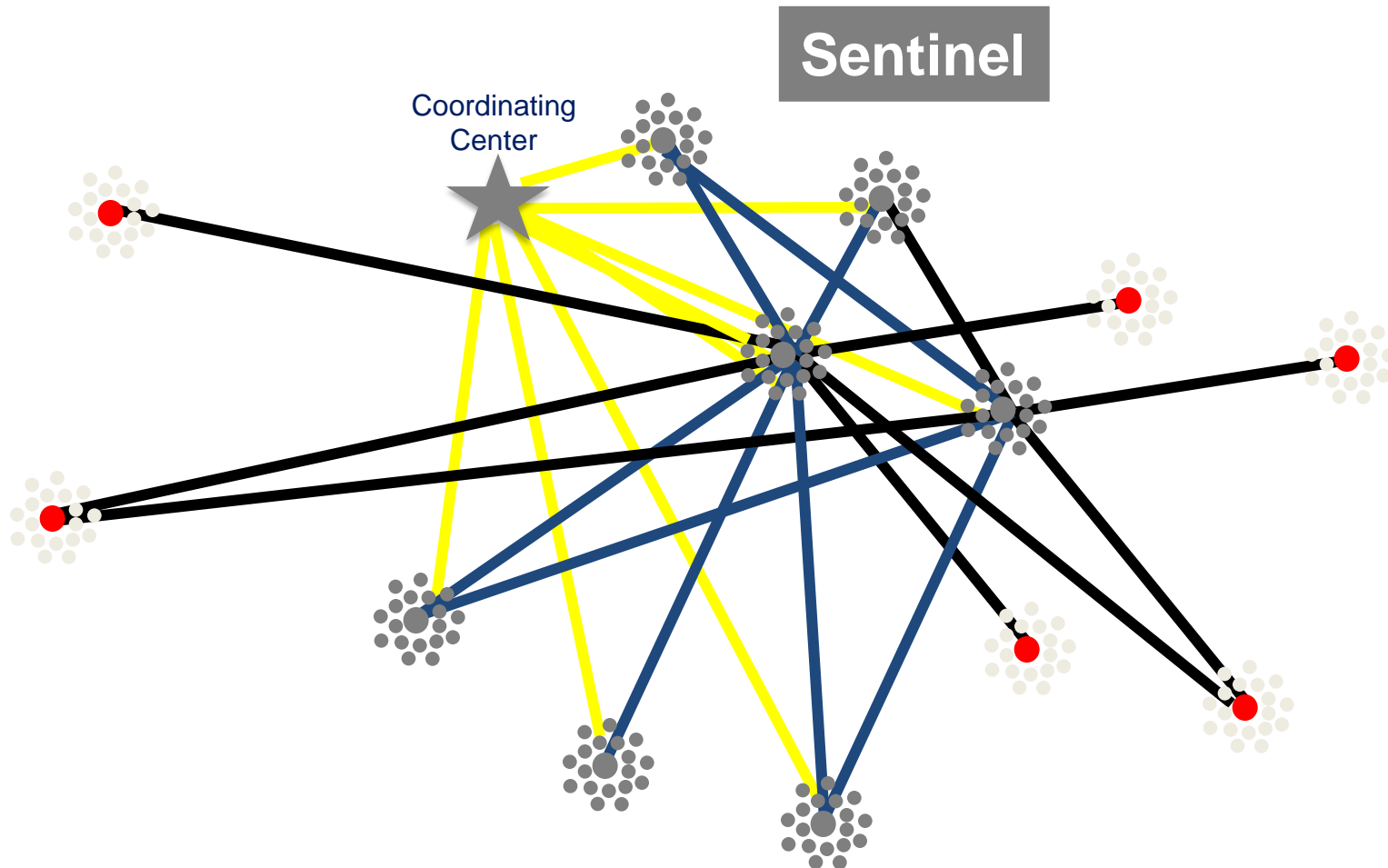


Device Surveillance and Trials

NEST

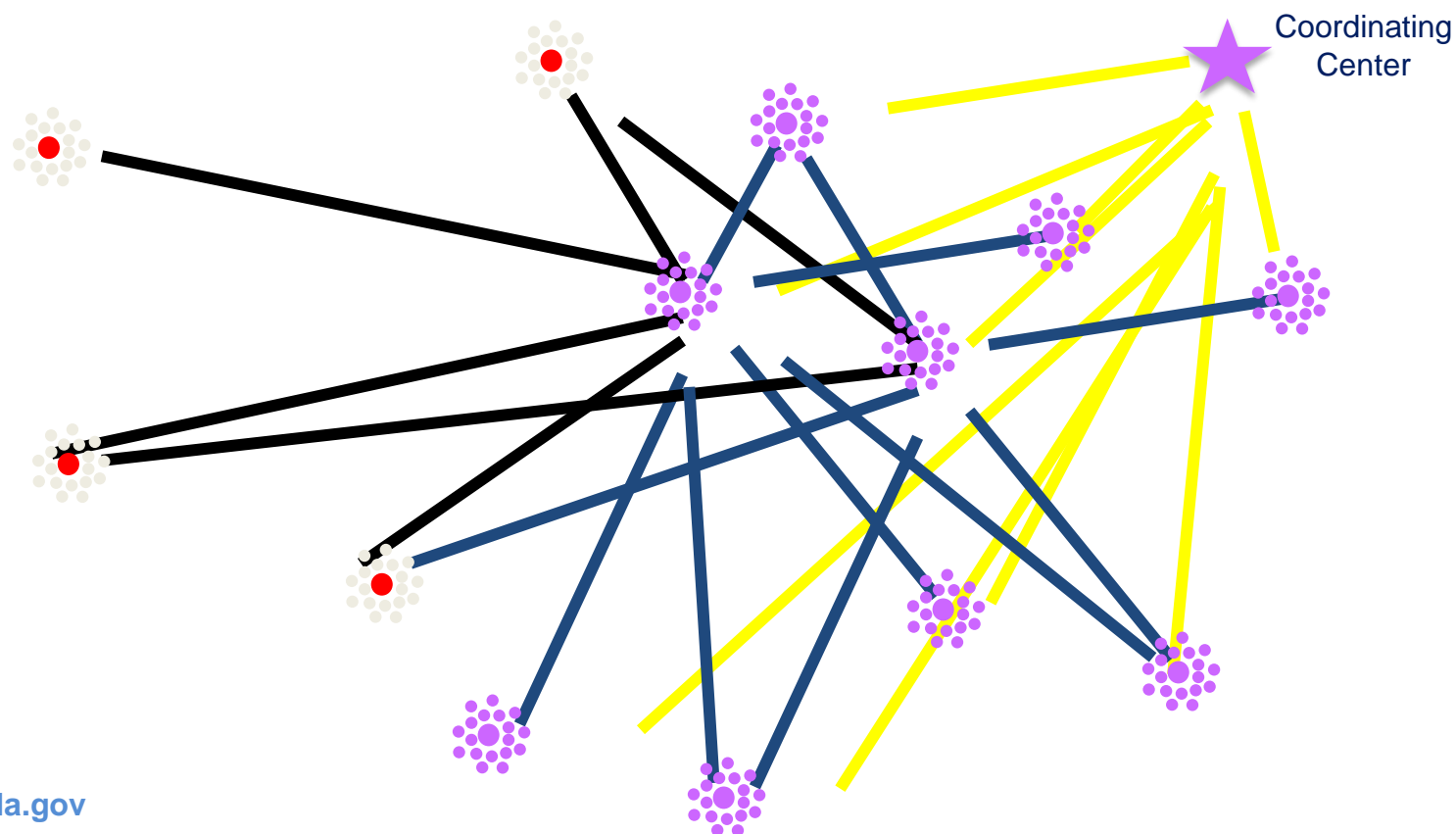


Drug Surveillance and Trials



Post Market Studies, including comparative effectiveness

PCORnet



Key Points from FDA Perspective

- RWE and experimental methods are 2 different axes in designing studies
 - Source of data
 - What is the source of data?
 - Where is the research conducted?
 - What populations are included or excluded?
 - Experimental design
 - If randomized, type of randomization
 - Planned registry
 - Purely observational
- Randomization within the context of real world is a major goal



Key Points from FDA Perspective

- FDA regulations and guidance about the standard in no way prohibit or should inhibit the use of RWE when RWE is appropriate in the views of competent experts in the field (experimental design is another issue)
- FDA and CMS should be able to use common evidence sources, but will appropriately apply different criteria for decision making
- As the evidence system changes consensus about substantial evidence and quality for different purposes (quality by design) will be critical
- Explaining why “doctors know from experience” doesn’t work as a policy remains a difficult challenge
- The business model for real engagement of doctors and other healthcare providers seems to be the main limiting factor

ACA Mandate

Requirement for “the coordination of relevant Federal health programs to build data capacity for comparative clinical effectiveness research in order to develop and maintain a comprehensive interoperable data network to collect, link and analyze data on outcomes and effectiveness from multipole sources, including electronic health records”

PPACA, Title VI. Transparency and Program Integrity. Subtitle D Section 6301

Multiple Developing Efforts

- FDA
 - Sentinel, National Evaluation System for health Technology (NEST), MDUFA data standardization
- NIH
 - CTSA, HCS Collaboratory, Multiple institute/Center Networks
- CDC Vaccine Surveillance Network
- ASPE—PCOR-Trust Fund
- PCORI-PCORnet
- CMS
 - Enclave, Coverage with Evidence Development
- Million Veterans' Program (MVP)
- Precision Medicine Initiative (PMI)

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

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

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)

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.

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

We believe several EvGen use-cases can be launched in the short and medium term making incremental changes to today's infrastructure

○ Least advanced ● Most advanced

	Data Creation	Aggregation	Utilization	Dissemination	Key requirements
Current state (U.S.)					
Use cases					
1A Real world data for more efficient clinical trials					<ul style="list-style-type: none"> • Maturity of methods • Regulatory pathways
1B Learning from historical clinical trial failures					<ul style="list-style-type: none"> • Aggregation of specialized data • Sophisticated collaboration/ usage models
1C Accelerating innovation in rare and ultra-rare diseases					<ul style="list-style-type: none"> • Specialized datasets with patient privacy challenges • Maturity of methods and decision making
2A Real world insights to evaluate efficacy of generics and biosimilars					<ul style="list-style-type: none"> • Maturity of methods • Regulatory pathways
2B Adapting the regulatory paradigm for rare and ultra-rare diseases					<ul style="list-style-type: none"> • Maturity of methods • Regulatory pathways
2C Enhancing active safety surveillance and information availability					<ul style="list-style-type: none"> • High quality data • Methods and regulatory pathways
2D Early warnings of epidemics and drug dev. for infectious diseases					<ul style="list-style-type: none"> • High quality data to act in a timely fashion
3A Patient-level coverage and pricing, based on real world outcomes					<ul style="list-style-type: none"> • High quality data • Maturity of methods
4A Insights for physicians to provide better care for patients					<ul style="list-style-type: none"> • High quality longitudinal data • Maturity of methods and decision making
4B Enabling precision medicine through big data					<ul style="list-style-type: none"> • Needs more sophisticated analytics and furthering of science to understand links between genotypes and phenotypes
4C Population-level insights into antibiotic usage and resistance					<ul style="list-style-type: none"> • Require large, interconnected data sets to make population-level correlations

Existing “EvGen-like” data initiatives in the US could form the foundation for the new future state vision

Initiative	Led by	Goal	Source of data	Size of database
		<ul style="list-style-type: none"> Support comparative clinical effectiveness research (CER) 	<ul style="list-style-type: none"> EHRs from 13 CDRNs and 20 PPRNs 	<ul style="list-style-type: none"> 110M covered lives <ul style="list-style-type: none"> – 33M clinical trials – 68M obs. studies
	   	<ul style="list-style-type: none"> Assist patients, their caregivers, and doctors in making better-informed decisions 	<ul style="list-style-type: none"> EHRs from Kaiser Permanente, Group Health Coop, HealthPartners and Denver Health 	<ul style="list-style-type: none"> 12M lives
		<ul style="list-style-type: none"> Monitor post-marketed safety in medical products 	<ul style="list-style-type: none"> Primarily claims data 	<ul style="list-style-type: none"> 193M lives
		<ul style="list-style-type: none"> New networking infrastructure for collaborative research to improve clinical trial design 	<ul style="list-style-type: none"> Sentinel data partners 	<ul style="list-style-type: none"> 90M lives
		<ul style="list-style-type: none"> Study observational health data (RWE) through analytics to better understand disease history, healthcare delivery, and the effects of medical interventions 	<ul style="list-style-type: none"> EHRs, claims, pharmacy records, health surveys and registries from 40 worldwide databases 	<ul style="list-style-type: none"> 500M lives
		<ul style="list-style-type: none"> To enable personalized medicine and more precise preventive care 	<ul style="list-style-type: none"> EHRs, claims, patient-generated data (health exam, surveys, passive data from mobiles and wearables) 	<ul style="list-style-type: none"> Currently data from <100K volunteers; goal of 1M volunteers by end of 2019
	  	<ul style="list-style-type: none"> To reduce medical costs for payors and to enable providers to improve performance in value-based payment models 	<ul style="list-style-type: none"> Currently, primarily claims; goal to integrate these with EHRs as more providers join 	<ul style="list-style-type: none"> 9M lives (25% of population of California)
<ul style="list-style-type: none"> CDC National Vital Statistics System 		<ul style="list-style-type: none"> To use statistics derived from vital records in public health research 	<ul style="list-style-type: none"> Registries of vital events (births, deaths, marriages, divorces and fetal deaths) maintained by states 	<ul style="list-style-type: none"> A few hundred thousand vital records captured every year

SOURCE: Initiative websites; press and literature search

If We Had An Efficient Evidence Generation System....

- Much more of clinical practice could be guided by high quality evidence
- Policy decisions would be more rational
- Clinicians and their practice organizations could focus on interpreting the evidence and applying it
- The role of opinion and expertise would be at least as important, but it would be put to a much higher purpose—providing precision healthcare

THE VISION OF PRESIDENT OBAMA



"My hope is that this becomes the foundation, the architecture, whereby in 10 years from now we can look back and say that we have revolutionized medicine."

- PRESIDENT BARACK OBAMA
