Learning Health Community: Essential Standards to Enable Learning (ESTEL) Initiative

Background and Update

R.D. Kush, PhD
ASCO, Alexandria, VA
8-9 December 2016
HOW STANDARDS PROLIFERATE:
(SEE: A/C CHARGERS, CHARACTER ENCODINGS, INSTANT MESSAGING, ETC)

SITUATION:
THERE ARE 14 COMPETING STANDARDS.

14?! RIDICULOUS!
WE NEED TO DEVELOP ONE UNIVERSAL STANDARD THAT COVERS EVERYONE'S USE CASES. YEAH!

[Soon:]

SITUATION:
THERE ARE 15 COMPETING STANDARDS.
WHEN CLINICAL RESEARCH DATA DOESN'T SPEAK THE SAME LANGUAGE, THE CONVERSATION CAN TURN DEADLY.

When we don’t share findings in clinical research, it’s as if billions of dollars get buried. When that happens, we all lose out on finding cures to diseases that affect people we love.
Information from healthcare (private, aggregated) to enable research

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Healthcare

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

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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

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Research findings to inform healthcare decisions

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Inefficient Cycle taking ~17 Years

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R.D. Kush, 2009
Science Translational Medicine
Medical Research

AHIC agreed that a Clinical Research Use Case is important and should be done – but there was “no funding left”.

HHS and CDISC raised $250K each
ANSI (through HITSP process) led the development of an Interoperability Specification recommending standards for the use of EHRs for Research.

Clinical Care Decisions
Synergistic Standards Available

- eSource Documents
- EHR
- CCDA
- Integration Profiles (e.g. RFD, RPE, DEX)
- CDISC ODM
- eCRFs
- CDASH Initiative
- HITSP IS # 158 (2010)
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.

~ December 2012
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/Regulations [Launch of eSource Stakeholders Groups-US, Europe; Strategy Session]
The Whole System is Chaordic, Unmanaged, approaching Ultra-Large Scale

The Essential Standards lie between the Whole System and the Tooling

The Tools come from a Standards-driven Innovation Marketplace

Standards-based Whole System Innovation

Essential Standards

Standards-based Tool Innovation
The Hourglass Model

The narrow neck of the hourglass defines a small set of core abstractions and protocols (e.g. TCP and HTTP) onto which many different high-level behaviors can be mapped (the top of the hourglass), and which themselves can be mapped onto many different underlying technologies (the base of the hourglass).

By definition the number of protocols defined at the neck must be small.

*The Anatomy of the Grid, Kesselman*
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

- World Wide Web
- HTTP, HTML
- Web Browsers
In our architecture, the neck of the hourglass consists of Resource and Connectivity protocols, which facilitate the sharing of individual resources. Protocols at these layers are designed so that they can be implemented on top of a diverse range of resource types, defined at the Fabric layer, and can in turn be used to construct a wide range of global services and application-specific behaviors at the Collective layer.

_The Anatomy of the Grid, Kesselman_
The Hourglass Model: LHS-ESTEL

**Fabric**
“Diverse range of resource types.”

**The Neck**
Resource & connectivity protocols.

**The Collective**
“A wide range of global services and application-specific behaviors”

- Healthcare Data
- ESTEL
- Tools
# New ESTEL Narrow Neck Model

<table>
<thead>
<tr>
<th>Name</th>
<th>Reference Standards</th>
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</thead>
<tbody>
<tr>
<td><strong>Meaning:</strong></td>
<td>BRIDG, SHARE, Therapeutic Area Standards, Semantic Web</td>
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<tr>
<td>Data Models</td>
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<tr>
<td>Data Element Definition</td>
<td></td>
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<tr>
<td>Concepts</td>
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<tr>
<td><strong>Structure:</strong></td>
<td>ODM, CDA</td>
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<tr>
<td>Metadata</td>
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<tr>
<td>XML schemas</td>
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<td><strong>Transport:</strong></td>
<td>RFD</td>
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<td>Data Exchange</td>
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<td>Messaging</td>
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<tr>
<td>Interaction Profiles</td>
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<tr>
<td><strong>Security:</strong></td>
<td>ATNA, XUA, TLS, etc</td>
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<tr>
<td>Participant identity</td>
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<tr>
<td>Authentication</td>
<td></td>
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<tr>
<td>Consent</td>
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## Agenda – 17 April 2014; ESTEL Hosted by AHRQ

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

A Problem of Interest

- Observe, Record
- Aggregate, Transform

Raw Data

Analytic Data

- Analyze

Healthcare Providers

Inference

- Inform
- Package

Guidance

- Interpret Results
- Take Action
- Decision to Study

Customized Feedback to Decision-Makers

Representation

Reality

Knowledge

Learning
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.
Five Steps of the Learning Loop Framework

1. **Observe, Record**
   - Healthcare Providers
   - Raw Data
   - Analytic Data

2. **Aggregate, Transform**
   - Analytic Data
   - Inference
   - Inform

3. **Analyze**
   - Inference
   - Guidance

4. **Package**
   - Guidance
   - Step 5

5. **Inform**
   - Healthcare Providers
   - Raw Data
   - Analytic Data

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ESTEL Framework Document
Structure and Standards

Example of Framework
Applied to Clinical Research

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
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.
eSource = data entered electronically first, i.e. EHRs, eDiaries….

FDA @ CDISC Interchange FAA:

"What is it Going to Take?"
What Study Data Standards Will be Required?

For the full list of study data standards, see the Data Standards Catalog at www.fda.gov/ForIndustry/DataStandards/StudyDataStandards

Dr. Ron Fitzmartin, FDA
FOR IMMEDIATE RELEASE
CDISC to Convene eSource Stakeholders Group to Encourage Use of EHRs for Research

Austin, TX – 14 January 2016 – The Clinical Data Interchange Standards Consortium (CDISC) announced today the establishment of the “eSource Stakeholders Group,” an open, inclusive forum which will provide coordination and focus to the increasing community of stakeholders interested in realizing the benefits of using eSource, also known as electronic source data, in clinical trials and meeting regulatory requirements for eSource data, provenance and electronic records.

This news follows the FDA’s announcement in June 2015 encouraging organizations to propose demonstration projects, the September 2013 FDA Guidance encouraging the use of electronic source data in the conduct of clinical investigations, and, most recently, the updated Electronic Health Record (EHR) eSource webpage on the FDA-CDER website.

In response to:
• CDISC BAA Grant from FDA on eSource
• FDA Federal Register Notice on eSource

“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 (leaders)
  - Primer (Angela Gill-Nelms; Dave Gemzik)
  - eCRF concept (Michael Ibara, Mitra Rocca)
  - System Validation / Privacy (Robert Barr; Liz Murphy)
  - Economics / Cost vs Benefit (Lee Walke; Keith Marsolo)
  - Scalability requirements (Bart Phillips; Rob Poorvin)
  - Data Provenance (Robert Barr; Liz Murphy)
  - Implementation / Demo (Amy Nordo; Michael Ibara)
  - Wearables (pending leader recruitment)

Contact Michael Ibara: mibara@cdisc.org
“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.”

What We Mean When We Talk About EvGen

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

Dr. Robert Califf – Moderator
Dr. Rebecca Kush - Moderator
Participating Organizations

- Abbvie
- Accenture
- ARO Council, Japan
- Allergan
- Amgen
- AstraZeneca
- Athena Health
- Aventi Health
- Becton Dickinson
- Biogen Idec
- BIO
- CDISC
- CHDI Foundation
- Cohen Veterans Association
- Covance
- Critical Path Institute
- Eli Lilly
- Elligo Health Research, Inc.
- FasterCures
- FDA Commissioner
- FDA/CDER
- Gates Foundation
- GlaxoSmithKline
- Harvard MRCT
- HHS/ONC
- Helmsley Foundation
- IMI eTRIKS Project
- Imperial College London
Participating Organizations

- Johnson & Johnson
- Kyoto University Hospital
- Merck
- NIH/NCATS
- NIH/NIAID/DAIDS
- NIH/OD
- NCATS
- NYU Langone Medical Center
- NexTrials, Inc.
- OneMind for Research
- PCORNet
- PPD
- PMDA, Japan
- Quintiles
- Roche
- Radiological Society of North America (RSNA)
- Sanofi
- SCRS
- Sentinel
- Pew Charitable Trusts
- University of Chicago
- TransCelerate Biopharma, Inc.
- Translational Research Institute, Japan
- UCB Biosciences
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

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.
THIS IS THE BLACK HOLE OF CLINICAL RESEARCH.

Billions of dollars are spent on clinical research, but when data isn’t shared, results get buried. Along with patients needing cures.

There’s a Problem We Need to Talk About.

www.unlockcures.org
The Future of ESTEL

• **Opportunities**
  - Use EHRs for prospective research (evidence generation)
  - Streamline clinical trials
  - \( \rightarrow \) 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…
WHEN CLINICAL RESEARCH IS DONE IN SILOS, WE CAN'T HARVEST CURES.

When we don’t share findings in clinical research, it’s as if billions of dollars get buried. When that happens, we all lose out on finding cures to diseases that affect people we love.

Strength through Collaboration
Information from healthcare (private, aggregated) to enable research

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

Culture
Incentives
STANDARDS
Governance
Trust and Engagement

Healthcare

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

Research findings to inform healthcare decisions

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