INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

LARGE SIMPLE TRIALS AND KNOWLEDGE GENERATION IN A LEARNING HEALTH SYSTEM

An Institute of Medicine Workshop

NOVEMBER 26 & 27, 2012

ROOM 100
KECK CENTER
500 FIFTH ST NW, WASHINGTON DC

ROUNDTABLE ON VALUE & SCIENCE-DRIVEN HEALTH CARE
FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

Meeting objectives

1. Explore accelerating the use of large simple trials (LSTs) to improve the speed and practicality of knowledge generation for medical decision making and medical product development;
2. Consider the concepts of LST design, examples of successful LSTs, the relative advantages of LSTs, and the infrastructure needed to build LST capacity as a routine function of care;
3. Identify structural, cultural, and regulatory barriers hindering the development of an enhanced LST capacity; and discuss needs and strategies in building public demand for, and participation in, LSTs; and
4. Suggest near-term strategies for accelerating progress in the uptake of LSTs in the United States.

Agenda

Monday, November 26th

1:00 pm	**Welcome, introductions, and overview**

Welcome, framing of the meeting, and agenda overview
- o Michael McGinnis (Institute of Medicine)
- o Richard Kuntz (Planning Committee co-Chair, Medtronic)
- o David DeMets (Planning Committee co-Chair, University of Wisconsin)

1:15pm	**Introduction to Large Simple Trials**

Session chair: David DeMets (Planning Committee co-Chair, University of Wisconsin)

➢ **Session objectives:**
- o Set vision for LSTs as part of learning health system
- o Discuss advantages of LSTs over current trial approaches
- o Discuss opportunities for LSTs as way to embed trials in growing digital infrastructure

- ➤ **Presentations:**
  - o **A vision for LSTs in the learning health system**
    Michael Lauer (National Heart Lung and Blood Institute)
  - o **Opportunities and challenges for LSTs**
    Ralph Horwitz (GlaxoSmithKline)

- ➤ **Session Questions:**
  1. What is a LST?
  2. How would these trials fit into the larger clinical research ecosystem in a learning health system?
  3. What need would this approach to clinical trials fill? (RCT cost, efficiency, generalizability)
  4. What are the advantages/disadvantages to this approach? (Heterogeneity, sub group analysis)
  5. How does the increased adoption of EHRs provide an opportunity for LSTs?
  6. Are there modifications to current design and conduct of LSTs that would enhance their value to a LHS?
  7. What are some examples of the areas still in need of work in order to realize this vision? (eg. Culture shift needed to adopt potentially disruptive technologies)

  Q&A and Open Discussion

1:55pm	**Highlighted examples of LSTs**

Session chair: James Young (Cleveland Clinic)

- ➤ **Session objectives:**
  - o Highlight 4 examples of LSTs that each exemplify a different defining characteristic of LSTs
  - o Emphasize tradeoffs in trial design by discussing pros and cons, giving examples of how these play out, and suggesting alternative approaches
  - o Foreshadow rest of workshop by asking LST example speakers to address their experiences (successes and failures) with stakeholder engagement, infrastructure, and policy.

- ➤ **Presentations:**
  - o Very large, population-based trial with broad inclusion criteria, high cost-efficiency, and hybrid design (mail-based plus in-clinic component)
    - ▪ **VITamin D/ OmegA 3 triaL (VITAL)**
      JoAnn Manson (Harvard University)
  - o Trial assessing role of waiving medication copayments for improving drug adherence and health outcomes, collaboration with health insurance company (Aetna)
    - ▪ **Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MIFREE) trial**
      Niteesh Choudhry (Brigham and Women's Hospital)

2

- o Cluster randomized trial involving pediatric practices, utilization of EHR and decision support tools for obesity interventions
  - **High Five for Kids Trial/ Study of Technology to Accelerate Research (STAR)**
    Elsie Taveras (Harvard Pilgrim Health Care Institute)
- o Industry trial for regulatory approval with global component
  - **Heart Outcomes Prevention Evaluation (HOPE) trial**
    PJ Deveraux (McMaster University)

➢ **Session questions:**
1. Please give a very brief introduction on the specifics of the trial and why it is considered a LST.
2. How does the trial address the issues of generalizability of evidence produced, simplification of research processes, and cost effectiveness?
3. In retrospect, what were the risks and tradeoffs associated with the choice of an LST design? (eg. Risk of not collecting data that could be subsequently requested) Please discuss pros and cons, giving examples of how these play out and suggesting alternative approaches, and any design changes you would make based on lessons learned.
4. What were your team's experiences (successes and failures) with the following issues, which will be discussed in further detail during the course of the workshop:
   a. Stakeholder engagement – health system leaders, clinicians, patients
   b. Infrastructure – research infrastructure, health IT
   c. Policy – privacy, consent, IRB issues, regulatory

   Q&A and Open Discussion

3:15pm	**Break**

3:30pm	**Partners perspectives on LST uptake**

Session chair: Joe Selby (Patient-Centered Outcomes Research Institute)

➢ **Session objectives:**
- o Identification of stakeholders relevant to the increased use of LSTs—focusing on patients, clinicians/health care systems, and payers—and incentives they face that could impede or advance uptake
- o Engage issues of most importance to stakeholders and deliberate on what it will take from each of their respective points of view

➢ **Presentations:**
- o **Patient perspective**- Nancy Roach (Fight Colorectal Cancer)
- o **Health systems/ Clinician perspective**- Alan Go (Kaiser Permanente)
- o **Payer perspective**- Lew Sandy (UnitedHealth)

➢ **Session questions:**

3

1. What are the top three issues for patients/clinicians/payers in *considering the use* of an LST approach to generate clinical evidence?
2. What are the top three considerations for patients and clinicians in contemplating the greater *integration of trials into routine care* settings?
3. What are the top three priorities for *raising awareness and participation* of patients and clinicians in trials integrated into routine care?
4. What are your priorities regarding the types of evidence that can be generated through LSTs?
5. What are the roles for health systems and payers in a) setting priorities, b) dedicating staff support, and c) providing funding for LSTs in routine care settings?

Q&A and Open Discussion

4:30pm	**Summary and preview of next day**

5:00pm	**Adjourn**

****

Tuesday, November 27th

8:00 am   Coffee and light breakfast available

8:30 am	**Welcome, brief agenda overview**

Welcome, framing of the meeting, and agenda overview
- o David DeMets (Planning Committee co-Chair, University of Wisconsin)
- o Richard Kuntz (Planning Committee co-Chair, Medtronic)

8:45 am	**Infrastructure needs**

Session chair: John Orloff (Novartis)

➢ **Session objectives:**
- o Highlight infrastructure needs and barriers to greater performance of LSTs
- o Discuss needs and potential approaches to merge goals of care system with research, focusing on the current state and future potential of the use of EHRs as platform for LSTs
- o Discuss establishment and sustainability of trial networks as an infrastructure to host and facilitate LSTs

➢ **Presentations:**
- o **Aligning care and research to reduce burdens and improve integration** – Rich Platt (Harvard Pilgrim Health Care Institute)
- o **Point-of-care trials using EHR platforms**- Ryan Ferguson (VA Boston Healthcare System)

- o **Getting to comparable, computable data**- Rebecca Kush (Clinical Data Interchange Standards Consortium)
- o **Building reusable research networks**- Carole Lannon (Cincinnati Children's)

➢ **Session questions:**
1. What are the current infrastructure needs for more widespread performance of LSTs? Would you consider conducting LSTs on your network?
2. What opportunities and challenges currently exist in using EHRs as a platform for LSTs? What are the priorities for change to maximize this potential going forward? How can we minimize disruption to delivery of healthcare in order to incentivize more practicing physicians to engage in knowledge generation?
3. What is the current state of the use of routinely collected clinical data for trials? What role will data standards play in facilitating LSTs? What are the priorities for change to maximize this potential going forward?
4. What is the current state of reusable research networks in the US? What is their role in LSTs? What are the major opportunities and barriers to the reusable network approach? Are there alternative community-based settings with lower infrastructure costs and greater access to patients that should be considered? Are existing research networks (including perhaps CTSA institutions, or PBRNs) fit for purpose? What business models (e.g. "hub and spoke") would be most effective?

Q&A and Open Discussion

10:45am	**Break**

11:00am	**Policy needs: Ethics, trial processes**

Session chair: Rob Califf (Duke University)

➢ **Session objectives:**
- o Spotlight and differentiate real and perceived policy barriers to greater use of LSTs
- o Highlight examples of ways these have been dealt with (or overcome)
- o Anticipate potential policy issues as trials move to leverage electronic systems
- o Suggest components of a policy framework that would facilitate LSTs

➢ **Presentations:**
- o **Policy overview-** Robert Califf (Duke University)
- o **Ethical issues of bringing research and care closer together-** Ruth Faden (Johns Hopkins University)
- o **Trial process challenges (privacy, IRBs)-** Deven McGraw (Center for Democracy and Technology)

➢ **Session questions:**

5

1. What are the major policy barriers to the more widespread performance of LSTs? How have these barriers been overcome in the past? What are the priorities for change going forward?
2. What are the important ethical issues to consider in bringing research and care closer together? What are the components of a new ethical framework to support a learning health system?
3. What are the major privacy and human subjects research policy-associated considerations for LSTs? How have these challenges been overcome? What are the priorities for change going forward?
4. What are the relevant ethical and policy considerations associated with randomization without additional consent in situations of equipoise?

Q&A and Open Discussion

12:00pm	**Lunch keynote**

- ➢ Randomized evaluations of accepted choices in treatment ([REACT](#)) trials
  Tjeerd-Pieter van Staa (Clinical Practice Research Datalink (UK))

- ➢ **Session questions:**
  1. What are the REACT trials? What was the impetus for these trials? How do they compare to LSTs?
  2. What are the stakeholder engagement-related challenges you have faced in setting up/running these trials? How have the relevant stakeholder groups responded?
  3. What are the infrastructure-related challenges and opportunities you have faced? What role has the level of EHR adoption placed in facilitating or inhibiting them? What are the most crucial non-IT infrastructure resources?
  4. How have you addressed concerns about the accuracy and validity of data in the electronic medical record?
  5. What are the policy-related challenges you have faced? What are the differences between the UK and US systems that have facilitated or impeded these challenges?
  6. What lessons learned and/or best practices would you pass along to LST investigators? What would you do differently?

Q&A and Open Discussion

1:00pm	**Policy needs: Medical product regulatory issues**

Session chair: Rick Kuntz (Planning Committee co-chair, Medtronic Inc.)

- ➢ **Presentations:**
  - o **Trial complexity**- Ken Getz (Tufts University)
  - o **Simplifying clinical trials**– Christopher Granger (Duke University)
  - o **FDA perspective**- Rachel Sherman (FDA/CDER)

- ➢ **Session questions:**

1. Generally speaking, what is the optimal role of LSTs in the medical products regulatory approval pathway? Are there areas of medical product development in which LSTs are not useful?
2. How can an understanding of those policy/regulatory issues that drive complexity in traditional RCTs, and the strategies to counteract them, be applied to the adoption and use of LSTs in medical products regulatory contexts?
3. What are the real and perceived regulatory barriers hindering the development of an enhanced LST capacity?
4. What are some near-term strategies for accelerating progress in the uptake of LSTs in the United States?
5. What is the current thinking from the FDA in terms of how and when LSTs might be used without jeopardizing the medical products development process?

Q&A and Open Discussion

2:00pm	**Break**

2:15pm	**Strategies going forward**

Session chair: David DeMets (Planning Committee co-Chair, University of Wisconsin)

➢ **Session Objectives:**
   o Identify and discuss issues and key themes from the workshop
   o Consider strategies and priorities for accelerating progress in the uptake of LSTs in the United States

➢ **Brief summaries and key stakeholder perspectives from workshop:**
   o Representatives from key stakeholders groups will provide an overview of key themes and issues identified from their perspectives

      ▪ Federal funders – Michael Lauer (NHLBI)
      ▪ Non-governmental funders – Robert Ratner (American Diabetes Association)
      ▪ Food and Drug Administration – Bram Zuckerman (FDA/CDRH)
      ▪ Centers for Medicare & Medicaid Services – Rosemarie Hakim (CMS)
      ▪ Private payers – William Crown (Optum)
      ▪ Industry – Peter Held (AstraZeneca)
      ▪ Patients – Kate Ryan (National Women's Health Network)
      ▪ Clinical researchers – Elizabeth Chrischilles (University of Iowa)

➢ **Panel questions:**
   1. What are the themes of today's presentations and discussions that have resonated most strongly with you?

2. Where do you see the most opportunity for the application of LSTs? What do you see as the biggest barriers?
3. What will it take to seize these opportunities and overcome the barriers?
4. Based on the presentations and discussions, can you identify issues that need to be resolved by others before progress can be made? For example, as lead of the Ethics and Processes section, can you identify critical needs in infrastructure or regulatory issues that need to be resolved before you can achieve your goals?
5. If you were granted one wish to move LSTs forward, what would that wish be?

Q&A and Open Discussion

4:15 pm	**Next steps**

> **Session Description:** Workshop will conclude with a brief discussion and summary of next steps.

5:00pm	**Adjourn**

<center>***</center>