Key Regulatory Opportunities for Neuroscience Clinical Trials

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Commissioner of Food and Drugs

March 4th, 2016

Disclaimer

- My comments today do not represent FDA Policy
- Instead I offer some thoughts that may be useful as you think about clinical trials involving neuroscience issues
- For policy issues, go directly to FDA division leadership in CDER, CDRH and CBER

Direct Leaders

- **CDRH Neuro Devices Division**
  - Carlos Pena Director
- **CDER Office of Drug Evaluation I**
  - Ellis Unger-Acting Director
  - Bob Temple—Acting Deputy Director
- **ODE-I Division of Neurology Products (DNP)**
  - Billy Dunn Director
- **ODE-1 Division of Psychiatry Products (DPP)**
  - Mitchell Mathis Director

Use of Medical Practice and Learning Health System

- Best outcomes occur when use of medical practice is guided by high quality evidence of benefit risk balance
- This is most likely to happen when clinical trials and high quality observational studies are part of the practice
- Is the CNS field different in this regard?

"Regulatory Trials?"

- **Are there 2 parallel worlds of medical evidence?**
  - Develop evidence used to determine ***whether*** a product should be marketed
  - Develop evidence to determine ***how*** the product should be used
- **Or one world of medical evidence?**
  - Provides clinicians and patients with the evidence they need for the safe and effective use of a medical product

Regulatory Trials?

- **The most fundamental source of information about a medical product is approved labeling , which by regulation must contain the critical prescribing information.**
- **This information is widely available and serves as a trusted and vetted platform for other sources of information, notably compendia and clinical practice guidelines.**

Regulatory Trials

- **A useful way to think about designing development programs for medical products would be to envision both the product label and the corresponding clinical practice guideline, which includes context about how and when to use a therapy in the context of therapeutic alternatives and societal factors.**

Off Label Prescribing

- **46,021 patients from primary care clinics in Quebec, CA**
- **Off label use 11.8%**
  - With strong evidence 2.3%
  - Without strong evidence 9.5%
- **Proportion of total off-label use:**
  - CNS 25.4%; CV 23%; Hormones 13.6%; Anti-infective 10.4%;
    - JAMA Intern Med. 2016;176(1):55-63.

Off Label Prescribing

- **25% of "CNS" use was off-label**
  - Antidepressants, antipsychotics, anticonvulsants, anxiolytics, antimgraines, etc.
  - Other fields: ENT 17%; anti infective 16%; GI 12%; others < 5%
- **21% of CNS use was off-label without strong scientific evidence**
  - Other fields: ENT 17%; anti-infective 15%; GI 11%; others < 4%
- **For some CNS drugs over 70% of use was off-label**
  - Gabapentin, Clonazepam, Amitriptyline, Trazodone, Betahistine, Oxazepam, Quetiapine
    - » JAMA Intern Med. 2016;176(1):55-63.

From: **Association of Off-label Drug Use and Adverse Drug Events in an Adult Population**

JAMA Intern Med. 2016;176(1):55-63. doi:10.1001/jamainternmed.2015.6058

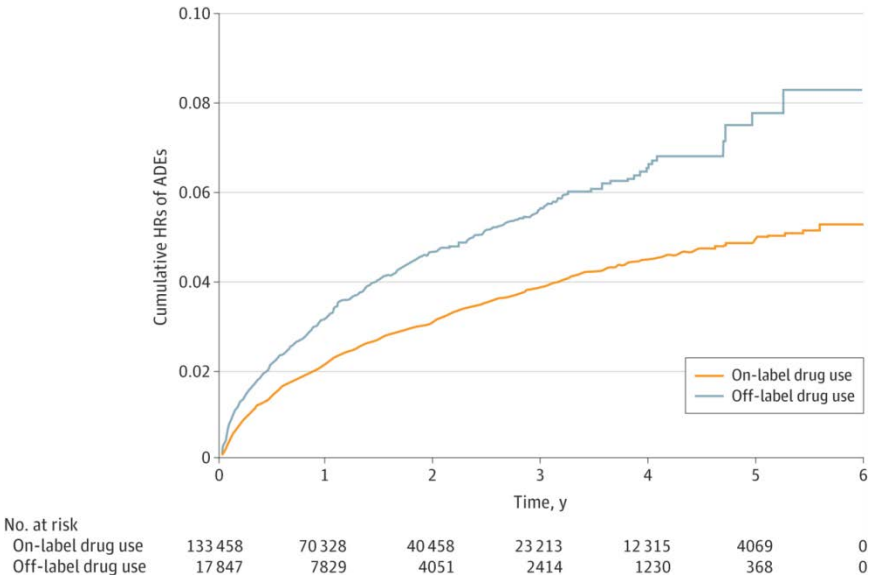

Figure Legend:

Cumulative Hazard Ratios (HRs) of Adverse Drug Events (ADEs) According to On-label and Off-label UseThe comparison has not been adjusted for drug and patient characteristics (HR, 1.48; 95% CI, 1.35-1.64). After adjustment for such variables on multivariate analysis and taking into account the correlation within the patient, the difference between the 2 groups was statistically significant (adjusted HR, 1.44; 95% CI, 1.30-1.60; P < .001).

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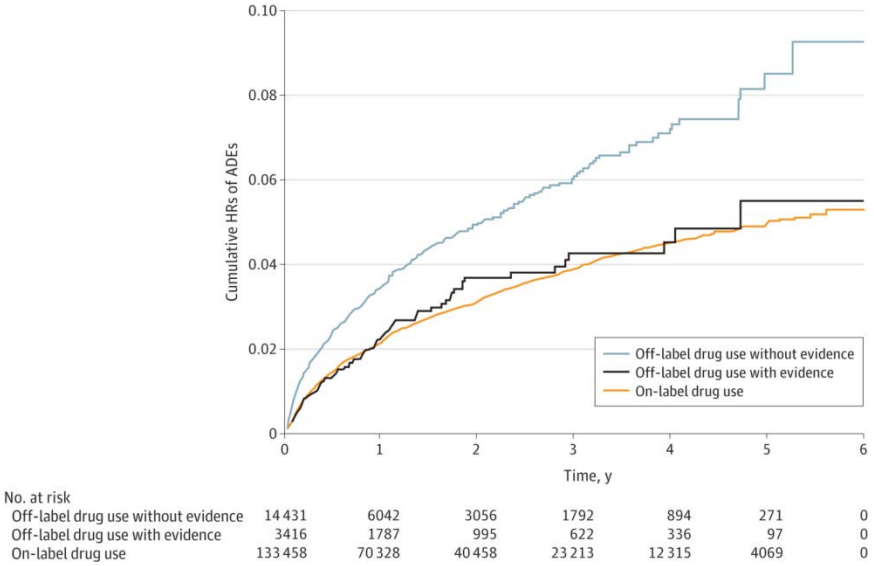
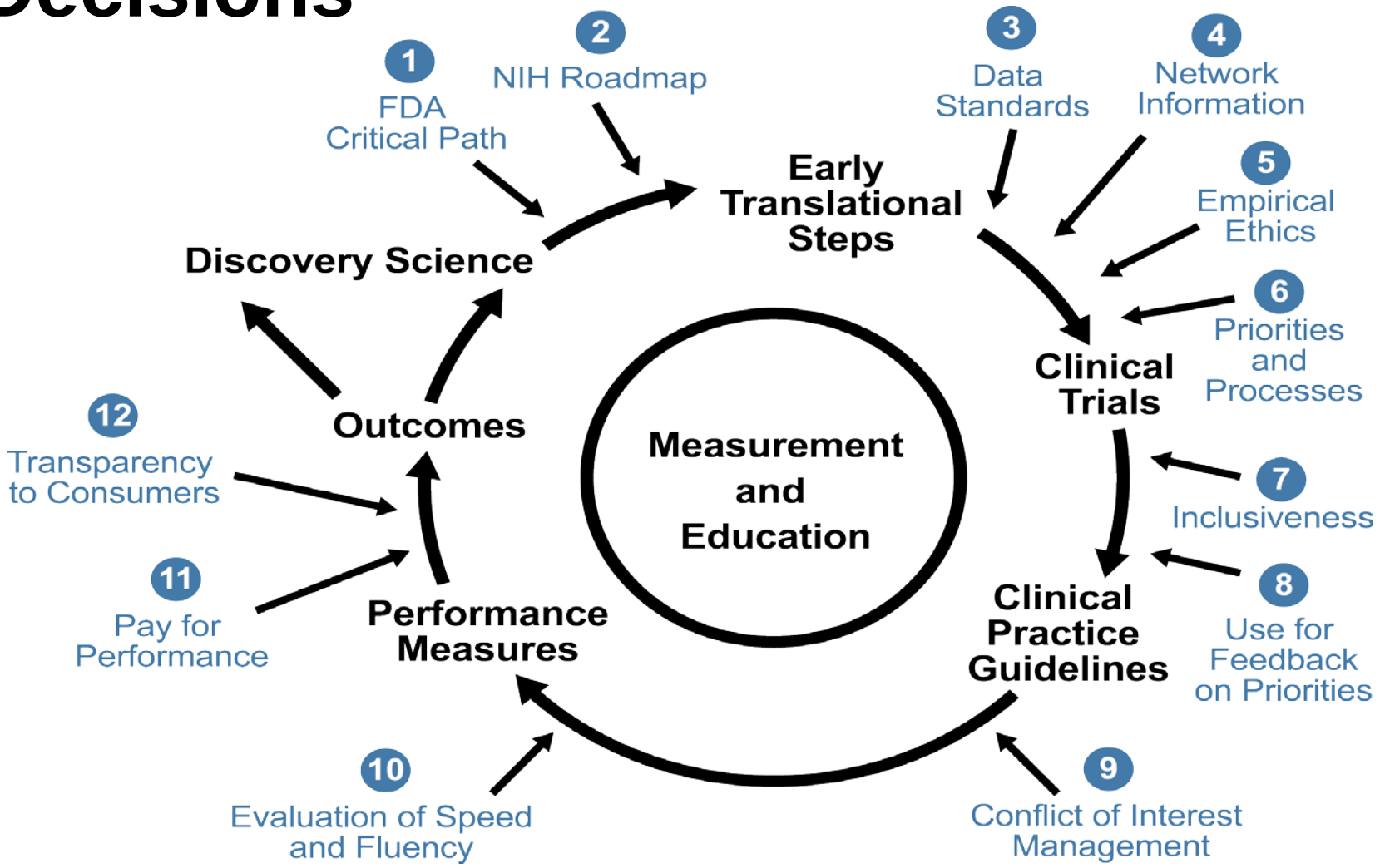


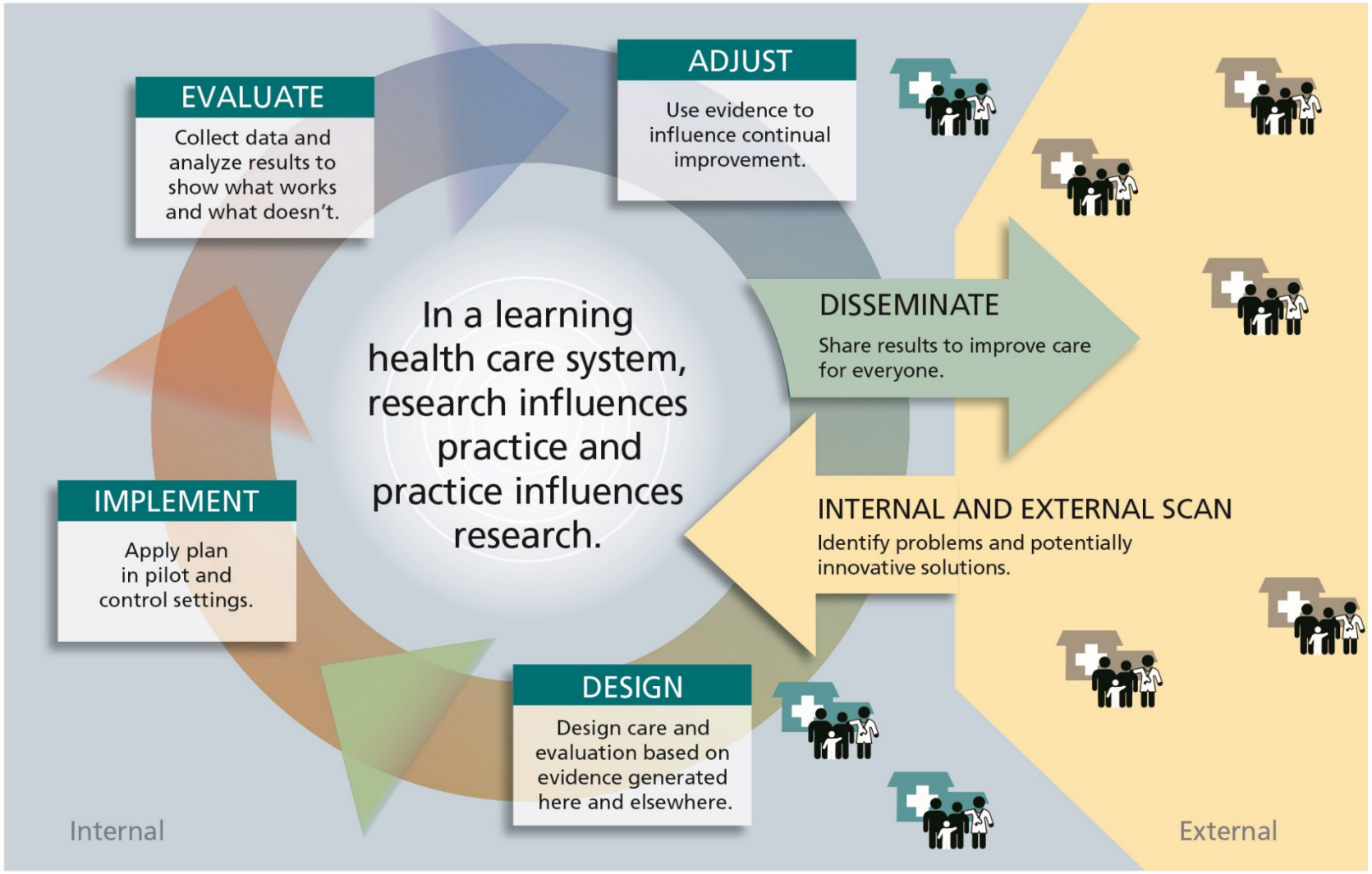
Figure Legend:

Cumulative Hazard Ratios (HRs) of Adverse Drug Events (ADEs) According to On-label and Off-label Use With and Without Strong Scientific EvidenceThe comparison has not been adjusted for drug and patient characteristics. The unadjusted HRs (95% CI) for off-label use with and without strong scientific evidence were 1.04 (0.84-1.30) and 1.62 (1.45-1.80), respectively. After adjustment for such variables on multivariate analysis and taking into account the correlation within the patient, the adjusted HR (95% CI) for off-label use with and without strong scientific evidence were 1.10 (0.88-1.38; P = .40) and 1.54 (1.37-1.72; P < .001), respectively.

Generating Evidence to Inform Decisions

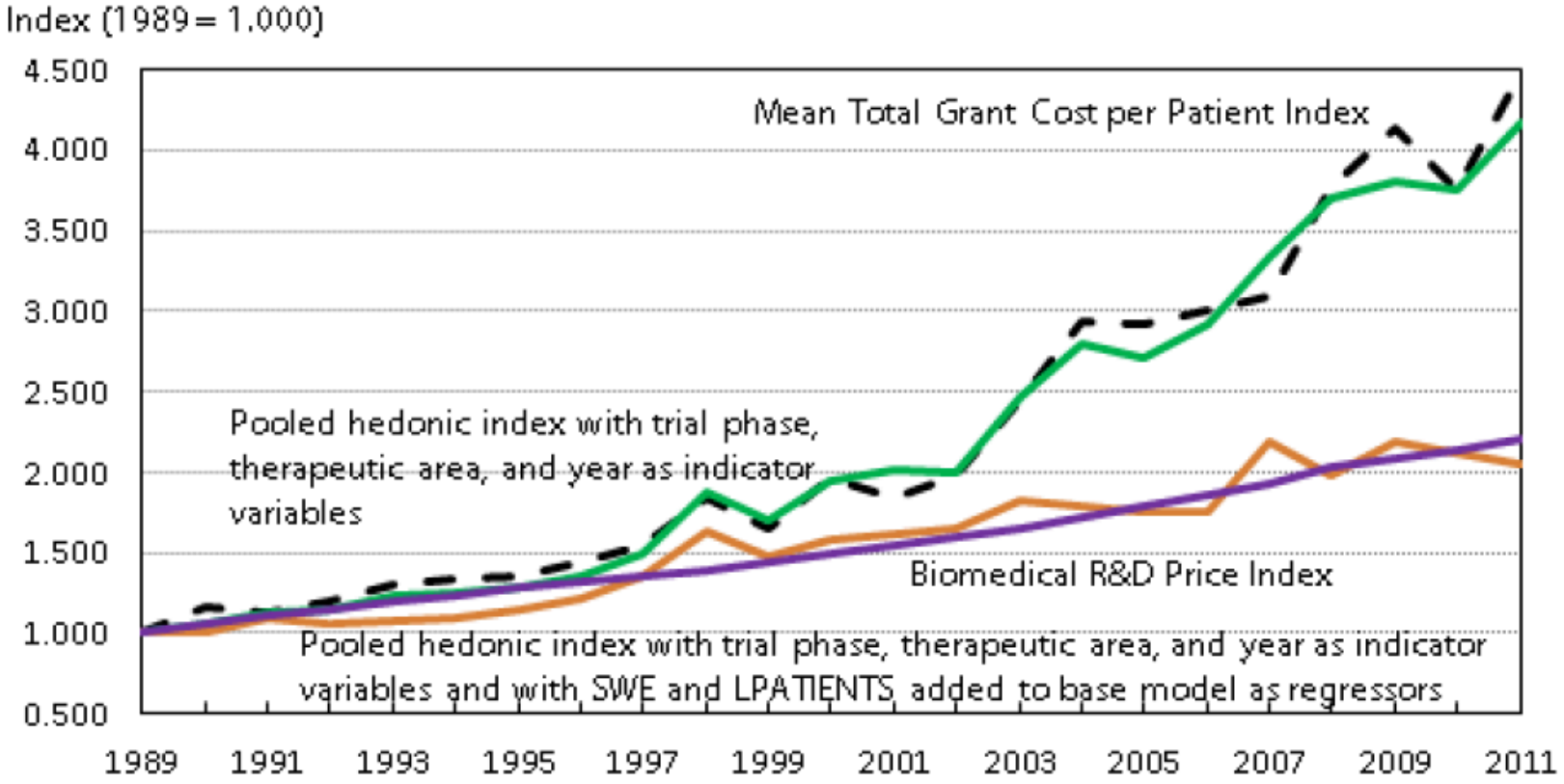


Learning health care systems



Trial Hyperinflation

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

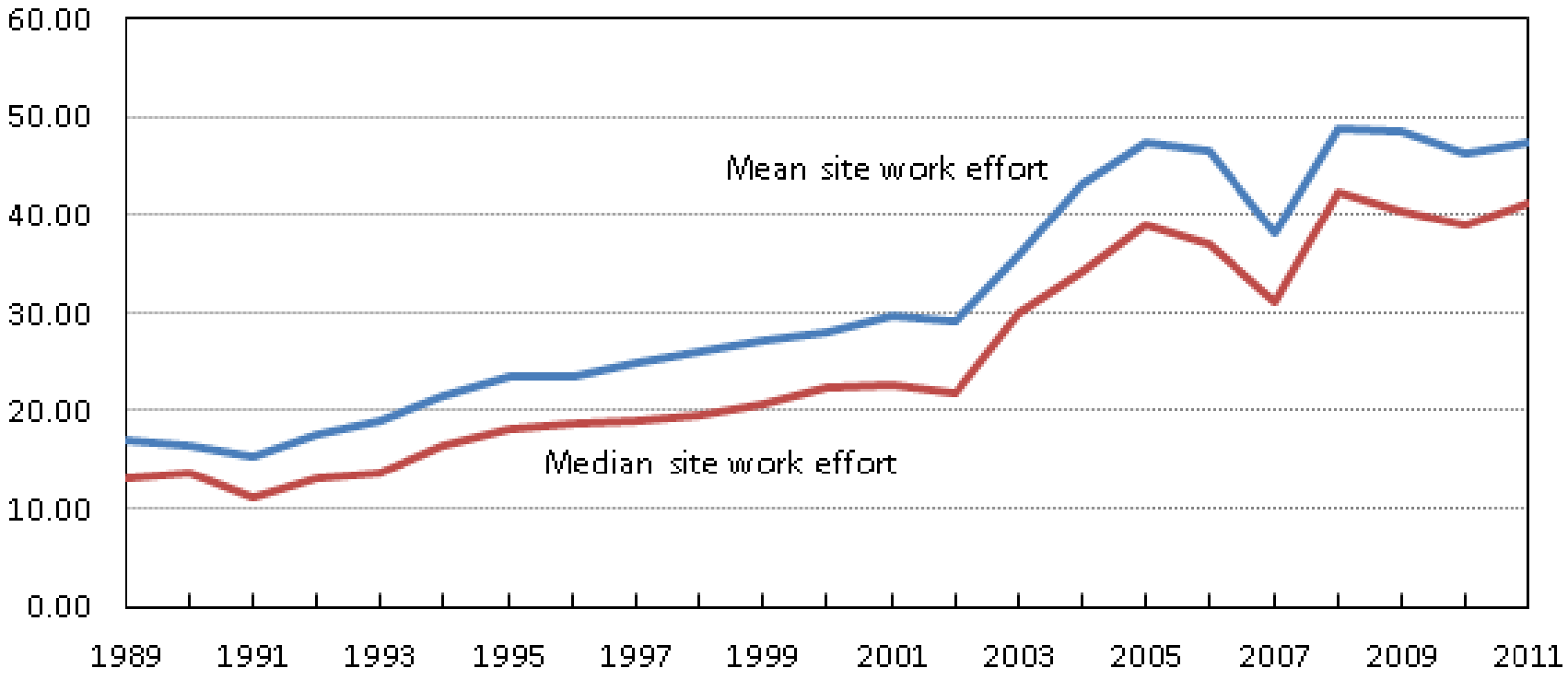


Source: Authors' calculations based on Medidata Solutions, Inc.'s, PICAS® database.

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

The Driver is Complexity

Figure 1. Mean and median site work effort, 1989–2011



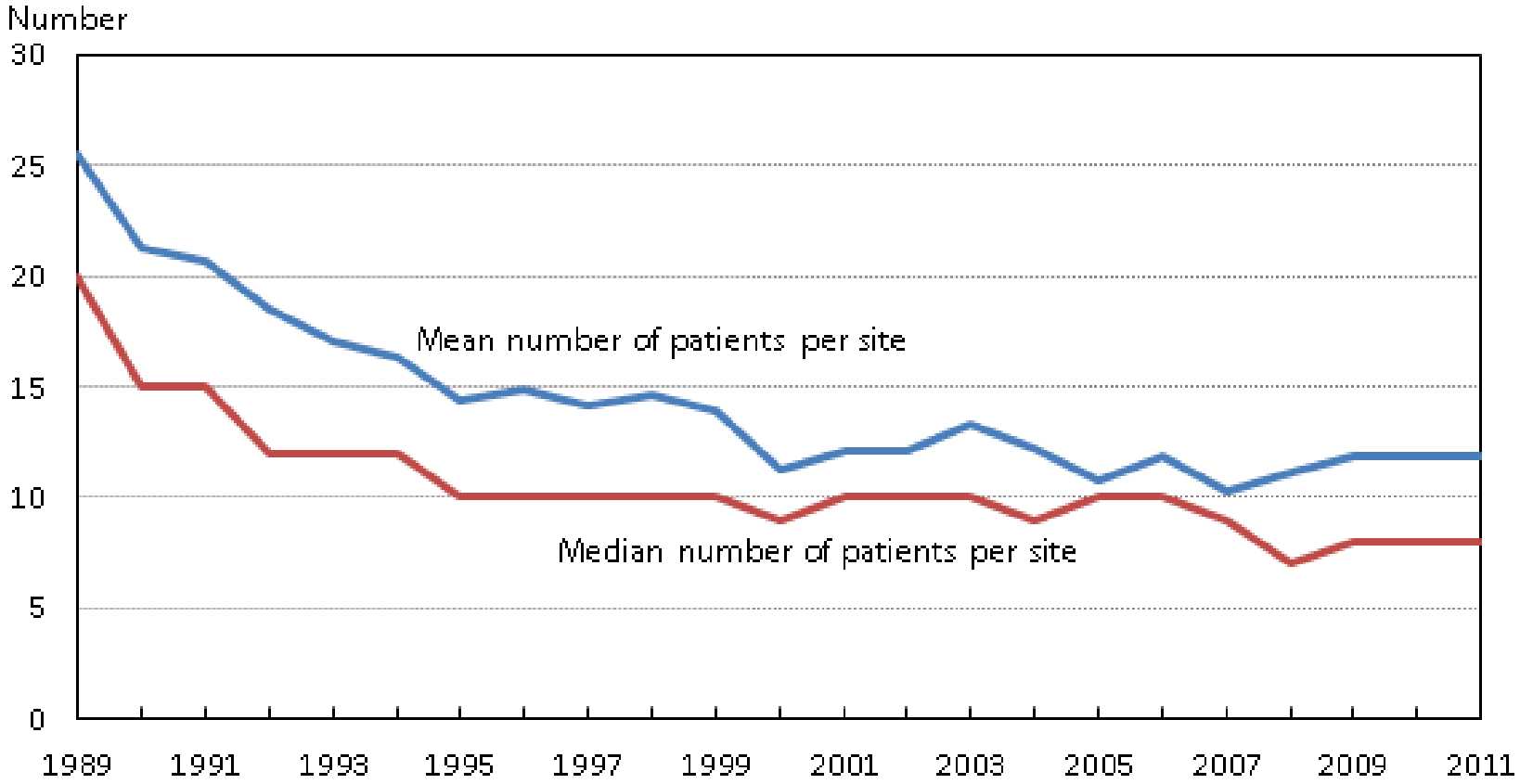
[1] RVUs = relative value units (see text); WEUs = work effort units (see text).

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

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

Sponsors See – Pay More, Get Less

Figure 2. Mean and median number of patients per site, 1989–2011



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Don’t unnecessarily restrict enrollment in trials (Billy Dunn)

- Examine enrollment criteria, especially exclusion criteria, critically. Don’t include things in a knee jerk fashion.
- Think about the parameter, ask yourself do you need it, and eliminate it if possible.
- Ensure a strong justification for those that remain. Define your populations as broadly as is reasonable.
- Think ahead about external generalizability.
- Recognize that we are increasingly interested in inclusive enrollment and we want to be able to describe subpopulations.

Neurological diseases are not well understood (Billy Dunn)

- **While it is understandable that folks are interested in devoting valuable and limited resources to trials that have the capacity to contribute to approval of a new drug, too often we're shooting in the dark or following the latest trendy molecular characteristic that is viewed in isolation, rather than recognizing the pressing need for a comprehensive pathophysiological understanding of these diseases in order to inform subsequent larger trials.**
- **Committing resources to achieve this understanding of the diseases should ultimately result in more efficient demonstration of larger and more well-targeted effects.**
- **Industry has shifted to an emphasis on small trials in rare diseases.**
  - We understand that and are eagerly working with companies to accommodate needs, restrictions, and limitations in this area and we are prepared to be as flexible as we can.
-

Concepts from Ellis Unger

- **Clinical trials have traditionally been designed in such a way as to increase efficiency by reducing variability (i.e., controlling/restricting baseline characteristics).**
- **In the end, we receive relatively small trials with numerous inclusion/exclusion criteria – trials that are less generalizable to the 'real world.'**
- **Another concern for companies that drives them to restrict baseline characteristics is that higher-risk patients experience more (serious) adverse events, and they'd rather not have to deal with them.**

Concepts from Ellis Unger

- **Making trials more inclusive: By making trials more inclusive, we ultimately receive a richer database that is more informative with respect to various subgroups, and also more representative of the 'real world.'**
- **And by enrolling some patients at higher risk, we can glean important information about the safety profile of the drug, as the drug would likely be used in higher risk patients in the 'real world.'**
- **With more inclusiveness, however, comes increased heterogeneity, such that sample size must be larger.**
- **But the cost of enrolling greater numbers of patients could be offset by reducing the complexity of the trials, i.e., reducing cost per patient.**

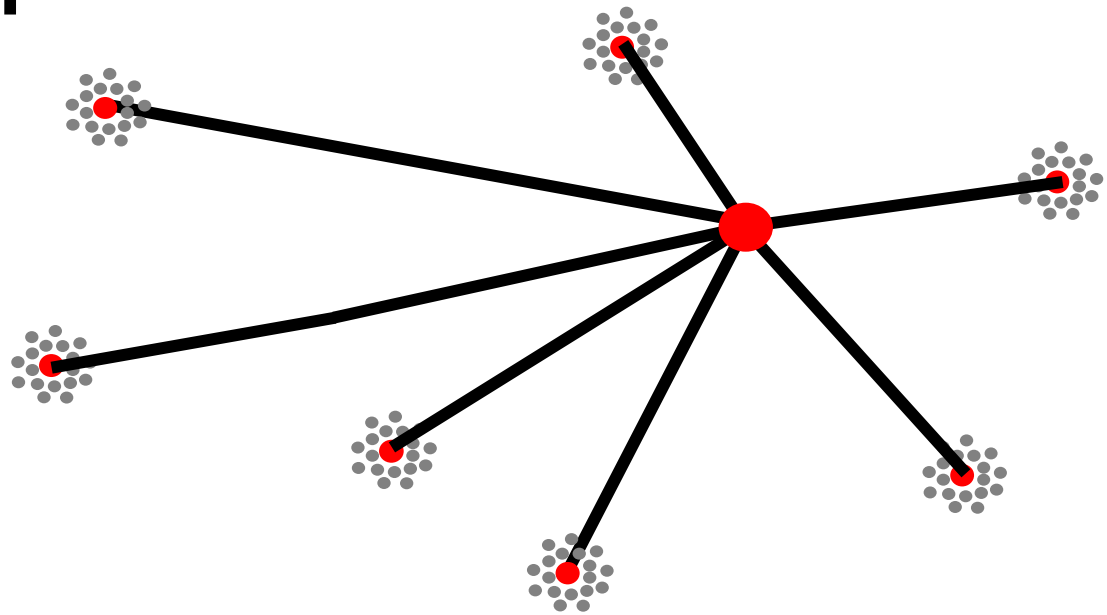
Reducing cost—Ellis Unger

- **We don't really need 12,000 individual CBCs to determine whether a drug causes neutropenia.**
- **And we don't really need to collect non-serious adverse events on every single patient in a large trial.**
  - Yes – we care about rare, serious, medically important adverse advents, but we can obtain that information by eliciting serious adverse events from all patients, while collecting non-serious adverse events and comprehensive laboratory data from only a subset (for example, US patients, or US plus EU patients, or the first n% of patients enrolled).

Reducing cost- from Ellis Unger

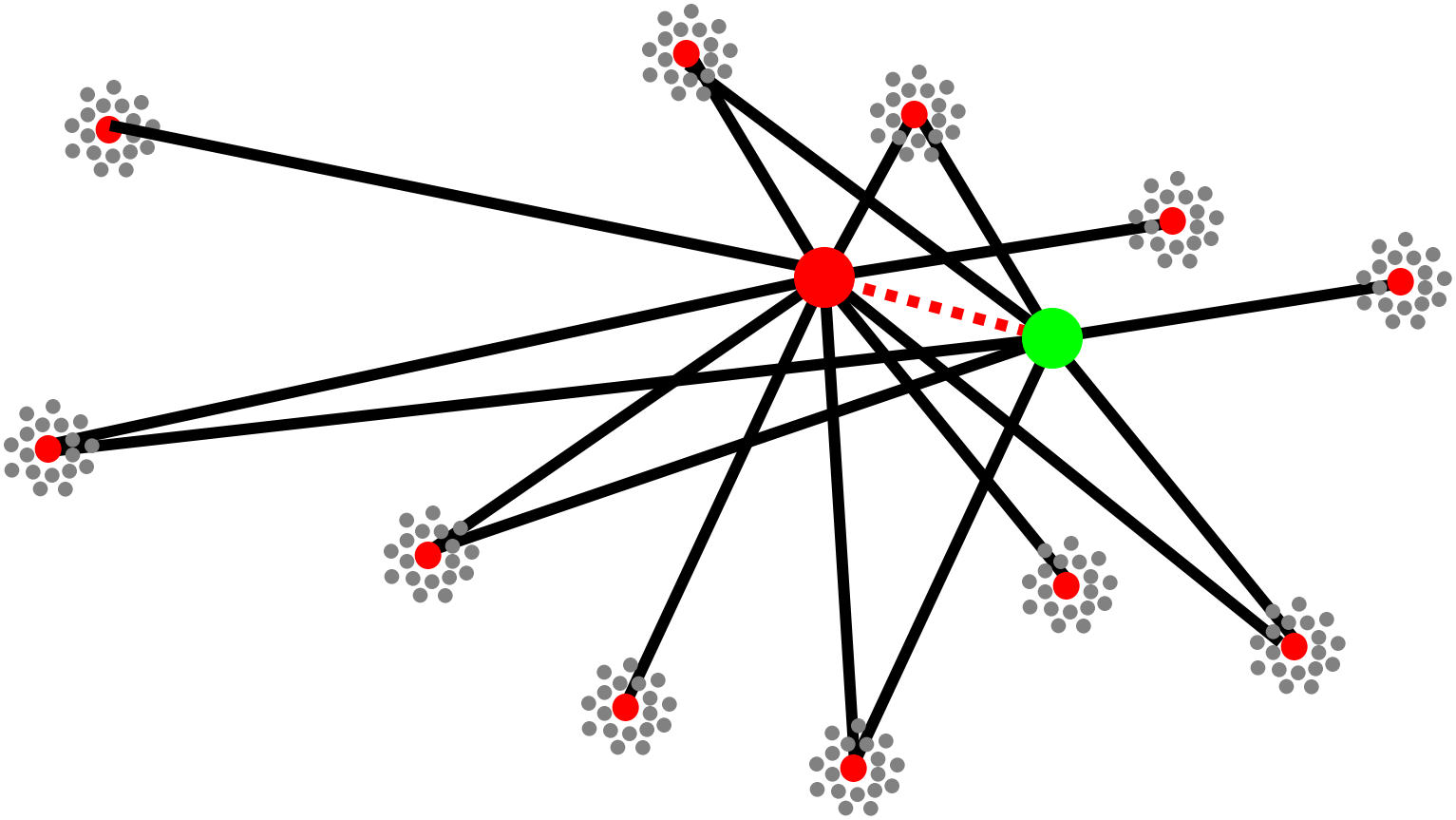
- A complementary approach would be to schedule patient visits less frequently, and some might say that patients who are monitored less frequently are more representative of the 'real world.'
- Reduced frequency of monitoring could also be considered for a subset of the patients.

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



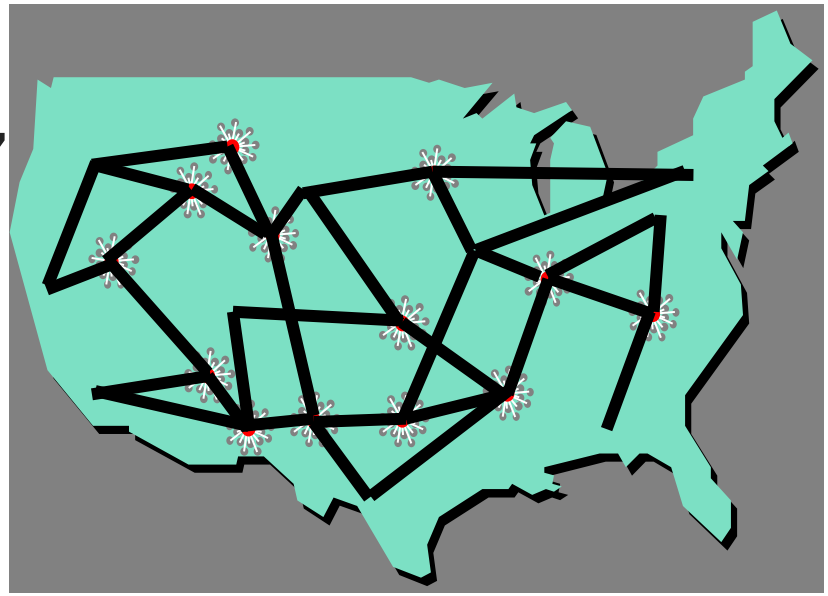
- Hub & spoke model
- Top-down decision-making
- Sites operated independently

Interoperable Networks Share Sites and Data

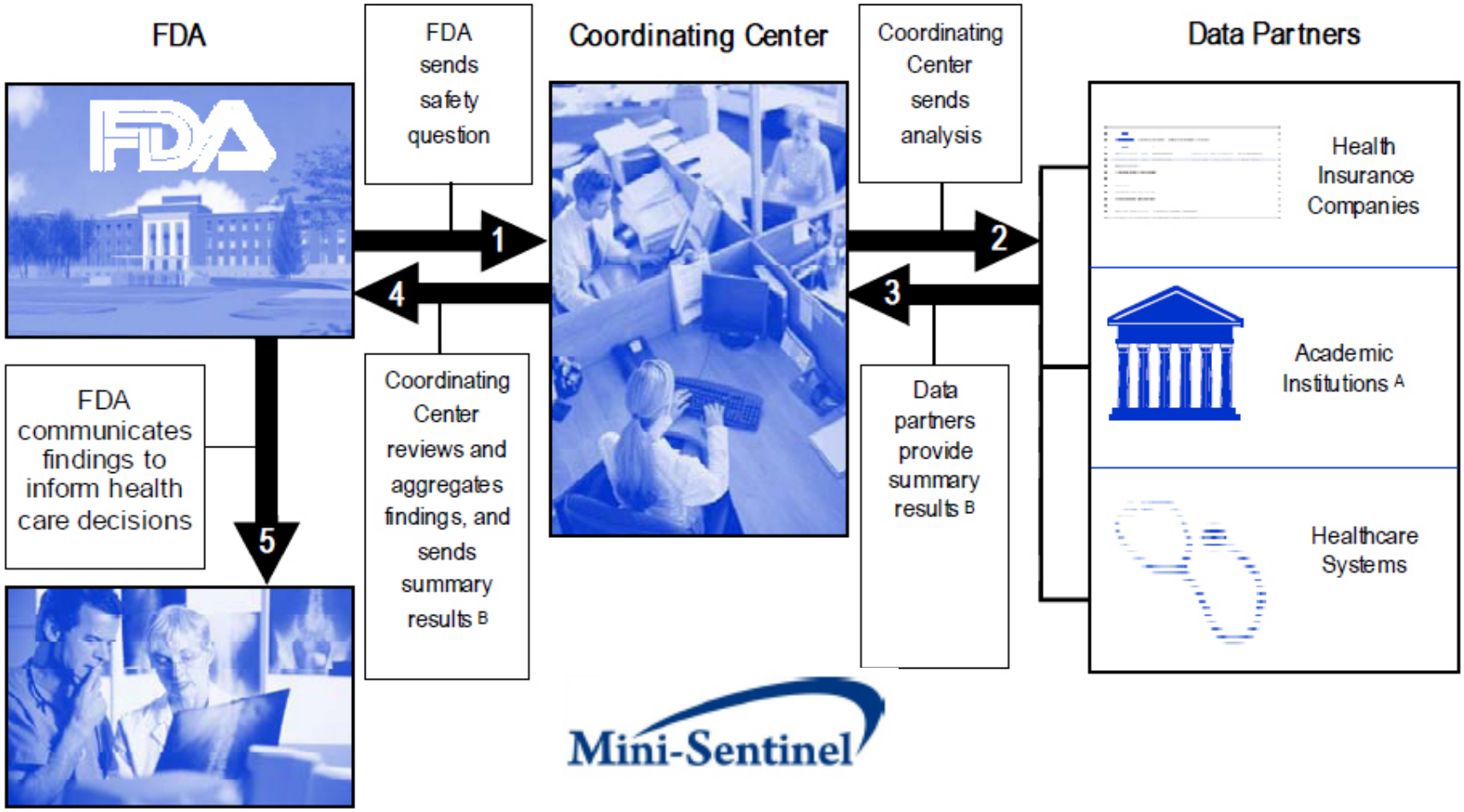


Researchers and funders now recognize the value in integrating clinical research networks

- Linking existing networks means clinical studies and trials can be conducted more effectively
- Ensures that patients, physicians, and scientists form true “communities of research”
- Creates “interoperability” – networks can share sites and data



Sentinel: Distributed Data Networks
(Over 150,000,000 people included)



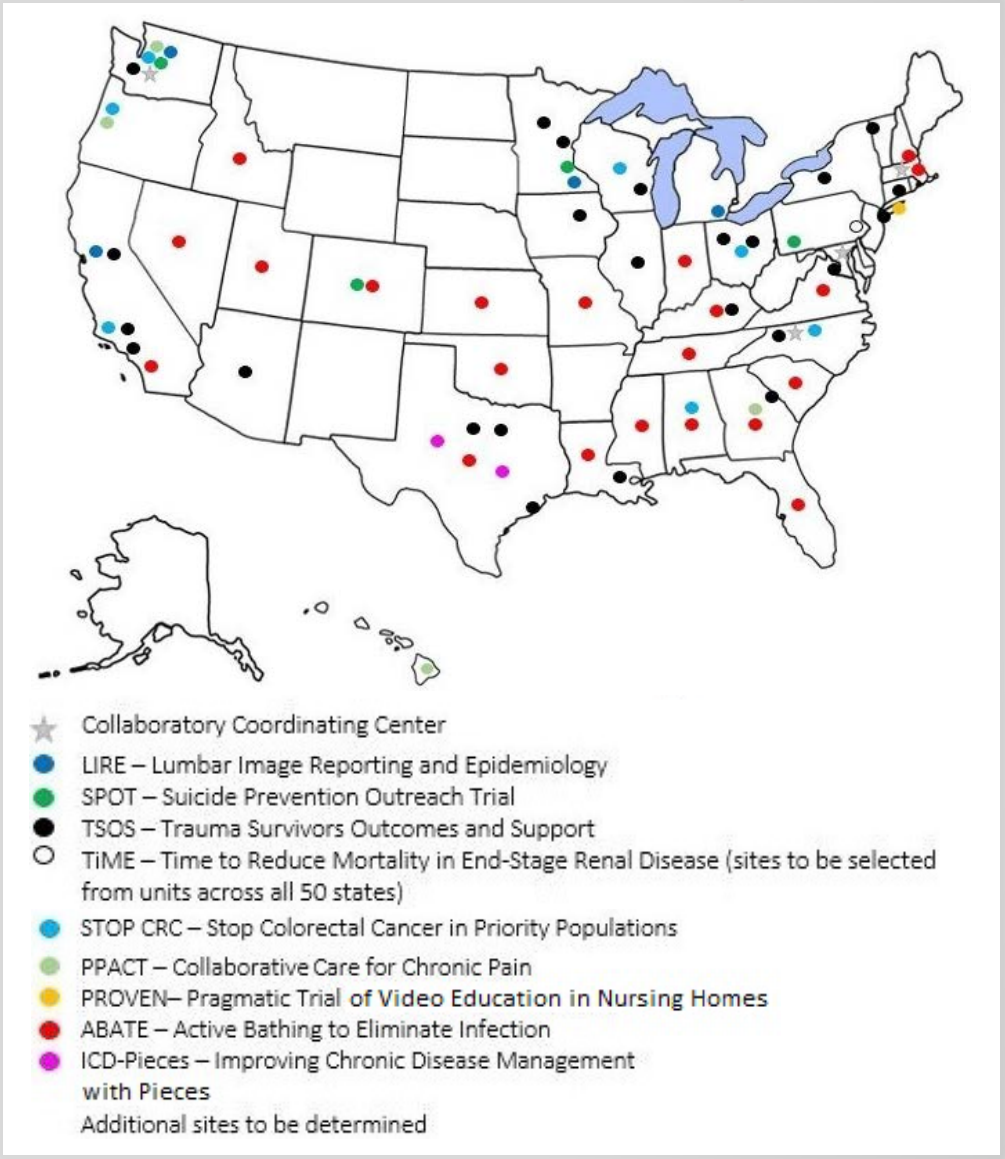
FDA, The Sentinel Initiative
July 2010

Demonstration Project Overview-NIH Healthcare Systems Research Collaboratory

10 Demonstration Projects spanning 12 NIH institutes and centers

1-year planning phase (UH2)

Implementation phase (UH3)



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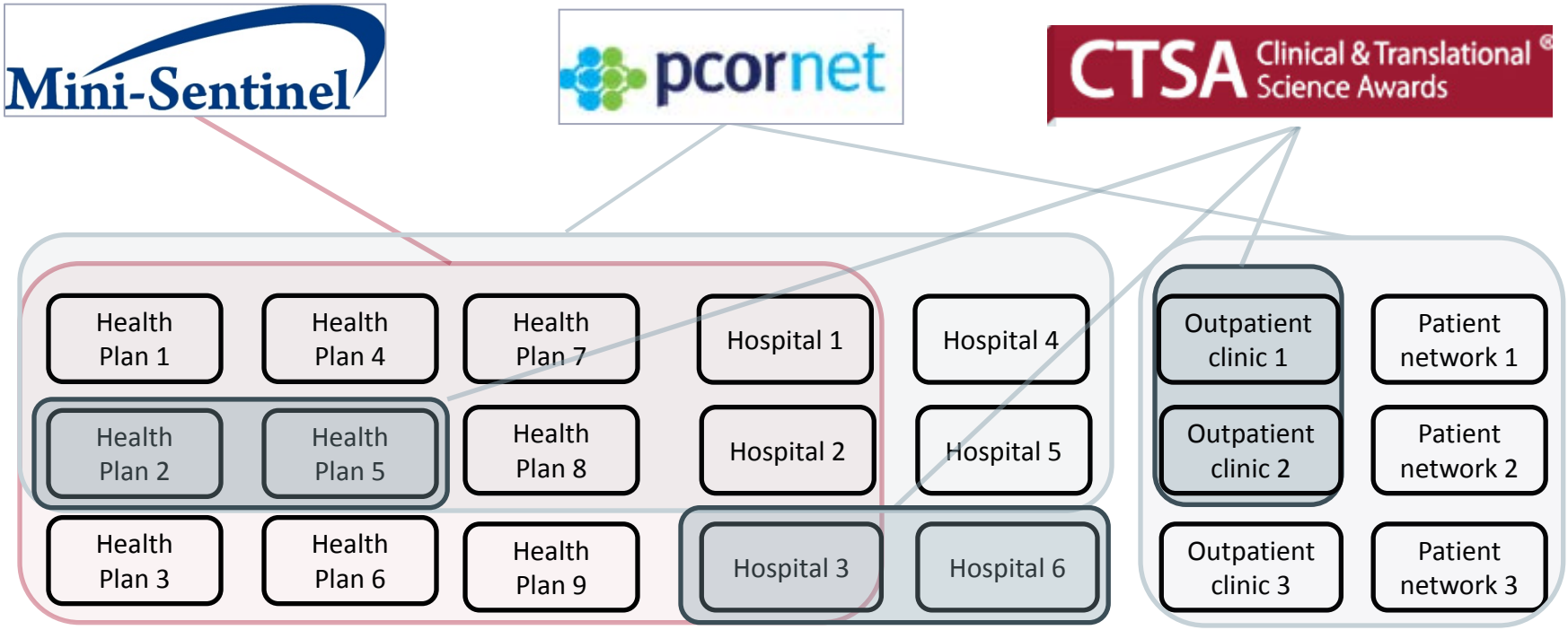
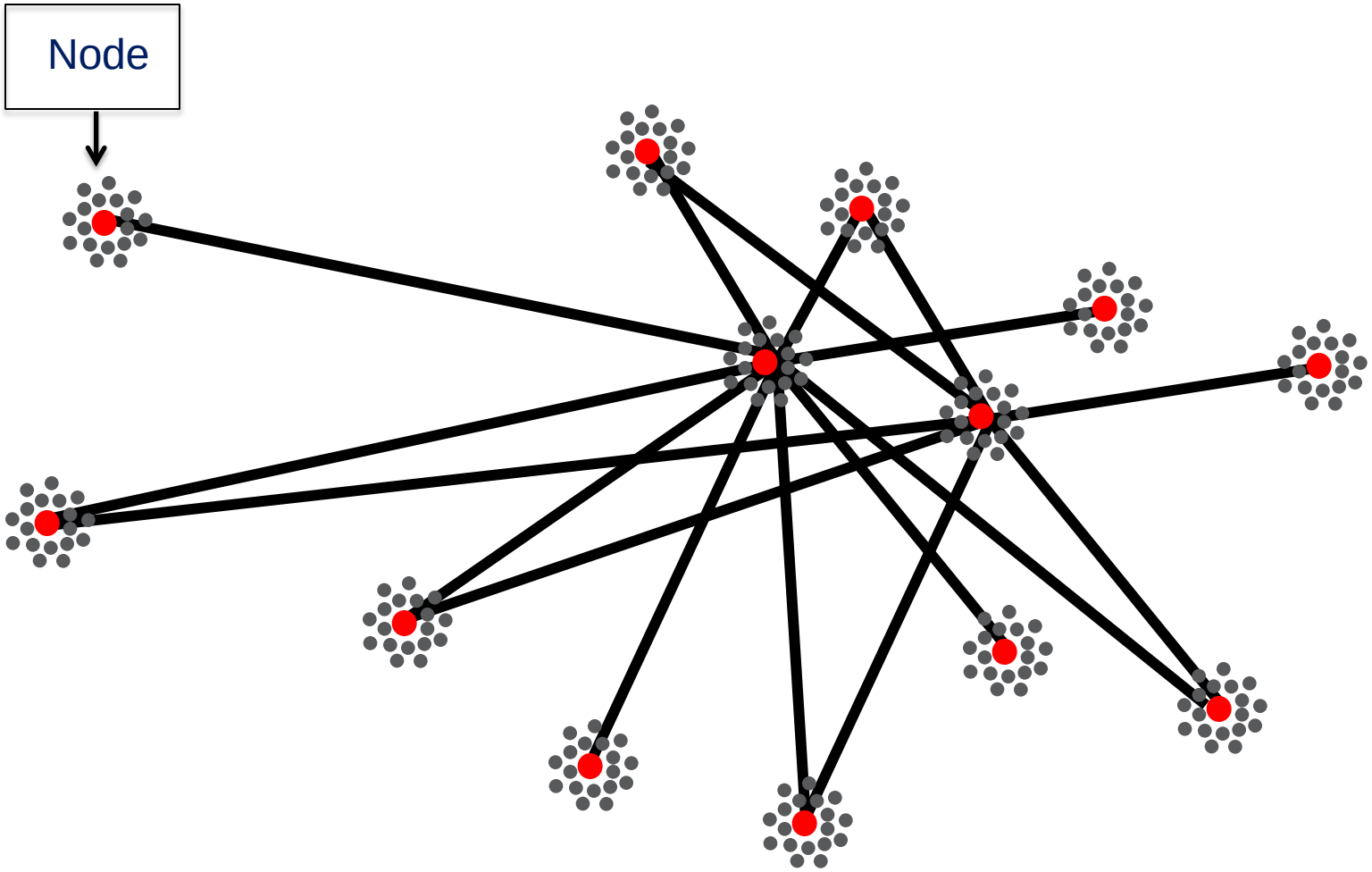
Learn more about @joevselby's views on #healthdata in research: buff.ly/1Q3KeR5 via @Health_Affairs #hdpalooza

Critical Partners in a National Infrastructure

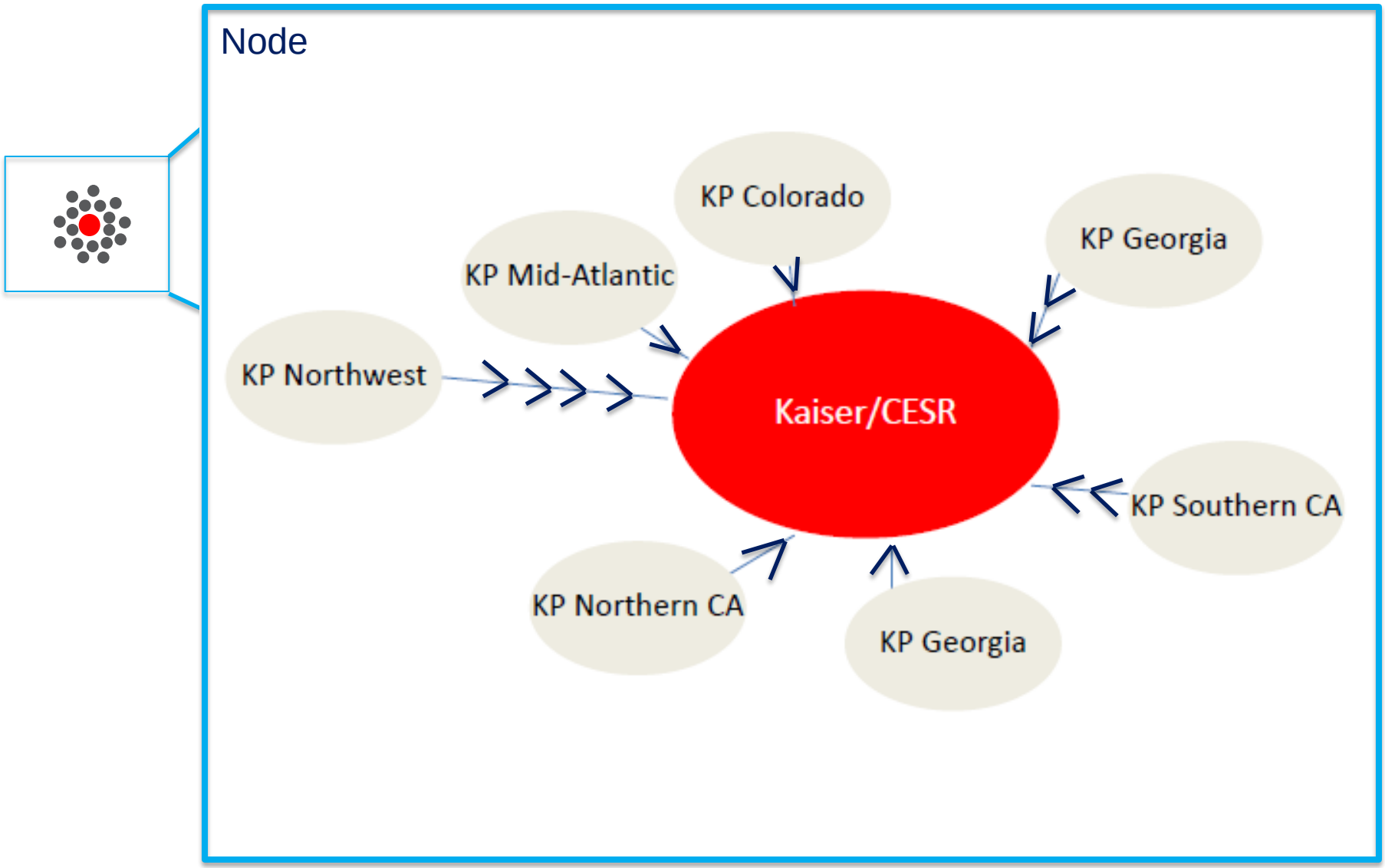


- Each organization can participate in multiple networks
- Each network controls its governance and coordination
- Networks share infrastructure, data curation, analytics, lessons, security, software development
- Other potential partners: disease or treatment-specific networks; :

Neural Network
Share Sites and Data



Neural Network
Nodes are Clusters of Accessible Data



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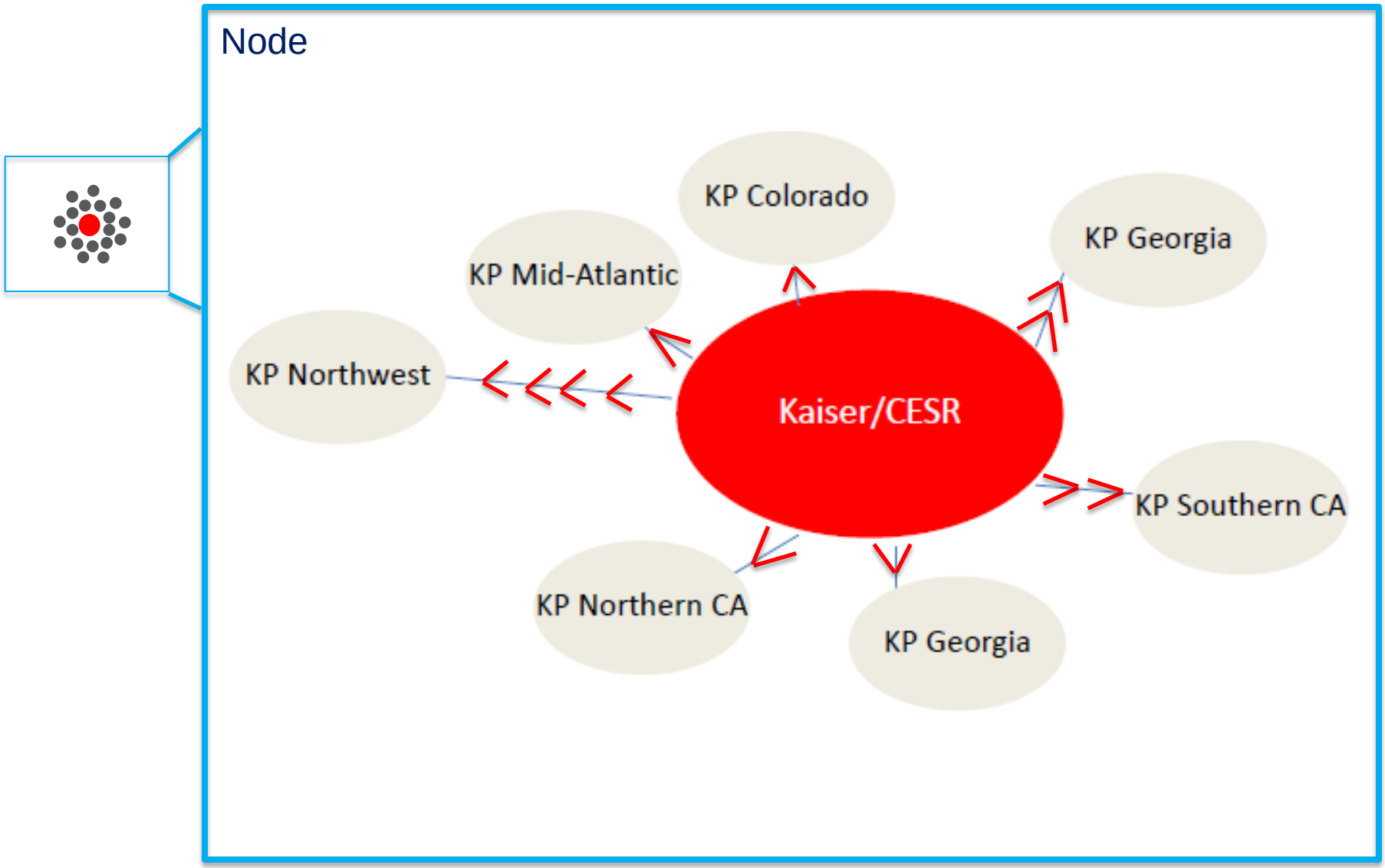
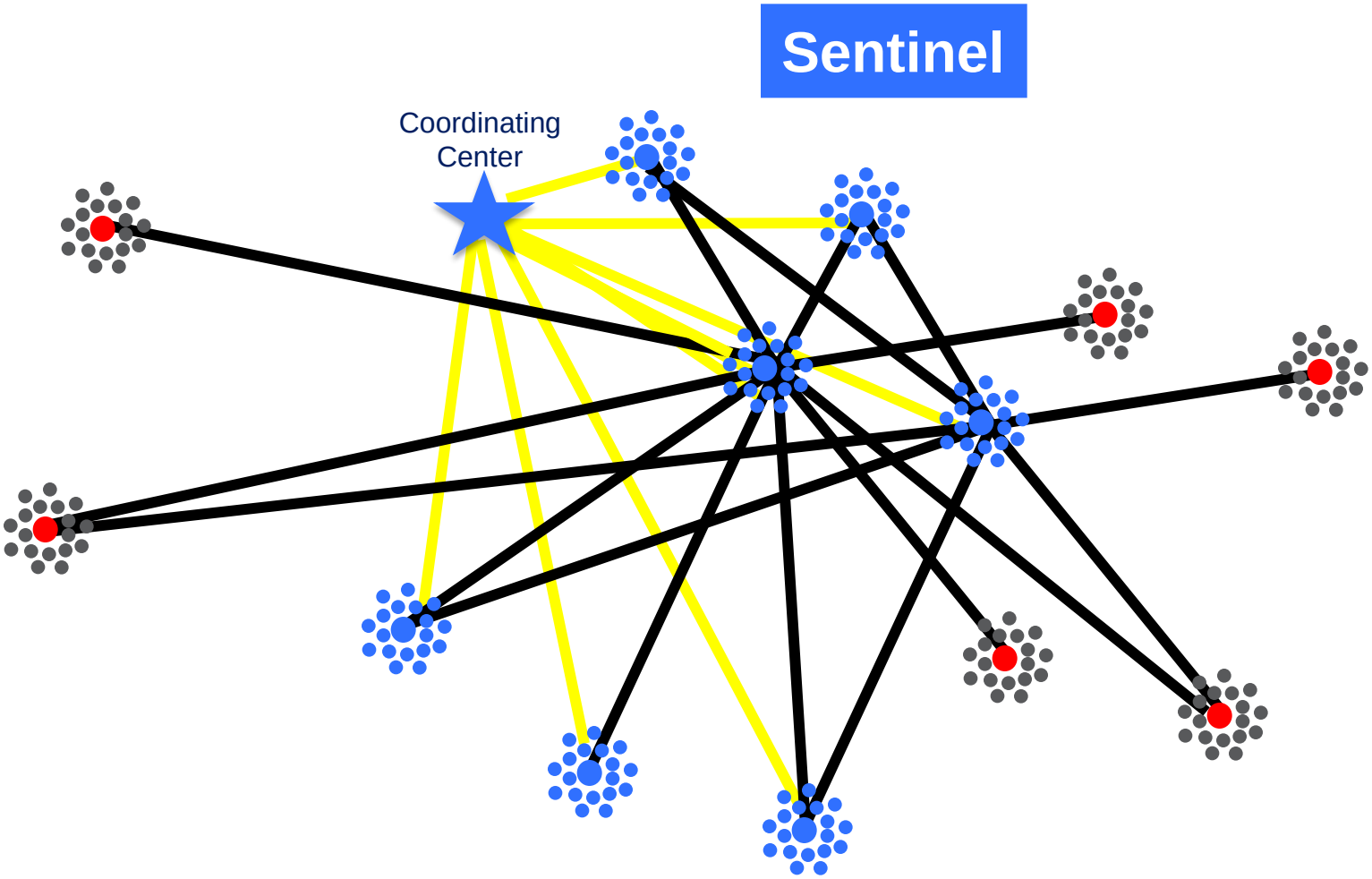
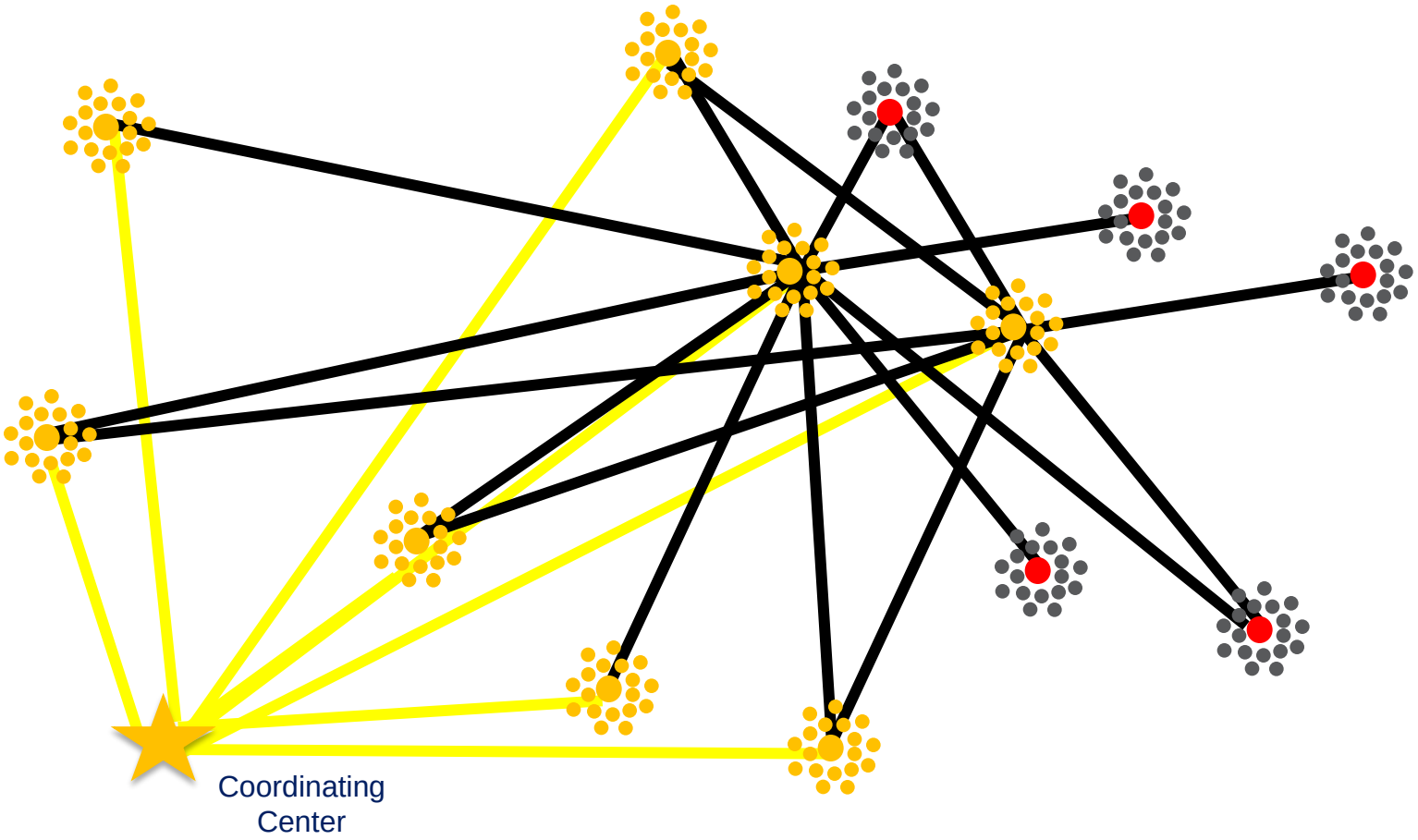


Neural Network
Share Sites and Data



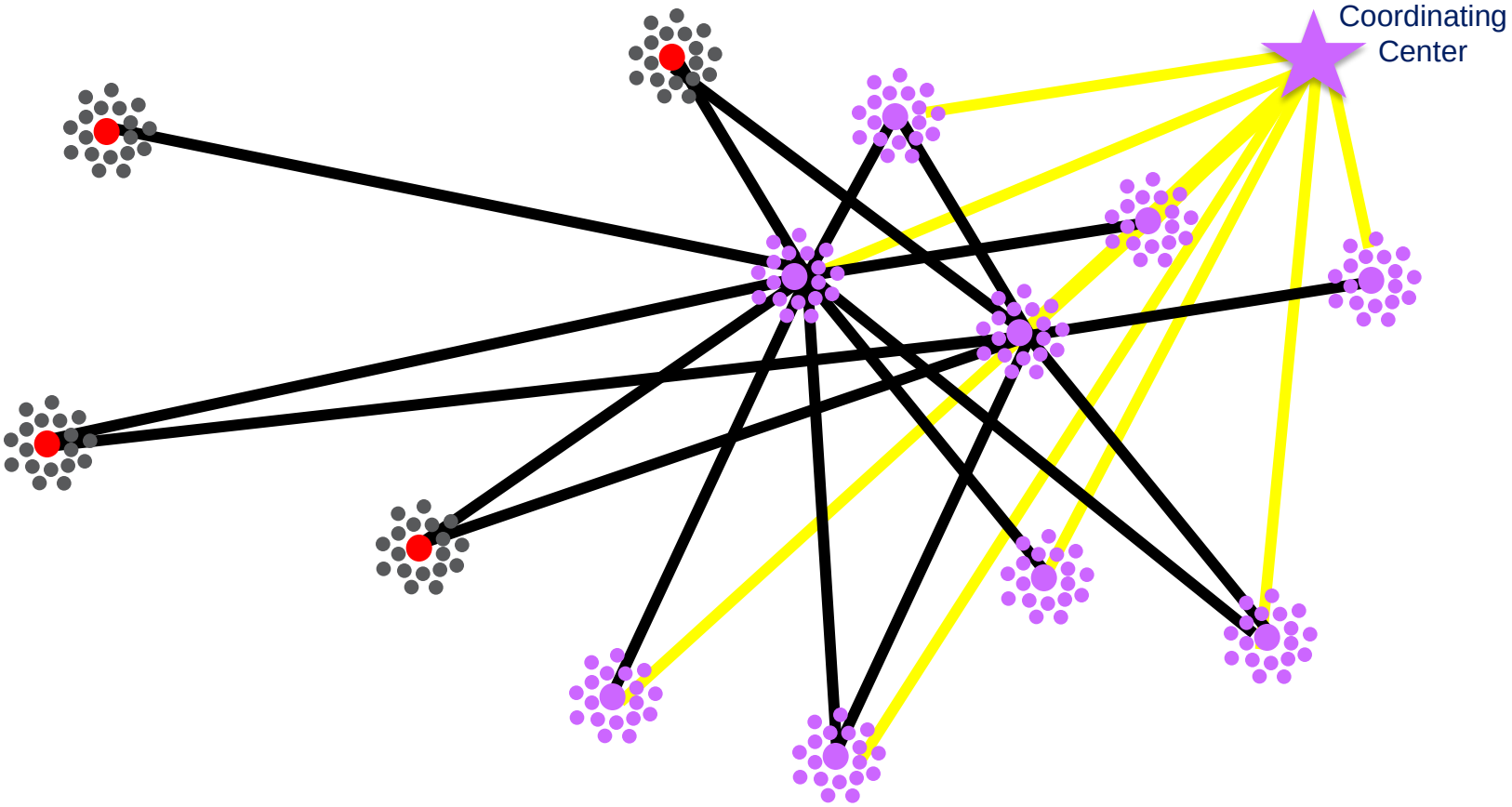
Neural Network
Share Sites and Data

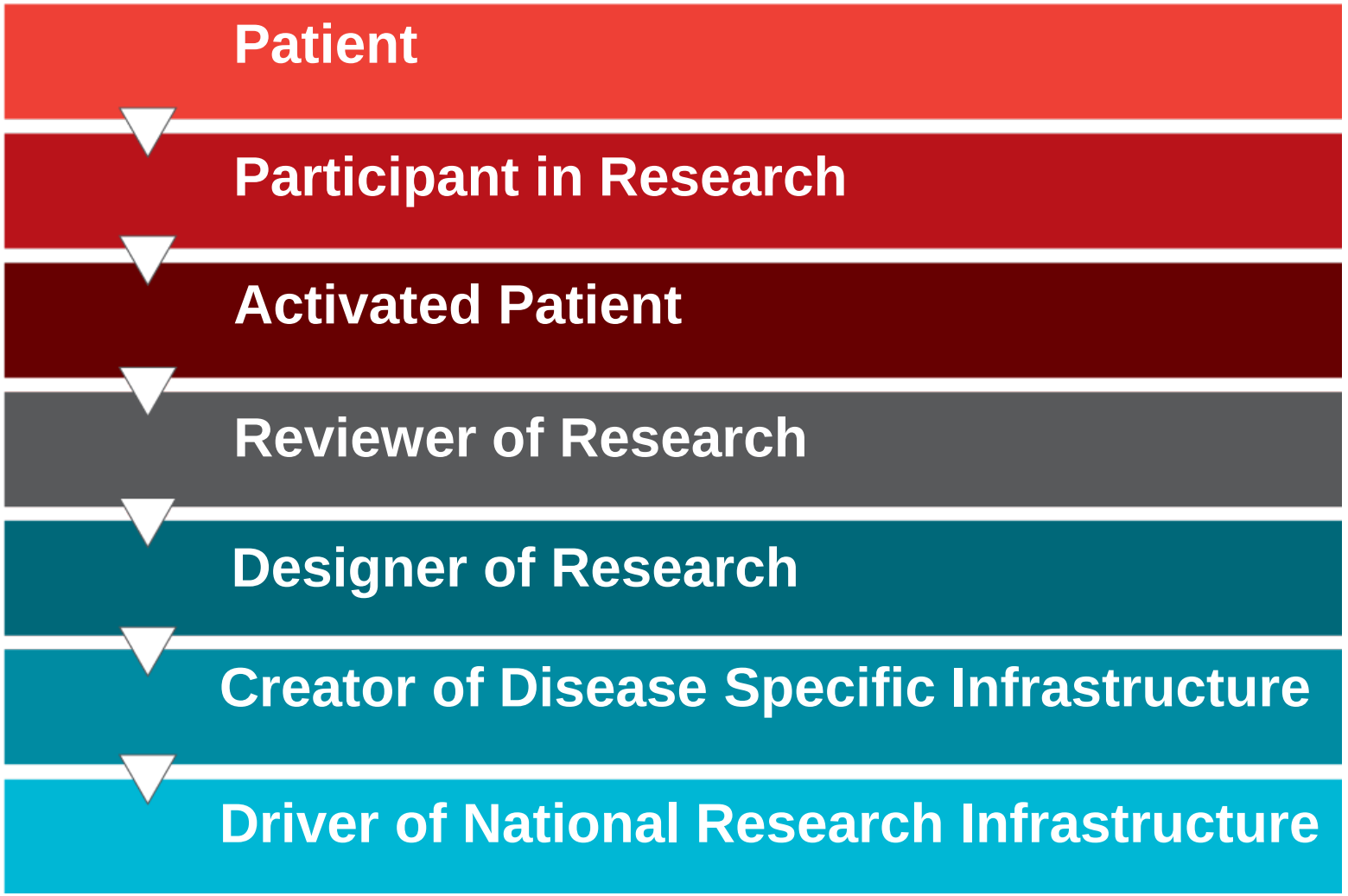
National Device Evaluation System



Neural Network
Share Sites and Data

PCORnet




Patient
Participant in Research
Activated Patient
Reviewer of Research
Designer of Research
Creator of Disease Specific Infrastructure
Driver of National Research Infrastructure

The U.S. Precision Medicine Initiative

“And that’s why we’re here today. Because something called precision medicine … gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen.”

President Barack Obama

January 30, 2015

We Want you to help us Develop a National Evidence Generation System