Update and Discussion on the Learning Health System Initiative: Essential Standards to Enable Learning (ESTEL)

4 May 2018

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Fellow, TRI/Foundation for Biomedical Research and Innovation

Founder, Clinical Data Interchange Standards Consortium (CDISC)

Information from healthcare (private, aggregated) to enable research

Healthcare

- Quality healthcare
- Informed decisions
- Personalized medicine
- Patient safety and privacy
- Public health
- Improved therapies
- Efficiencies/reduced costs

Research

- Discovery of new therapies
- Understanding diseases
- Testing/comparing therapies (CER)
- Assessing efficacy
- Monitoring safety
- Understanding responses (genomics, biomarkers)
- Public health/quality evaluations
- Post-marketing surveillance

Research findings to inform healthcare decisions

R.D. Kush, 2009
Science Translational Medicine

Learning Health Community – Genesis of ESTEL

- Fall 2012 - Learning Health System Summit sponsored by the Joseph H. Kanter Family Foundation
  - 80 organizations built consensus around 10 Core Values
  - At the request of Dr. C P Friedman, R. Kush volunteered to launch the first initiative around standards
  - Named Essential Standards to Enable Learning (ESTEL)

- February 2013 – ESTEL Initiative Kick-off Meeting in Austin, TX
  - ~ 24 participants
  - Charter, proposals, working groups

LEARNING HEALTH COMMUNITY

Essential Standards to Enable Learning (ESTEL) Charter

Purpose and Scope:

To define a parsimonious/essential/minimum core set of standards that could enable a standards-based yet flexible and scalable LHS in accordance with the following goals:

a) Ease the burden for any clinician to participate in a research study or other learning activity;

b) Increase the capacity for learning from data;

c) Obtain knowledge and results in an actionable form to contribute to building the LHS;

d) Ensure that the data obtained can be readily aggregated and/or compared; and

e) Ensure that the data uphold scientific integrity.

LEARNING HEALTH COMMUNITY

Activities Related to LHC - ESTEL

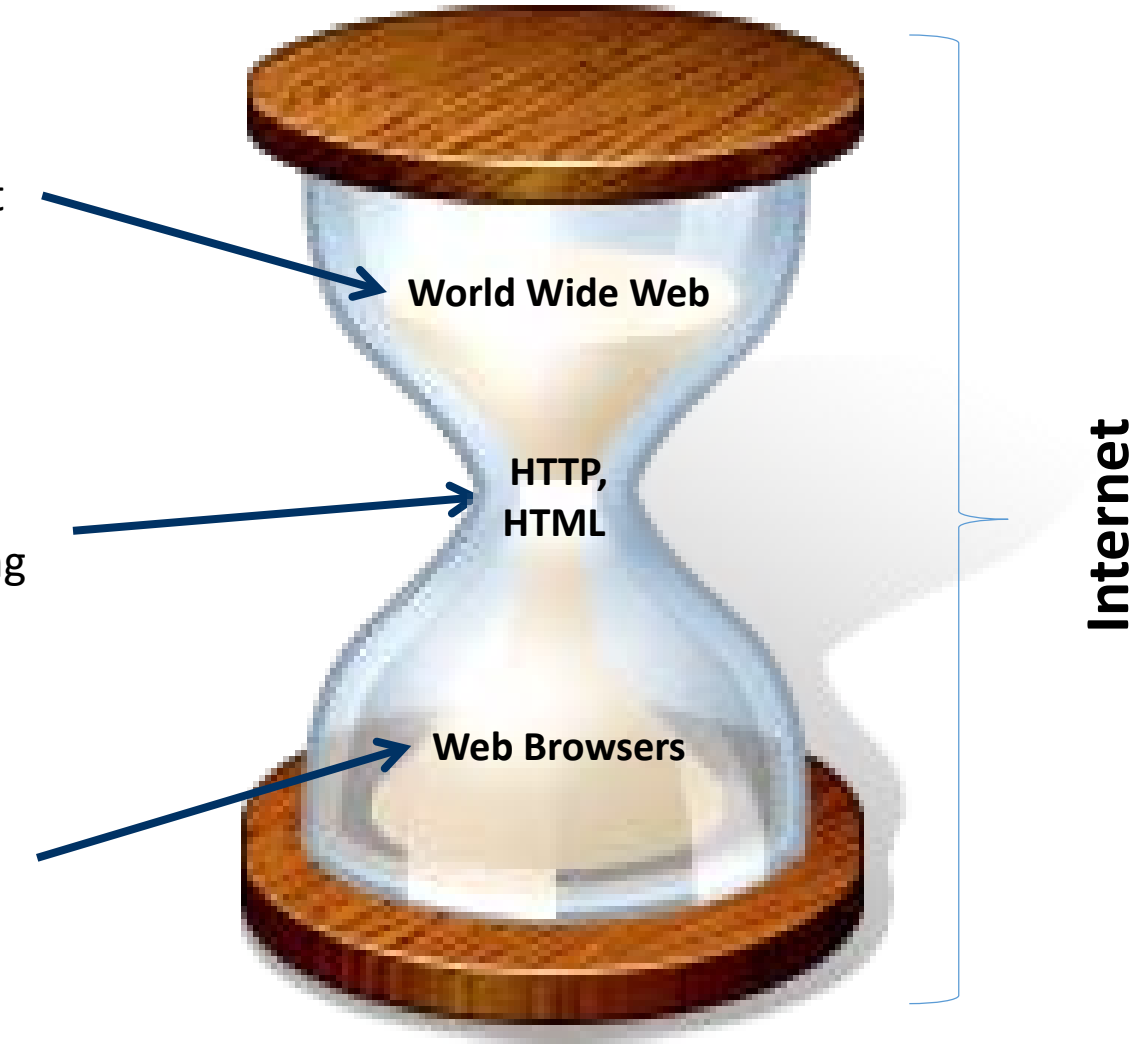
- May 2012 – Learning Health Community Summit
- **Q4 2012 – ESTEL - Charter Developed**
- **February 2013 – ESTEL Launch @ CDISC Office, Austin, TX**
- March 2013 – ESTEL Webinar
- July 2013 – ESTEL "Exec" Group @ IOM
- **September 2013 – Second ESTEL F2F @ Duke**
- Fall 2013 – CDISC requested to 'host' LHC
- Oct 2013 – March 2014 - Teleconferences
- April 2014 – Third ESTEL F2F @ AHRQ
- **May 2014 – IOM Meeting (DLC) on EHR-enabled Research**
- **September 2014 – Small Group of 'Big Thinkers', Austin, TX**
- **March 2015 – Framework Document; Criteria for Standards**
- April – September 2015 – Presentations [Webinar, KanterHealth Annual Meeting, 'LHS Europe' in Brussels]
- March 2016 - Kanter Health meeting in Miami
- **March – October 2016 - CDISC Healthcare Link Activities [Launch of eSource Stakeholders Groups-US, Europe; Strategy Session]**

The Hourglass Model: World Wide Web

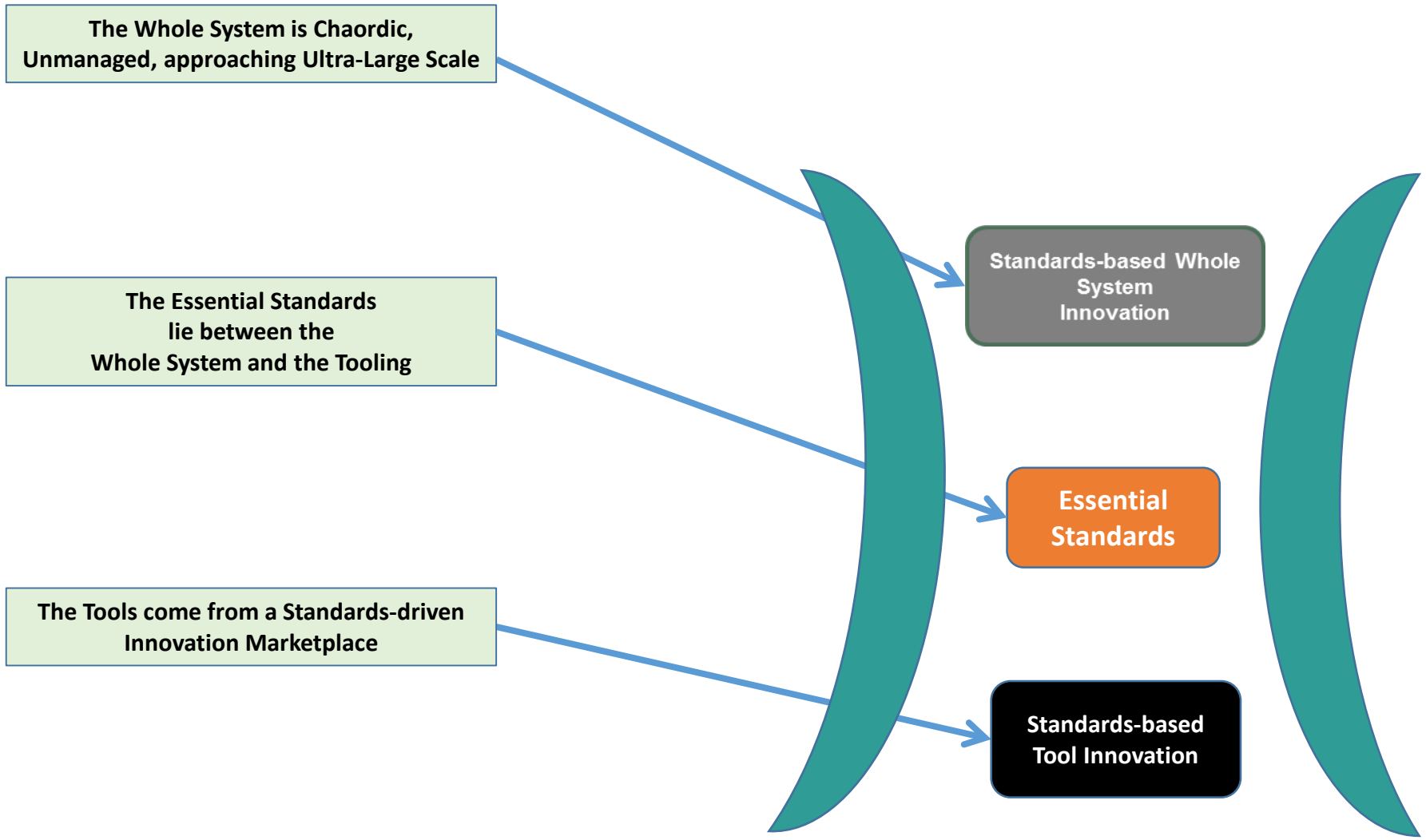
High-level Behaviors
"Anyone can say anything about any topic"

Essential Standards
Enable high-level behaviors through standards-based tooling

Tools
Come from a standards-driven innovative marketplace



Standards and the Learning Health System ESTEL Meeting at Duke – Sept 2013

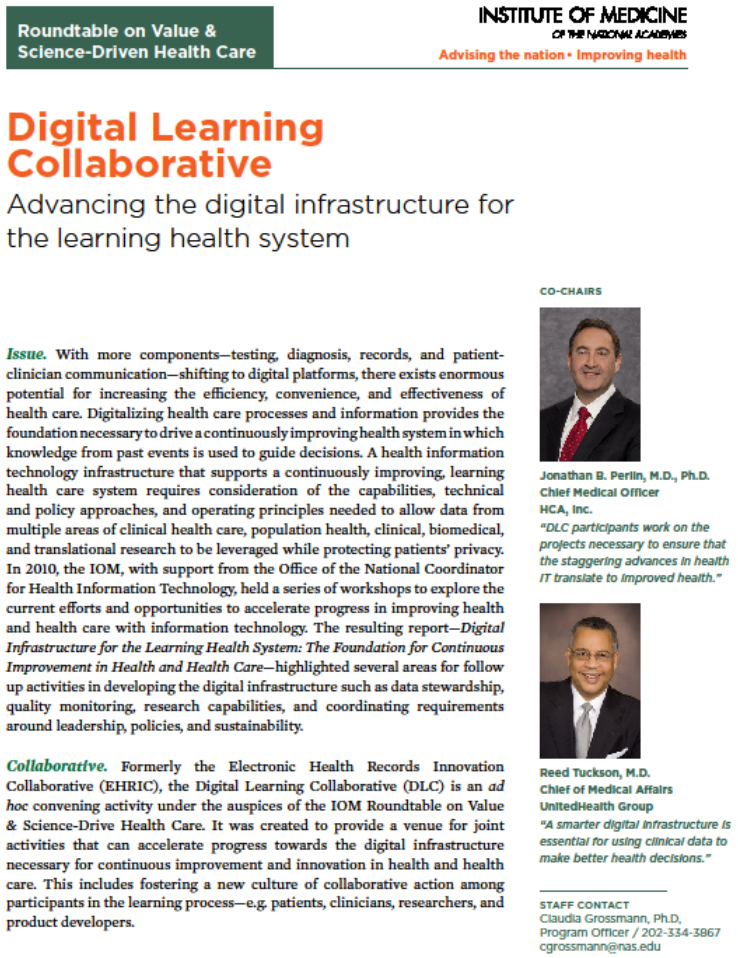


Agenda – 17 April 2014; ESTEL Hosted by AHRQ

12:30 -1:00	Call to Order, Introductions of Participants	Becky Kush
1:00 - 1:30	Background and Setting the Stage for this LHC ESTEL Meeting	Chuck Friedman Ken Pool and Landen Bain
1:30 – 3:00	**Current Projects-** ***Updates, specifically focusing on the use of standards as enablers in these projects/initiatives and how they fit into the 'narrow neck' categories*** • HHS/ONC – Doug Fridsma • ONC Structured Data Capture Initiative – Ken Pool • PCORI and Standards – Jeff Brown • IOM – Digital Learning Collaborative – Claudia Grossman • BRIDG, SHARE, CFAST - Bron Kisler • Research Match and keyCRF – Landen Bain • FDA Regulatory Guidances and HIT Plans – Ron Fitzmartin • TRANSFoRm – Theodoros Arvanitis	Facilitator: Becky Kush
3:00-3:30	Break	
3:30-5:30	Preparation for Breakout Groups on Wednesday • Definitions/descriptions of the three areas to address at the Narrow Neck of the Hourglass • Descriptions of three exemplars of learning cycles: research, public health, quality	Landen Bain, Ken Pool

IOM - Digital Learning Collaborative:
Meeting on EHR-enabled Research
(May 2014)

The Digital Learning Collaborative (DLC) was created to provide a venue for joint activities that can accelerate progress towards the digital infrastructure necessary for continuous improvement and innovation in health and health care.



Roundtable on Value & Science-Driven Health Care

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES
Advising the nation • Improving health

Digital Learning Collaborative

Advancing the digital infrastructure for the learning health system

Issue. With more components—testing, diagnosis, records, and patient-clinician communication—shifting to digital platforms, there exists enormous potential for increasing the efficiency, convenience, and effectiveness of health care. Digitalizing health care processes and information provides the foundation necessary to drive a continuously improving health system in which knowledge from past events is used to guide decisions. A health information technology infrastructure that supports a continuously improving, learning health care system requires consideration of the capabilities, technical and policy approaches, and operating principles needed to allow data from multiple areas of clinical health care, population health, clinical, biomedical, and translational research to be leveraged while protecting patients' privacy. In 2010, the IOM, with support from the Office of the National Coordinator for Health Information Technology, held a series of workshops to explore the current efforts and opportunities to accelerate progress in improving health and health care with information technology. The resulting report—*Digital Infrastructure for the Learning Health System: The Foundation for Continuous Improvement in Health and Health Care*—highlighted several areas for follow up activities in developing the digital infrastructure such as data stewardship, quality monitoring, research capabilities, and coordinating requirements around leadership, policies, and sustainability.

Collaborative. Formerly the Electronic Health Records Innovation Collaborative (EHRIC), the Digital Learning Collaborative (DLC) is an *ad hoc* convening activity under the auspices of the IOM Roundtable on Value & Science-Drive Health Care. It was created to provide a venue for joint activities that can accelerate progress towards the digital infrastructure necessary for continuous improvement and innovation in health and health care. This includes fostering a new culture of collaborative action among participants in the learning process—e.g. patients, clinicians, researchers, and product developers.

CO-CHAIRS

Jonathan B. Perlin, M.D., Ph.D.
Chief Medical Officer
HCA, Inc.
"DLC participants work on the projects necessary to ensure that the staggering advances in health IT translate to improved health."

Reed Tuckson, M.D.
Chief of Medical Affairs
UnitedHealth Group
"A smarter digital infrastructure is essential for using clinical data to make better health decisions."

STAFF CONTACT
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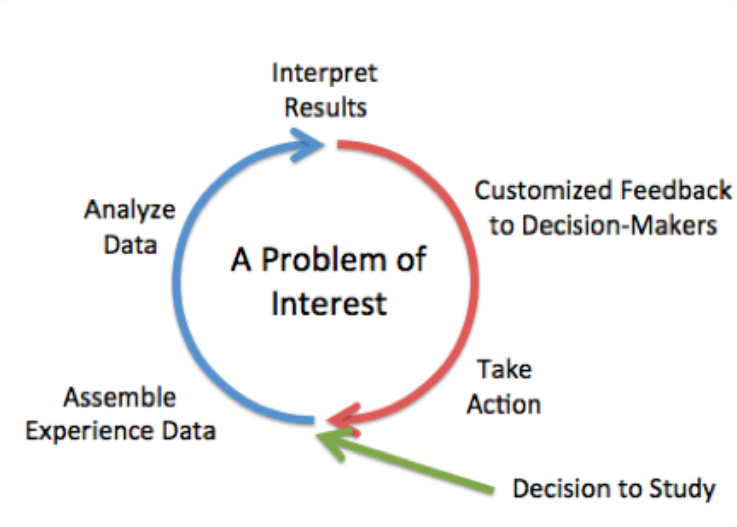
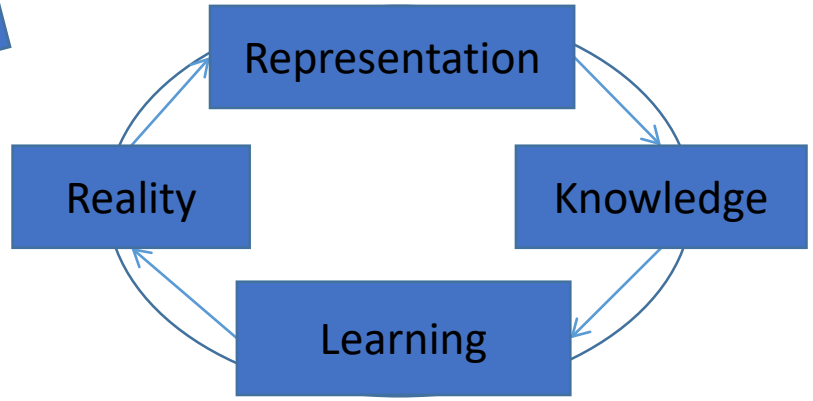
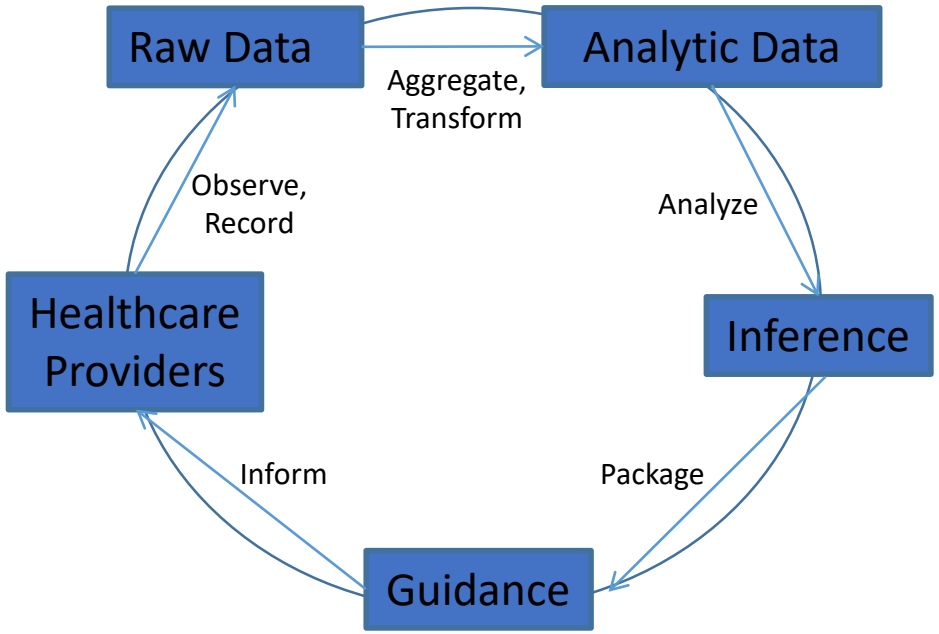
Charge for 11 September 2014 ESTEL Meeting: Small Group of "Big Thinkers"

- Draft a straw man of an ideal architecture that 'leapfrogs conventional thinking but lands on dry land'. Take the long view, then back off towards conventional thinking as required by our realities.
- Participants (small meeting of 'big thinkers')
  - Landen Bain, research/healthcare perspective
  - Ken Pool, public health software developer's perspective
  - Wes Rishel, the best of historical and current thinking
  - George Cole, EHR pragmatist
  - Kevin Sullivan, computer scientist unshackled by healthcare background
  - Frederik Malfait, Semantic web developer with pharma and Euro perspectives
  - John Loonsk, public health architecture advocate

Learning Cycle –
From Concept to Framework to Entities and Activities







ESTEL Learning Health Cycle Framework

The Learning Health Cycle Framework can serve as a tool leading to specifications of Essential Standards to Enable Learning. It can also become a standard in its own right. The Learning Health Cycle Framework:

a) defines what it means to be a player in this ecosystem;
b) provides a way to identify when a set of activities qualify as a Learning Health Cycle;
c) requires the articulation of key entities and key relationships among the entities;
d) requires efferent and afferent arms of the cycle with the proposed 'cycle points' shown in the final cycle depicted above;
e) creates a benchmark for identifying consensus-based standards to work in specific implementations for the domain of interest at each step of the loop;
f) will require that data accumulating at one step in a learning loop be semantically annotated to a sufficient degree to fulfill requirements for the next stage in the loop;
g) adheres to the Learning Health Community Core Values;
h) meets the ESTEL goals; and,
i) is scalable.

Criteria for ESTEL Standards

- A good standard for a Learning Health Cycle meets the following criteria**:**
- meets the purpose for intended use;
- is not redundant to another standard;
- developed through a robust, consensus-based standards development process, preferably by a global standards development organization;
- mature and broadly used/adopted;
- is open and freely available (not proprietary) and is protected by an IP policy to remain that way;
- is maintained, with support, education and certification where applicable.

ESTEL Framework Document: Structure and Standards

ESTEL Structure and Standards:
A Framework for the Learning Health Community

According to the Institute of Medicine of the National Academies (US), "A Learning Health System (LHS) is one in which progress in science, informatics, and care culture align to generate new knowledge as an ongoing, natural by-product of the care experience, and seamlessly refine and deliver best practices for continuous improvement in health and health care."

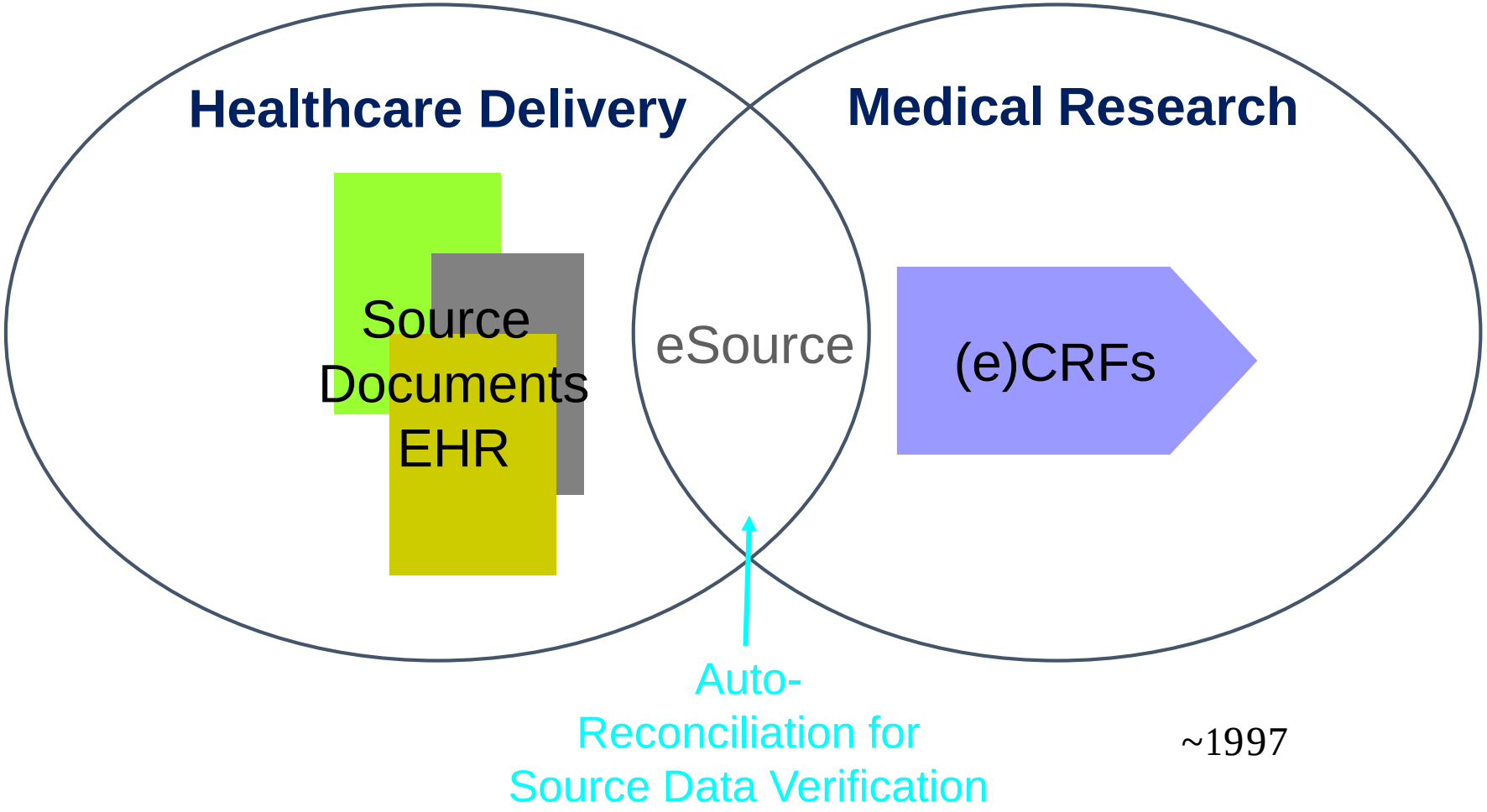
ESTEL Framework Document
Draft: 7 March 2015

Example of Framework
Applied to Clinical Research

Attachment: Learning Health System – ESTEL Framework (Standards and Structure): One Illustrative Example for Research and Public Health

Cycle Point (Structural Step)	Description of Activities between Points	Available Standards (for research, public health, outcomes)	Support for LHS Values, Comments
Health Experience			
	Clinicians or patients make observations and record them, recordings become EHRs, Case Report forms, eDiaries or PROtocol, or devices. Observations may be correlated.	CDISC Study Data Model (SDM) as a subset of the Protocol Representation Model (PRM) CDISC Clinical Data Acquisition Standards Harmonization (CDASH) CDISC Therapeutic Area Specific Standards CDISC Operational Data Model for research HHS's Retrieve Protocol for Processing HHS's Retrieve form for Data Capture (The last two are workflow standards for use of EHRs to support Quality, Research and Public Health.)	The standards named support: Data Integrity and Quality, Provenance Regulatory 21 CFR 11 FDA and EMA Guidance documents Complementary HIT standards exist for Security and Privacy Value – using standards from the start.
Raw Data			
	The data are aggregated into a database, from which tables, listings and analysis datasets can be developed.	CDISC Study Data Tabulation Model (SDTM) and Analysis Dataset Model (ADaM)	Standards support requirements of FDA and EMA (Janet)
Analysis Data			
	Documents the meaning and relevance of the data (typically done by statisticians working with SMEs)	Standards support various sophisticated analyses.	Analysis Integrity needs to be ensure, standards support traceability
Inference, Interpretation			
	Develop guidelines or guidance, results presentations or summaries of the learnings to be presented to clinicians and/or patients, comprehensible findings are presented in a format to be understood by the recipients.	ADaM (analysis datasets with interventions/groups) for summaries – layman's terms.	Standards support traceability Accuracy of reasoning should be ensured.
Guidance			

GOAL: Optimize the Process



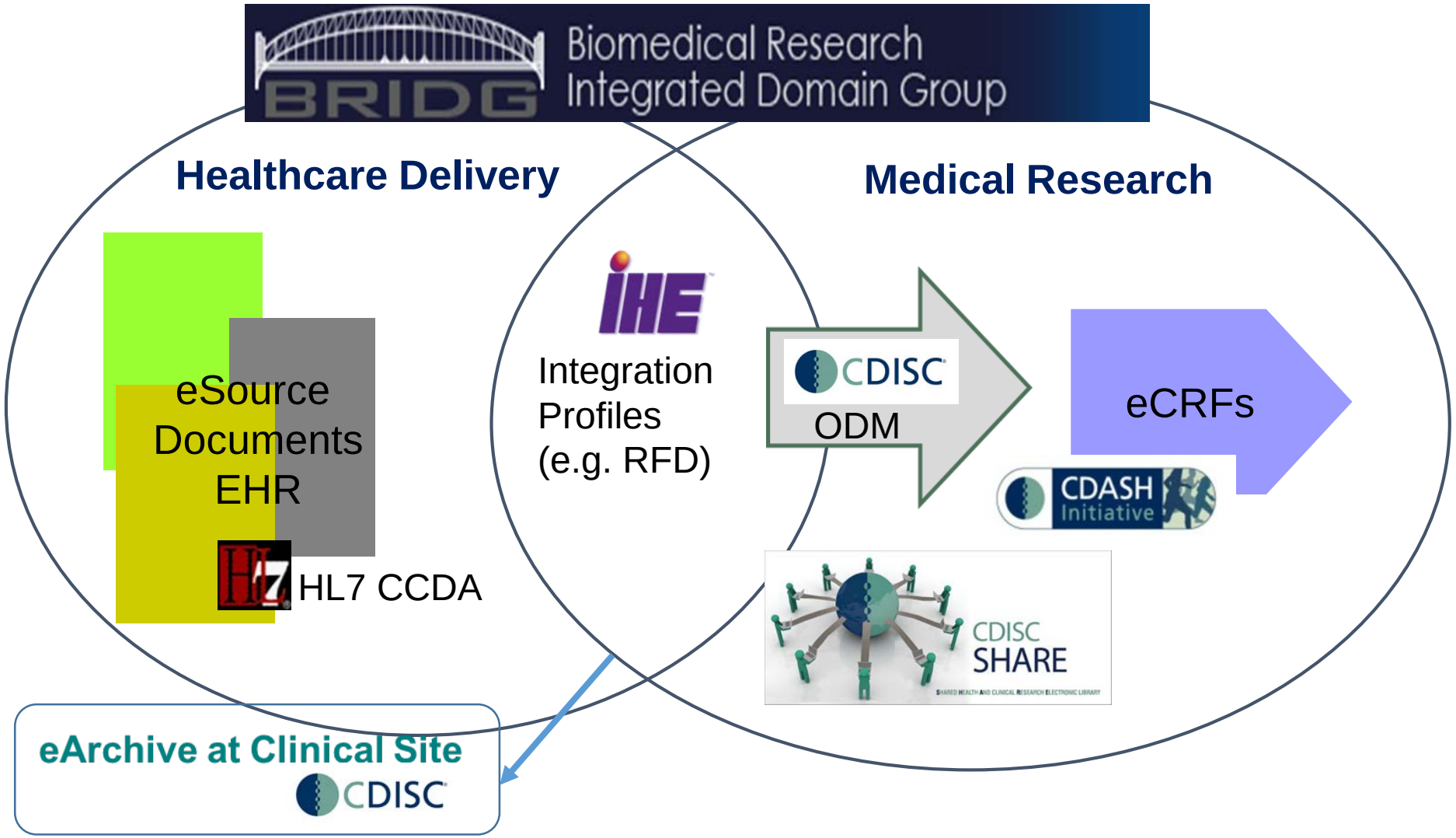
~1997

eSource Data Interchange (eSDI) Initiative

- **Purpose:** FDA initiative to facilitate the use of electronic technology in the context of existing regulations for the collection of eSource data in clinical research

Note: eSource pertains to collecting data electronically initially through eDiaries, ePatient Reported Outcomes, eData Collection, EHRs

- **Overarching Goals:**
  - To make it easier for physicians to conduct clinical research,
  - Collect data only once in an industry standard format for multiple downstream uses, and thereby
  - Improve data quality and patient safety
- **Product from multidisciplinary team:**
  - **eSDI Document**
  - **12 requirements for eSource**
  - **Available at www.cdisc.org/eSDI-document**
  - **Requirements cited verbatim in EMA guide for field auditors**
  - **Formed the basis for the Retrieve Form for Data Capture (RFD) Integration Profile**


BRIDG
Biomedical Research
Integrated Domain Group
Healthcare Delivery
Medical Research
eSource
Documents
EHR
HL7 CCDA
IHE
Integration
Profiles
(e.g. RFD)
CDISC
ODM
eCRFs
CDASH
Initiative
CDISC
SHARE
eArchive at Clinical Site
CDISC

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In response to:

- *CDISC BAA Grant from FDA on eSouce*

"The use of electronic health records has the potential to foster efficiency and further innovation in regulated clinical research," said Janet Woodcock, M.D., director of FDA's Center for Drug Evaluation and Research. "Demonstration projects that test and evaluate the performance of end-to-end EHR-to-EDC single-point data capture approaches are an important source of information as we collectively work to ensure the quality of data from electronic source to electronic regulatory submission."

eSource Stakeholders Group

- **Initiated March 2016 in U.S.**
- **Meeting October 2016 in Europe**
- **Teams**
  - Primer
  - eCRF concept
  - System Validation / Privacy
  - Economics / Cost vs Benefit
  - Scalability requirements
  - Data Provenance
  - Implementation / Demo
  - Wearables

FDA Commissioner's Office – April 2016

"Across the clinical research enterprise, there is a growing awareness of serious shortfalls in the current paradigm of **generating** the scientific **evidence** that supports medical product evaluation and clinical care decisions and the need to modernize methods and expectations surrounding this evidence base."

"….a national system for evidence generation that applied **common data standards and definitions** could 'lay the track' for significant improvements in the exchange of biomedical data."

<u>What We Mean When We Talk About EvGen</u>

Drs. Robert Califf and Rachel Sherman,16 April 2016, FDA Voice

Strategy Session on the Future of Medical Research and the Role of Standards: "Forming Connections Towards Complementary Systems"

2 August 2016

Idea generated by Dr. Ron Fitzmartin and M. A. Slack, FDA

Moderated by Dr. Robert Califf, FDA and Dr. Rebecca Kush

Representatives from 70 different organizations (biopharma, CROs, academia, NIH, ONC, patient advocacy groups, site organizations, Japan, Europe, etc.

Key Themes in Points Made By Participants

- The entire journey of each patient is important.
- There are parallel universes of patient care and research that need to be brought together.
- Bringing together parallel universes will require cooperation and collaboration among federal agencies, standards development organizations and researchers in academia, healthcare and biopharma; and, removing the uncertainty of EHR-enabled prospective research.
- Big data can be leveraged for certain use cases, but each bit of information is precious and quality matters, especially when data are scarce (e.g. outbreaks, rare diseases, clinical trials).
- Data standards have demonstrated value, but barriers to broader adoption remain to be addressed.
- Education and increased awareness around the availability and use of global standards to streamline research are necessary.
- Funding for standards development and maintenance is inadequate, but who should pay for this is unclear.

Proposed Next Steps from 2 Aug 2016 Strategy Session

1) **Harmonize a core set of data elements and models across agencies.**
2) **Harmonize Common Protocol Template for industry and government-funded clinical research.**
3) **Encourage the use of eSource and evidence generation from healthcare information for clinical research and 're-link' these two universes.**
4) **Determine a sustainable business model to make SHARE openly available globally.**
5) **Increase education across all parties in terms of the availability and use of standards for clinical research and their link with healthcare.**

The Future of ESTEL (presented at 2nd Summit December 2016)

- **Opportunities**
  - Use EHRs for prospective research (evidence generation)
  - Streamline clinical trials
  - →Shorten the 17 years!
- **Challenges**
  - Healthcare standards --- a “moving target”
  - Redundancies (e.g. caDSR, NLM CDE Repository, SHARE)
  - Non-harmonized models (e.g. PCORI, BRIDG, Sentinel)
  - Culture; ‘fear’ of being first; silos vs. sharing
  - Not glamorous or new (“plumbing”)
  - Political environment…

ARO Council

1st Global ARO Network Workshop

Strategic Initiative for Standardization & Harmonization in Clinical Research

The Grand Design of Global ARO Network and The Aim of This Meeting

2nd and 3rd Workshops held in U.S. Nov17 & Japan Mar18; 4th Workshop in planning stages (Europe)

Direction:

1. CDISC implementation & standardization
   i) 3C consolidation (J3C, C3C, AP3C)
   ii) Regulatory harmonization
2. Data Center standardization
   ECRIN Data Centre
   Certification programme

Standardization & Harmonization for sharing data in "Big Data" age

3. Sharing R&D Pipeline & global development

Data standardization
↓
Can share data
↓
Pooled, combine = Big Data
↓
Life course insight

Towards a Learning Health System

Patient and Clinician Participation

- Only ~1% of patients participate in trials
  - Due in part to lack of research site access
  - Fear of leaving their primary clinician
- Only ~1% of clinicians participate in trials
  - Significant infrastructure and regulatory requirements
- Big data identifies patients but it does not solve the “last mile”
  - Up to 99% of patients identified through big data are with clinicians who do not conduct clinical trials
  - These clinicians are not ‘sites’ and do not have the infrastructure to conduct regulated research

Role of EHRs for Clinical Research

Moving Towards a Learning Health System

4-5 April 2018
National Harbor, MD

Bridging
Clinical Research &
Clinical Health Care

a clinical research collaborative

PCOR Trust Fund Project on RWE led by FDA (M. Rocca)

PROBLEMS TO SOLVE

Networks of observational data use different CDMs.

Open, consensus-based standards might not be leveraged in these CDMs (ex: CDISC, HL7)

There is a need to facilitate interoperability among these collaborations

Mitra Rocca, FDA

Elligo Health Research, through an FDA grant, is partnering with 4-5 data sources on a use case (pharmacovigilance) to support this CDMH Project.

NOTE: ISO, HL7, CDISC Standard (the BRIDG Model) is being used by FDA as the 'ubermodel' to which the other CDMs are being mapped.

PROJECT GOAL AND OBJECTIVES

Goal:

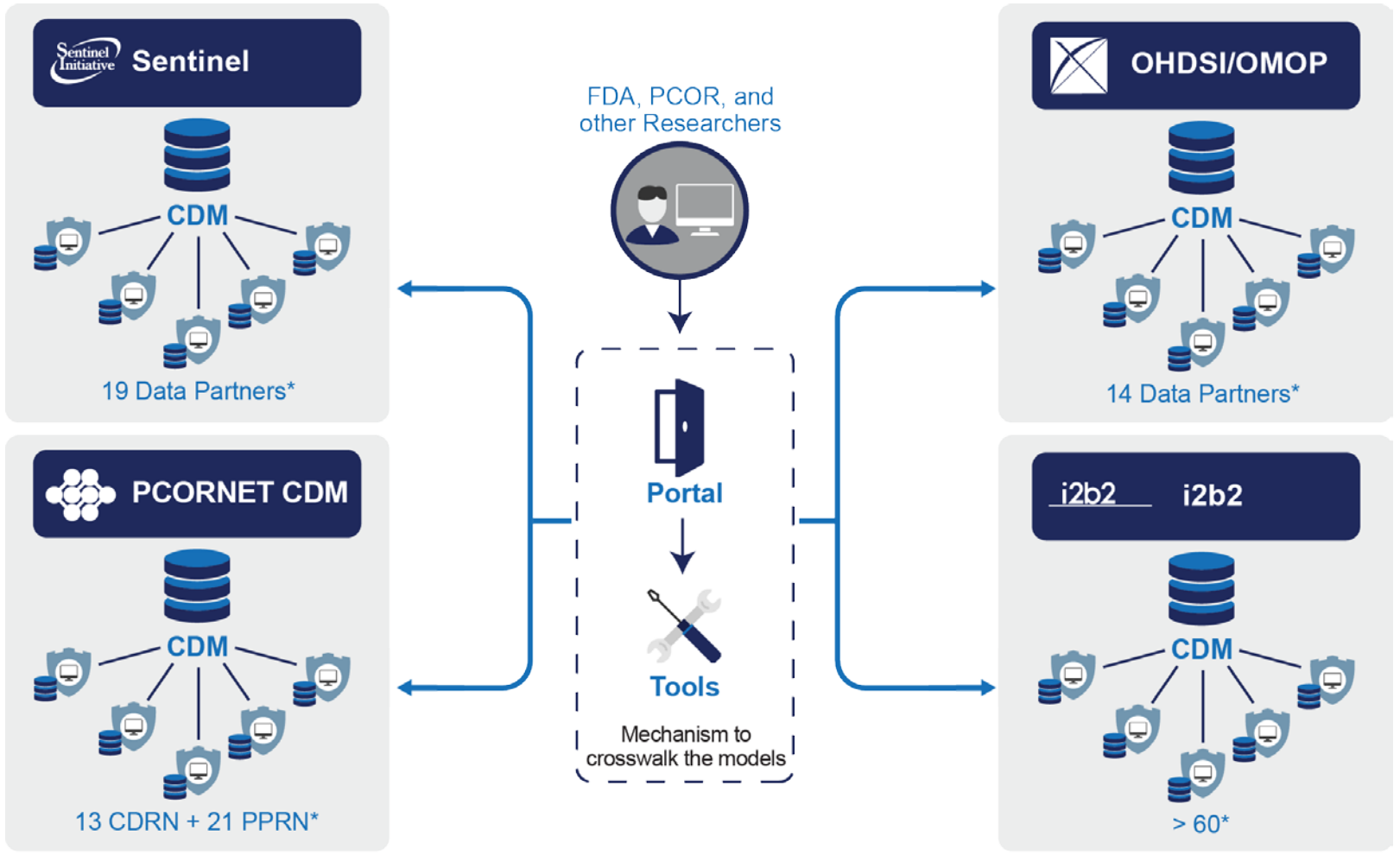
Build a data infrastructure for conducting patient-centered outcomes research using RWD/observational data* derived from the delivery of health care in routine clinical settings.

Objective:

Develop and apply an automated extract transform and load (ETL) process to harmonize various Common Data Models (CDMs) with each other, leveraging open standards and controlled terminologies to advance Patient-Centered Outcomes Research

*Observational Data: Examples of observational data are administrative claims, Electronic Health Records (EHRs), registry, mobile health, electronic patient reported outcomes (ePRO), …).

FUTURE STATE



* See the list of data partners on the back up slides

For Discussion: Current Situation for ESTEL

Barriers

- Data Sharing concerns (privacy, security) have been increasing
- More technology and complexity of research increasing cycle times
- U.S. FDA Commissioner and HHS Head changed with new administration
- CDISC CEO changed priorities for Healthcare Link→ eSource Stakeholder group dissolved; CDISC costs for developing new TA standard increased; BRC formed
- FHIR gaining traction as HL7 standard; FHIR research resources not yet available

- Opportunities
  - CORBEL Data Sharing Initiative – Document published BMJOpen-Dec2017
  - New FDA Commissioner still interested in RWE/RWD (PCOR TF Project)
  - Synergistic Standards exist; HL7 BR&R Group moving BRIDG, FHIR Resources forward
  - Publications coming on CFAST and LHS Journal Theme Issue (Oct 2018) on Learning Health Systems: Connecting Research and Practice Worldwide
  - Global ARO Network, Bridging Collaborative, CFAST, Elligo Health Research, IMI, C-Path and others have an interest in moving ESTEL-like initiatives forward
  - LHC now incorporated as new entity

Process Improvement: Collect Data Once for Many Uses