Enhancing the Application of Real-World Evidence in Regulatory Decision-Making

Public Conference

March 3 & 4, 2016

The Washington Plaza Hotel

Regulatory Applications of Real World Evidence: Observational Data

Jonathan P Jarow, MD
Office of Center Director
CDER

Evidence from Clinical Experience

- Definition
  - Evidence obtained from observational studies or clinical experience
  - Patient registry's, electronic health records, claims data, social media, etc.
- Uses
  - FDA Regulatory
    - Safety & Efficacy
  - Healthcare economic information: payers
  - Research: academic and drug development

Statutory Basis of FDA Regulatory Standards: Substantial Evidence

- Efficacy versus safety
- Drugs versus devices

Spectrum of Evidence

- Randomized controlled trials
- Pragmatic trials
- Prospective observational trials
- Retrospective observational trials
- Registries
- Case series/reports

History

- Safety
  - NMEs
  - Sentinel
- Efficacy
  - Rare diseases
  - Devices
- Labeling changes/updates

Use of Registries for Rare Diseases

- Lumizyme for Pompe disease –survival data from an international Pompe disease registry in patients with infantile-onset disease
- Carbaglu for N-acetylglutamate synthase deficiency –data on plasma ammonia level reductions in a case series
- Cholbam for bile acid synthesis disorders –data on growth, survival, and reduction in laboratory parameters of cholestasis in a case series
- Glucarpidase for MTX toxicity- data on a ~20 patient subset within what was essentially a treatment protocol at NIH
- Metreleptin for Leptin deficiency/lipodystrophy- case series out of NIH, similar to glucarpidase, was essentially a treatment protocol

Labeling Changes based on Real World Evidence

- High-dose influenza vaccine versus standard dose
  - Retrospective cohort study of Medicare claims
  - High-dose: 929,730
  - Standard dose: 1,615,545
- Rabies vaccine dose schedule
  - Standard five dose versus four dose used during drug shortage
  - Change in CDC recommendations

CURE-NTD

(Collaborative Use Repurposing Engine)

- Repurposing of drugs for neglected tropical diseases
- Website/mobile app
- Global reporting tool for cases
- Searchable curated database
- Fuel drug development for neglected tropical diseases

Methodology

- Random versus systematic errors versus falsification
- Analysis/review
  - Esophageal cancer and bisphosphonates
  - GPRD database
    - RR 0.96 (0.74-1.25)
    - RR 1.30 (1.02-1.66)

Cardwell JAMA 2010
Green BMJ 2010

Future Needs

- Demonstration projects in US
- Academic research
- Regulatory policy
  - Part 11
  - Part 50
- Federal evidence generation system

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National Medical Evidence Generation System

Melissa Robb

March 4, 2016

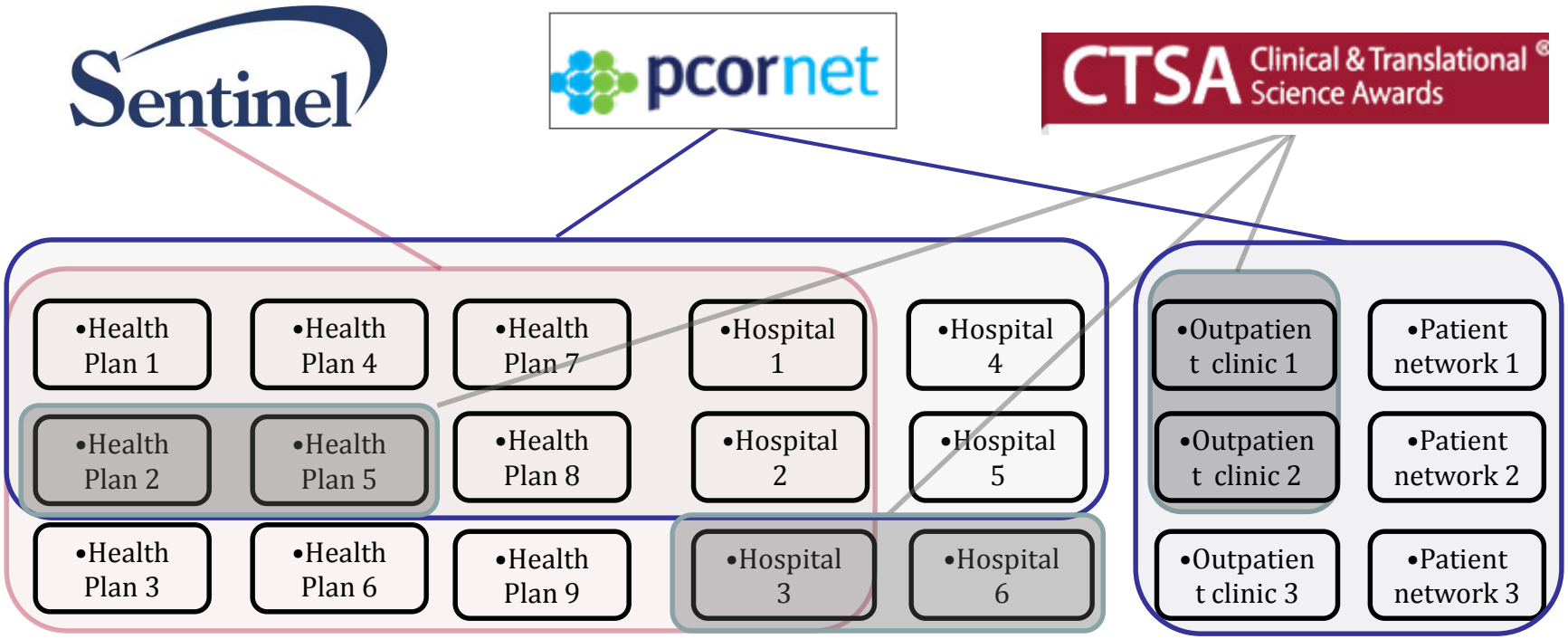
Vision

A national medical evidence generation system that allows for integration of clinical care and clinical research (for those systems and patients willing to participate), that would allow for the conduct of observational and interventional research and surveillance (learning) by leveraging and linking information collected by multiple entities

Call to Action

- Decisions about health and healthcare are best made when informed by high quality evidence
  - Medical product regulation
  - Payment
  - Individual consumer/patient/provider decisions
  - Policies
- Our current system of generating evidence has challenges
  - Generalizability
  - Feasibility
  - Efficiency
  - Sustainability

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

Informed by Ongoing Projects, Including:

- FDA
  - Sentinel Initiative
  - National Device Evaluation System
- NIH Health Care Systems Research Collaboratory
- CTSA
- PCORI-PCORnet
- Reagan-Udall Foundation IMEDS Project
- Precision Medicine Initiative
- VA Million Veteran Program
- Coordinating Efforts—ONC, ASPE

Governance Issues Are Key

- Patient Privacy
- Data Security
- Transparency and Confidentiality
- Access
- Conflict of Interest
- Intellectual Property
- Separate governance structures are likely to have different funding models

Crucial Steps to Progress

- Organize operational systems to enable clinicians, patients, consumers, industry, government, and healthcare systems to participate
- Establish a framework for confidentiality and security
- Adopt a common approach to configuring digital healthcare data
- Eliminate barriers that promote complexity, while ensuring appropriate safeguards
- Ensure that each linked group of projects has appropriate governance in place

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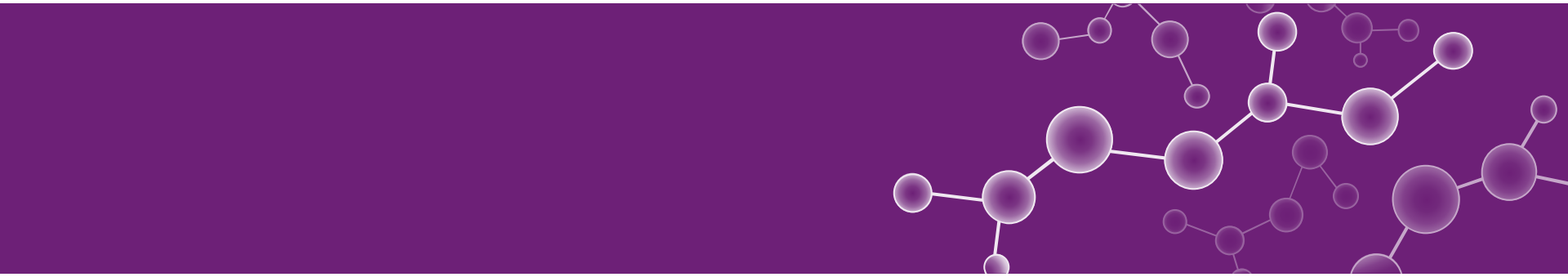
Building a Robust 21st Century Evidence Development Infrastructure

Nancy A. Dreyer
Chief of Scientific Affairs
Quintiles Real-World & Late Phase Research

March 4, 2016

Improve your probability of success™

Getting to a Better Infrastructure



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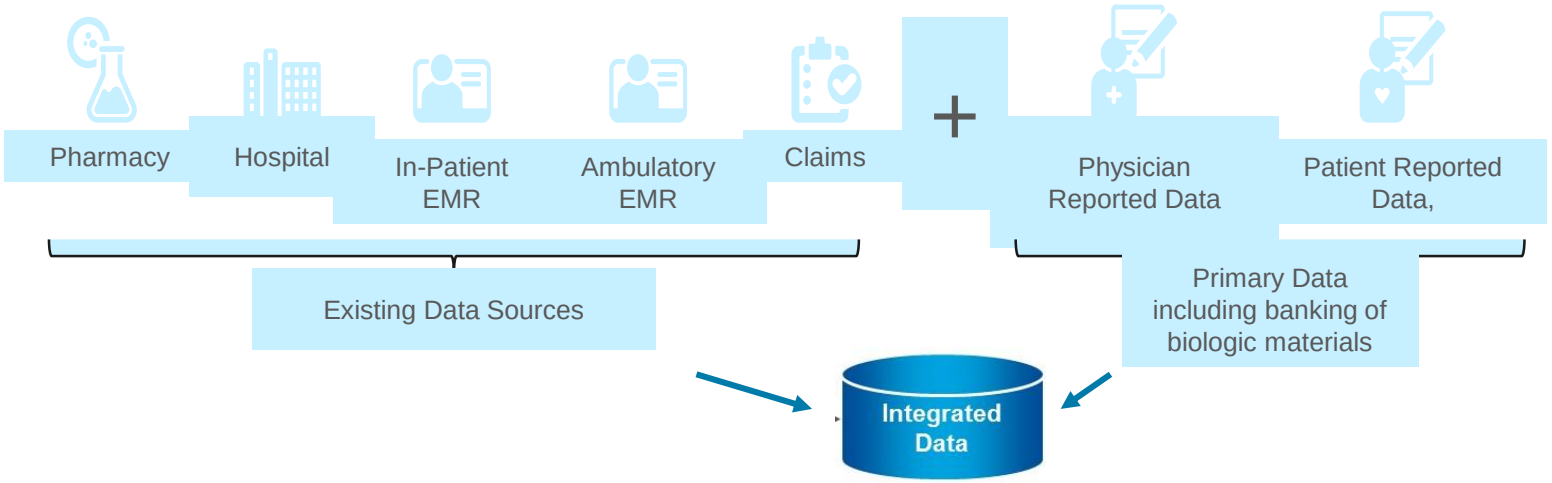
Integrating Multi-Source Data



- **Qualified partners are used on demand**
- **Health care records and health insurance claims can be individually linked to prospectively collected data**

Thorax Online First, published on March 6, 2014 as 10.1136/thoraxjnl-2014-205259

AUDIT, RESEARCH AND GUIDELINE UPDATE

Obtaining real-world evidence: the Salford Lung Study

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ABSTRACT

We need to assess clinical treatments in real-life
outside of randomised controlled trial
RCT (pRCT) data can supplem
effectiveness informat decisions.
Electronic he ncurrent safety
moni ithout direct patient
ised study populations in pRCTs.
Study is the world's first phase III pRCT
ma and chronic obstructive pulmonary disease (COPD), which aims to randomise over 7000 patients. This paper describes the hurdles overcome and the enormous effort and resource required to establish this comparative effectiveness study of a prelicence intervention.

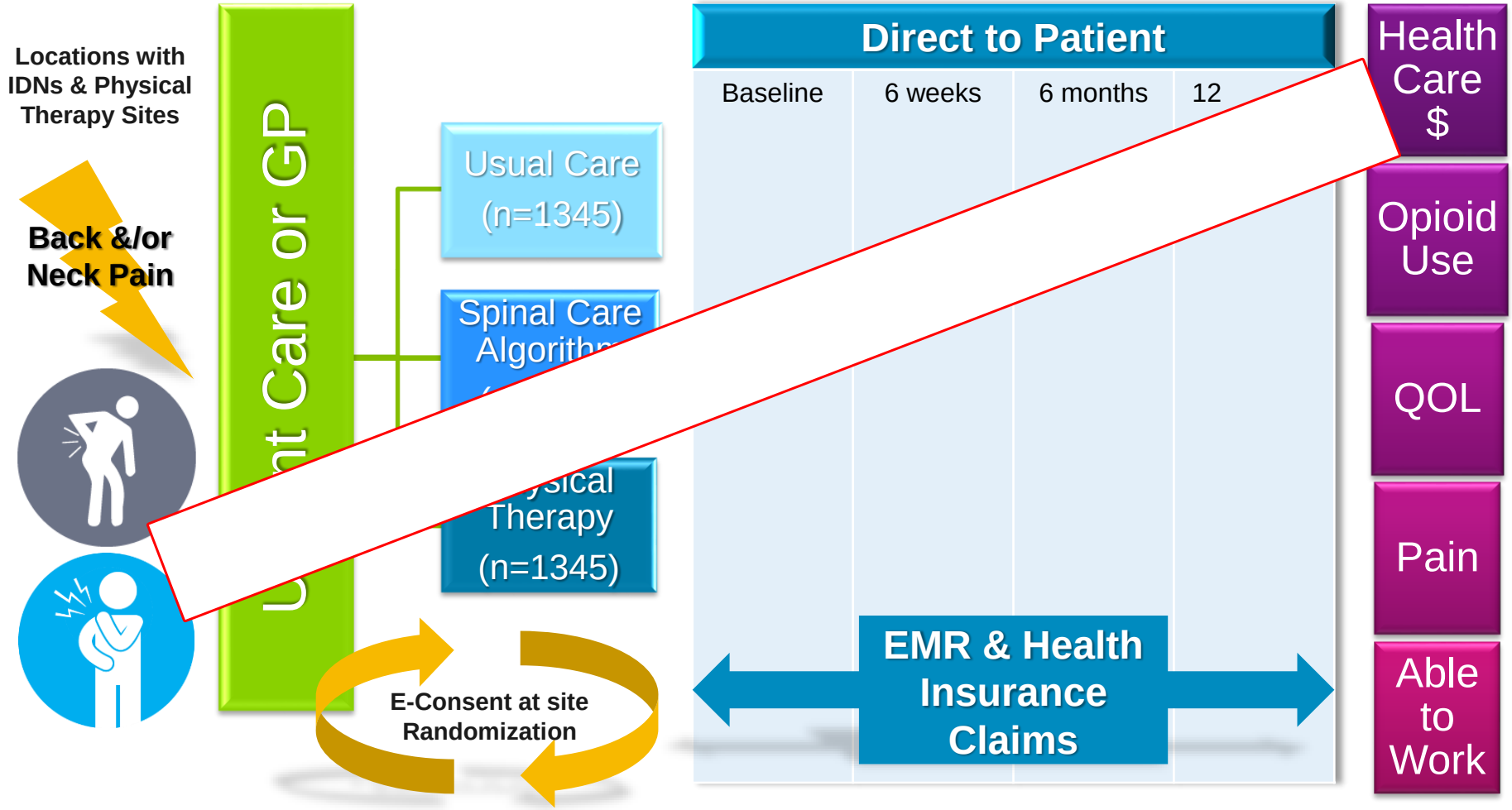
GlaxoSmithKline protocol HZC115151
Asthma study clinicaltrials.gov registration NCT01706198
COPD study clinicaltrials.gov registration NCT01551758

patients with asthma and COPD
e common inclusion criteria in RCTs has
estimated to be as low as 3% and 7%, respectively.[1] It is extremely difficult to extrapolate data from an RCT into real life for a number of reasons, including patient preference, lower adherence and comorbidities.

In contrast, 'real-world' studies assess *effectiveness* in large unselected populations, which include patients with comorbidities. Patients are under routine care, taking open-label treatment over a prolonged period, with no additional visits and no attempt to change adherence. Data are usually obtained using electronic health records, which provide long-term outcomes, including health economics, free from interviewer or recall bias. However, most effectiveness research is retrospective, limited by its non-randomised nature, and more robust study designs are required.[2] The International Society for Pharmacoeconomics and Outcomes Research has

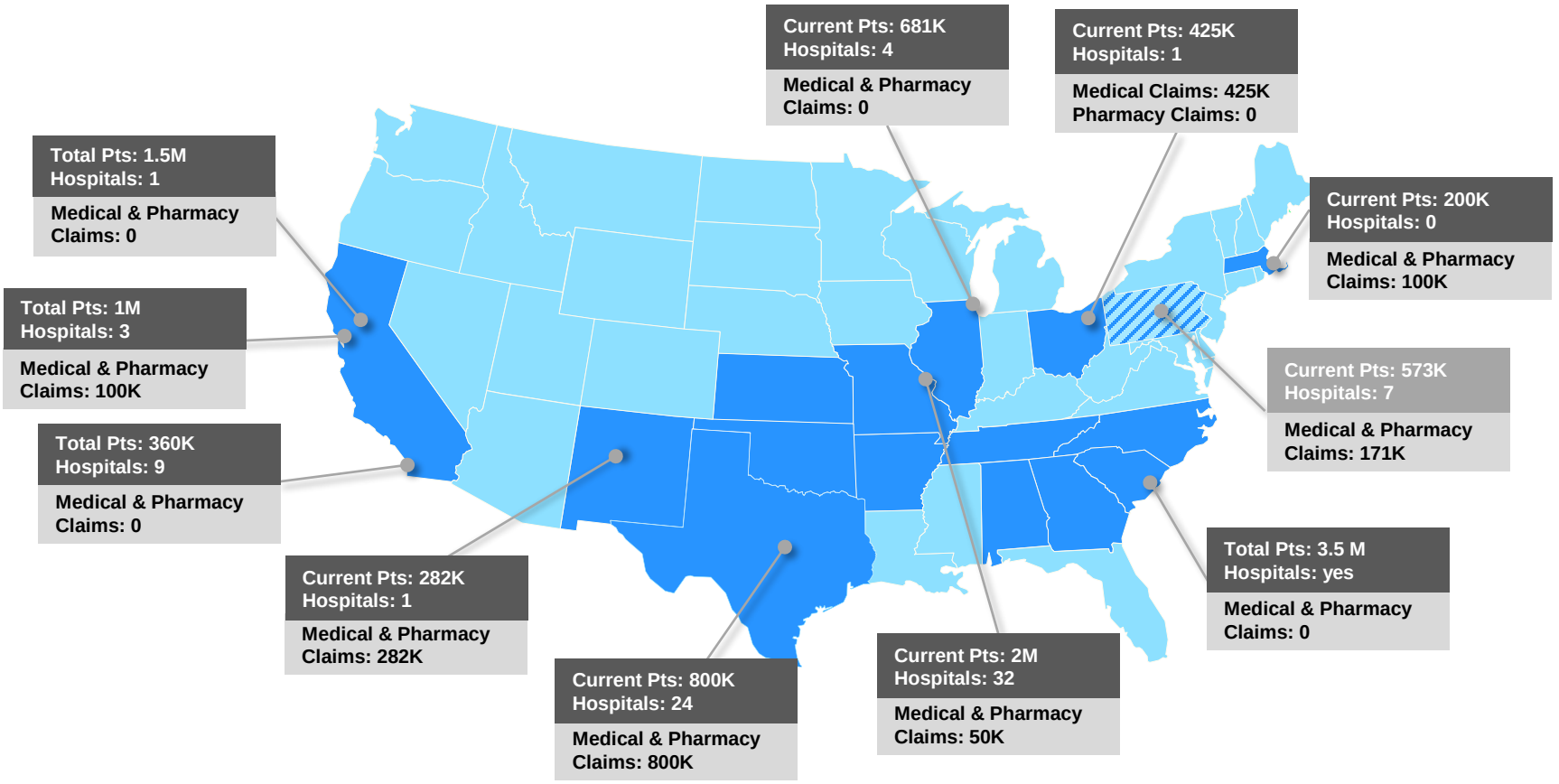
Pragmatic trial nested with a health system

Pragmatic Design Compare Spinal Care Algorithm, Usual Care and Rehabilitation-based Therapy



COMPASS: COMparative effectiveness and **PA**tient **S**afety & **S**urveillance

~8 million unique current* patients; ~21 million patients total



**current = a physician encounter within the past 18 months*

QUINTILES

As of December, 2015

Patient as a Reporter: PROTECT validation study*

Self-reported medication use in pregnant women / pregnancy outcomes

Objective: To assess the extent to which data collected directly from pregnant women provides information on medication use and other potential risk factors throughout pregnancy, and is suitable for research purposes

- Tested Internet v IVRS
- 2 v 4 weeks data collection
- How much medication usage (eg OTC or prescribed but not taken,) is not recorded in electronic health or prescription records?
- Are there additional risk factors not typically recorded?

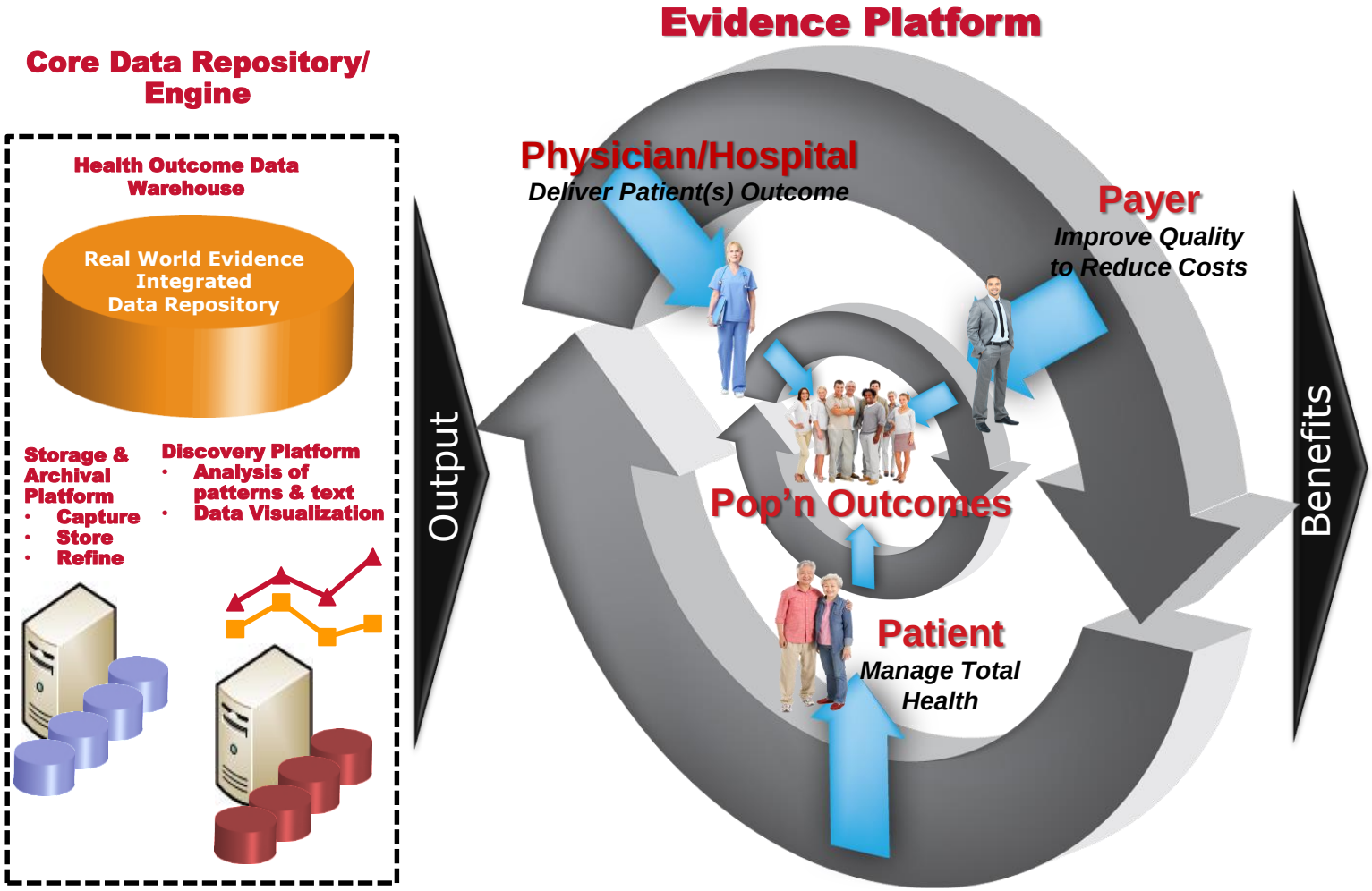
- Compare self-reported medication use with data from electronic health records and national prescription data.
- Data collected in 4 countries, 4 languages

Conclusion

- 83% used ≥ 1 non-pregnancy-related medication during pregnancy or the preceding month; 24% reported using OTC medications; 7 % reported not using prescribed medications
- Additional risk factors not found in EHR were reported.
- Validation of clinical outcomes of special interest may be warranted

*Dreyer et al. Direct-to-patient research: piloting a new approach to understanding drug safety during pregnancy. **JMIR Public Health & Surveillance** 2015; 1(2); e22. doi:10.2196

Using Existing Data Standards & Unique Patient Identifiers Allows Quick Generation of Evidence-Based Information*



Quickly generate data to address evidence needs

Better information about treatment heterogeneity

Evidence-based data driving medical practice and health insurance coverage

*Data standards have already been developed & other modern countries are using unique patient identifiers

QUINTILES

21st Century Robust Evidence Development

Key Challenges

- Knowing the limitations of existing data sets and when supplementary data are required
- Maintaining a system for re-identification of patients, providers and institutions
- Determining when informed consent is needed

Contact Information

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RWE INFRASTRUCTURE

A FOCUS ON OUTCOMES

Duke-FDA Symposium: RWE in Regulatory Decision-Making

Sean R. Tunis, MD, MSc

March 4, 2016

CMTP

CENTER FOR MEDICAL TECHNOLOGY POLICY

What is Patient-Centered CER?

- Involves patients, consumers, other stakeholders in conducting and disseminating the research
- Compares two or more options for prevention, diagnosis, or treatment (can include “usual care”)
- **Conducted in real-world populations and real-world settings**
- **Considers the range of clinical outcomes relevant to patients**
- Attends to differences in effectiveness (both benefits and harms) and preferences across patient subgroups
- Often requires randomized trial design

pcori
Patient-Centered Outcomes Research Institute

DMARD trials for rheumatoid arthritis

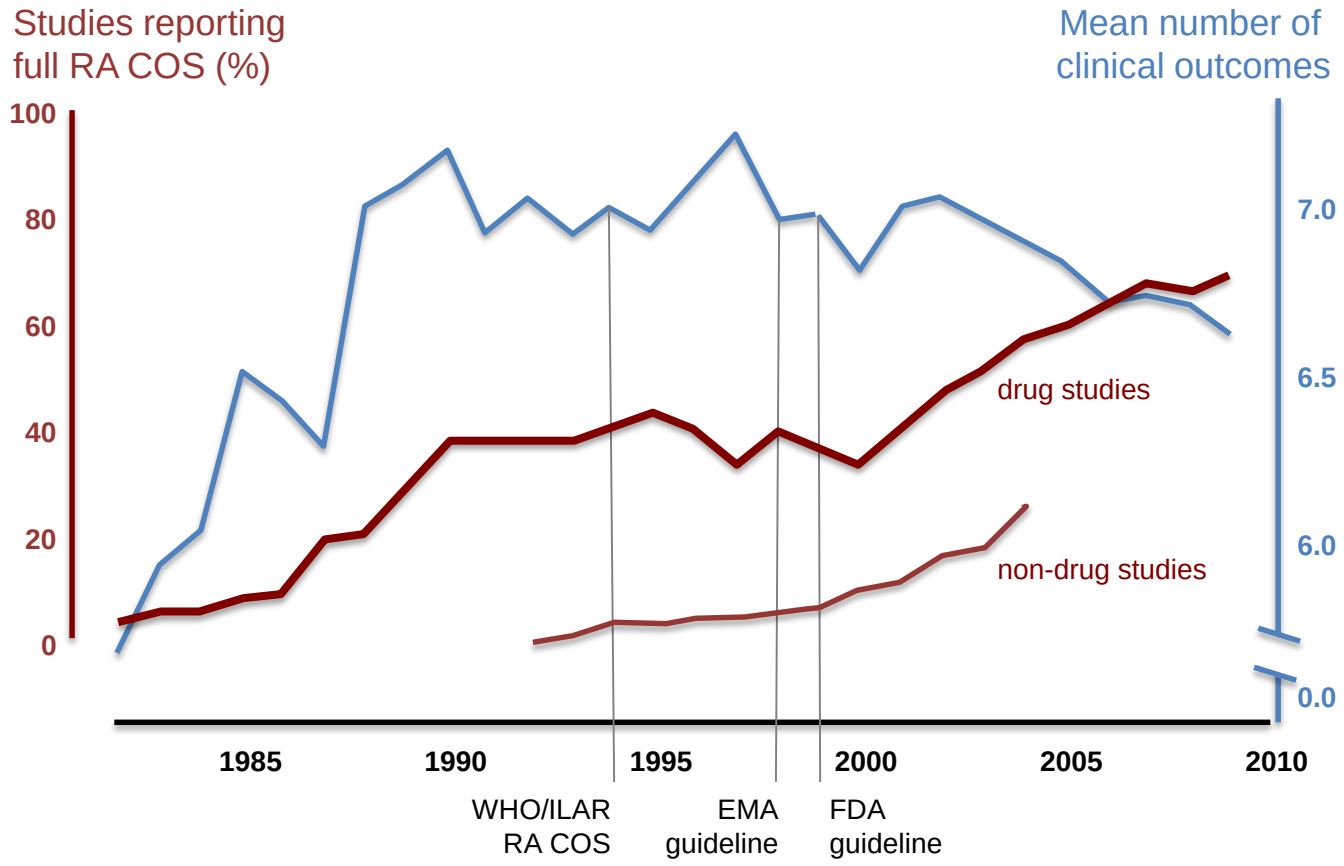
TRIAL	YEAR									
		PAIN	PT GLOB	SWOLLEN JOINT	TENDER JOINT	ACUTE PHASE	PHYSICIAN GLOB	FS	QOL	RADIOGRAPH
ERC	1960		Y			Y	Y	Y		Y
LEVY	1972				Y					
UROWITZ	1973			Y	Y	Y				Y
ANDREWS	1973	Y	Y		Y	Y	Y	Y		Y
CCC	1973					Y		Y		
SIGLER	1974					Y		Y		Y
DIXON	1975	Y				Y				
HUSKISSON	1976	Y			Y	Y				
MERY	1976		Y		Y	Y	Y			
SHIOKAWA	1977						Y			Y
WOODLAND	1981		Y		Y	Y		Y		
WILLIAMS	1983	Y	Y	Y	Y	Y	Y			
WARD	1983		Y	Y	Y		Y	Y		
ANDERSON	1985	Y	Y	Y	Y	Y	Y	Y		
WEINBLATT	1985		Y	Y	Y	Y	Y	Y		
WILLIAMS	1985	Y	Y	Y	Y	Y	Y	Y		
DOUGADOS	1988	Y	Y	Y	Y	Y		Y		
TUGWELL	1990	Y	Y			Y	Y	Y		
FURST	1990	Y	Y	Y	Y	Y	Y	Y		
DAVIS	1991			Y	Y	Y				
CLARK	1993	Y	Y	Y	Y		Y			
PINHEIRO	1993	Y			Y	Y		Y		
FORRE	1994	Y	Y	Y	Y	Y		Y		Y
ROZMAN A	1994		Y	Y	Y	Y	Y			

WHO/ILAR core set RA clinical trials

- global assessments patient & assessor
- pain
- painful joint count
- swollen joint count
- physical disability
- acute phase protein

- in studies ≥ 1 year: X-rays hands & feet

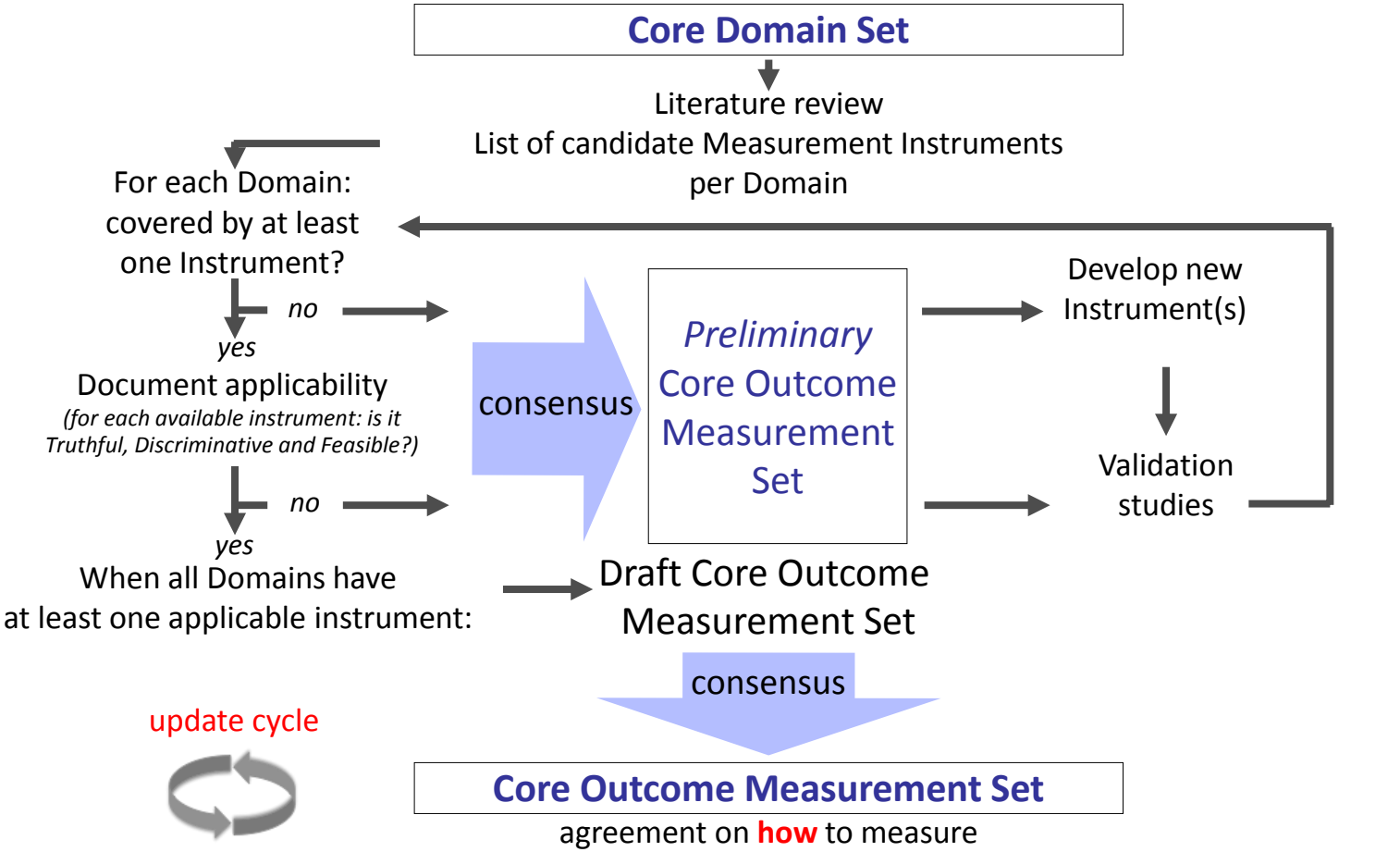
Improvements over time (Kirkham et al, *Trials* 2013)



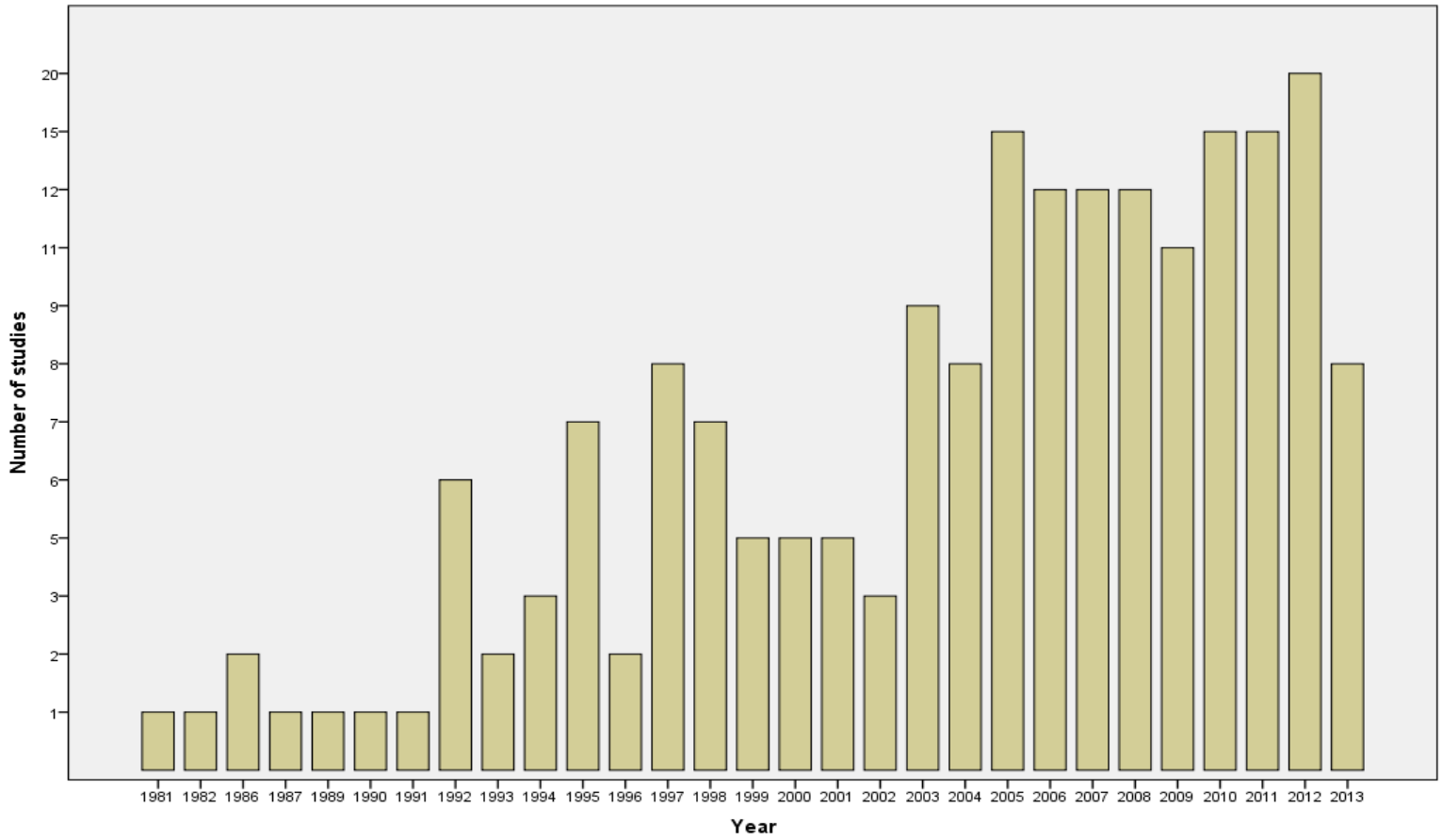
Core outcome set

- An agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care

Developing a Core Outcome Measurement Set



Year of COS publication



Core Outcome Measures in Effectiveness Trials

www.comet-initiative.org

A PROBLEM WITH STANDARDS

"Standards are like toothbrushes: everybody wants one, but nobody wants to use anybody else's."

Jerry Sheehan, NIH/NLM

(citing Doug Fridsma, AMIA)

Developing the PCORI Methodology Standards

- Congressional Requirements- Patient Protection and Affordable Care Act, Subtitle D, Paragraph (6)(C)(i)

"(C) FUNCTIONS.—Subject to subparagraph (D), the methodology committee shall work to develop and improve the science and methods of comparative clinical effectiveness research by, not later than 18 months after the establishment of the Institute, directly or through subcontract, developing and periodically updating the following:

"(i) Methodological standards for research. Such methodological standards shall provide specific criteria for internal validity, generalizability, feasibility, and timeliness of research and for health outcomes measures, risk adjustment, and other relevant aspects of research and assessment with respect to the design of research.

PCORI Methodology Committee

"Select outcomes based on input directly elicited from patient informants, people representative of the population of interest, either in previous studies or in the proposed research."

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