Public-Private Partnership co-founded by Duke University & FDA involves all stakeholders 80+ members

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials
A Viewpoint on the Current State of Clinical Trials and the Path to Transformation

Robert M. Califf, MD
State of Clinical Trials

• By old standards, the system of clinical trials has provided the basis for profound improvements in health and healthcare

• Early phase and traditional regulated clinical trials can benefit from continued incremental improvement
  – We can get more information at a lower overall cost!

• As our understanding of the ecosystem grows, it is clear that it is delivering a fraction of the reliable actionable evidence that we need

• Log order improvement is within sight for late phase and health delivery improvement trials

• Examples of successful new approaches are in place

• Risk taking impeded by:
  – Conservative nature of study sections
  – Fear of regulatory conservative behavior
  – Broad misunderstanding of principles
A Real Privilege

• A decade ago there was a sense of frustration with the clinical trials enterprise
• CTTI was formed as a public private partnership
• Then I spent 2 years at FDA
• I’m still frustrated, but looking back we’ve made real progress and transformational progress is now in sight!
Pathways to Transformation

• Education
• Continue on the path to transparency
• Human adaptation to the power of computation, information and analytics
• Carrying through key issues from Cures
  – Consumer/Patient activation
  – Biomarkers
  – Trial design and analytical improvements
  – “Real world evidence”
CTTI Strategic Plan

MISSION STATEMENT
To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

GOALS
Create recommendations & tools
Make data publicly available
Communicate broadly
Demonstrate impact
Characterize clinical trial landscape

AREAS OF STRATEGIC FOCUS
Systematic evidence generation
Patients as equal partners
Clinical trials designed with a focus on quality & efficiency
Trials addressing emerging public health concerns
Safe & ethical trials that are streamlined
General Thoughts about Types of Trials

• Early phase/mechanistic
  – Determine mechanisms
  – Preliminary evidence of safety/target engagement/biological effects

• Mid-phase regulated trials
  – Develop evidence of risk and benefit in selected populations

• Later phase and post-market trials
  – Develop generalizable evidence of risk and benefit
  – Improve delivery of effective therapies

• Health services trials
  – Develop generalizable evidence of best way to deliver health services
Early Phase/Mechanistic Trials

• Generally not employing best technology
• Most information lost since most medical products fail during development
• Real opportunity now to take advantage of the “measurement revolution” engendered by genetics, genomics, molecular biology, engineering and information technology
Many tools to dissect individualized health

Health records

Poverty

Food deserts

Proteomics

Genomics

Metabolomics

Patient-specific iPSC-derived cells

Images

mHealth
The challenge: integrating multiple datasets for discovery and implementation
Healthy gut microbiome

- SCFA-producing bacteria
- Clostridiales sp. SS3/4
- F. prausnitzii
- R. intestinalis
- R. inulinivorans

Functions
- Bacterial chemotaxis
- Flagellar assembly
- Butyrate biosynthesis
- Degradation and metabolism of xenobiotics
- Biosynthesis of hydrogen sulfide
- Resistance to oxidative stress
- Metabolism of cofactors and vitamins
- Metabolism of Peptide YY · lenta

Type 2 diabetes microbiome

- C. hathewayi
- C. ramosum
- C. symbiosum
- E. lenta

Functions
- Membrane transport of sugars
- BCAA transport
- Degradation and metabolism of xenobiotics
- Biosynthesis of hydrogen sulfide
- Resistance to oxidative stress
- Peptide YY · lenta

Inflammation↓

Nature Reviews | Microbiology
Same microbial markers at different body sites

- Lactobacillus salivarius

Environmental factors
- Smoking
- Female sex
- Cold temperature
- Obesity

Different microbial markers correlated at different body sites

Genetic predisposition
- HLA-DRB1
- PADI4
- TNFAIP3
- PTPN22

- Klebsiella pneumoniae
  - Positively correlated
  - Synovitis
- Lactococcus spp.
- Clostridium asparagiforme
- Prevotella intermedia
  - Negatively correlated
  - Cartilage damage and bone erosion
In 20 Years...

- All people in developed nations will have —
  - An electronic health record
  - Biological samples
  - Digitized images

- Healthcare will be personalized using an individual’s images, samples and clinical data.

- The health of a community will be monitored using aggregate records.
Clinical and Genomic Profiling to Prediction Outcome and Treatment

Diabetes

Clinical & Genomic Profiling

Exercised
Diet A

A-Exercise
Diet B

No Exercise
Diet + Medication
Traditional Regulated Trials

- Incremental improvement in quality
- Cost continues to escalate
<table>
<thead>
<tr>
<th>PROJECT PORTFOLIO</th>
<th>Systematic Evidence Generation</th>
<th>Patients as Equal Partners</th>
<th>Efficient &amp; Quality Trials</th>
<th>Public Health Concern</th>
<th>Safe &amp; Ethical Trials</th>
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<tr>
<td>Complete Projects</td>
<td>Large Simple Trials</td>
<td>GCP Training</td>
<td>ABDD Streamlining HABP/VABP Trials</td>
<td>Central IRB</td>
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<td>IND Safety</td>
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<td>SAE Reporting</td>
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<td>Active Projects</td>
<td>MCT Legal &amp; Regulatory</td>
<td>Patient Groups &amp; Clinical Trials</td>
<td>GCP Follow On Investigator Community</td>
<td>IND Safety Advancement</td>
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<td>MCT Mobile Devices</td>
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<td>MCT Novel Endpoints</td>
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<td>ABDD Peds Trials</td>
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<td>MCT Stakeholder Perceptions</td>
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<td>Real World Evidence</td>
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<td>State of Clinical Trials</td>
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*CTTI*
<table>
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<tr>
<th>COLLABORATIONS PORTFOLIO</th>
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<td><strong>Completed Collaborations</strong></td>
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<td>Clinical Trials for Comparative Effectiveness</td>
<td>Patient Engagement Survey</td>
<td>Clinical Trials Poll FDA Training Course Patient Engagement Survey</td>
<td>Cardiovascular Endpoints</td>
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<td>Electronic Healthcare Data</td>
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<td><strong>Active Collaborations</strong></td>
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<td>Sentinel IMPACT-AFib</td>
<td>Patient Engagement Collaborative</td>
<td>ABDD PTN</td>
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<td>Patient Engagement Survey</td>
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Later Phase and Post-Market
The Problem

• The public, patients, clinicians, regulators (FDA) and health systems need more evidence
  – To make better decisions
  – To improve labels to provide clinicians and patients with accurate and useful information for safe and effective use of drugs, devices and biologics in practice
  – To improve clinical practice guidelines to provide better evidence for recommendations

• Payors (CMS and private) and health technology assessors need evidence to calculate the value of medical products as used in practice

• The current system is not delivering adequate evidence in the face of
  – an explosion of new medical products and increased understanding of how to evaluate products already in clinical use
  – Major changes in delivery and payment systems
  – Increasing awareness of disparities
But it’s a good problem to have

- Current system producing highly effective medical products
- Pipelines are in good shape
- Life expectancy continues to increase every year
- We are doing very well compared with the past
- Now it’s a matter of going to the next level
Best Practices for Patient Group Engagement in Clinical Trials
Objective 1: Identify Best Practices for Engaging Patient Groups in Clinical Trials

Objectives

1. Conduct a literature review and survey to assess types of relevant PGs, querying a representative sample across disease states to highlight distinctions in missions, reach, infrastructures, governance models and interest and engagement in clinical trials.

2. Identify current research sponsor and investigator practices for engaging with PGs, and practices used by patient groups to engage with research sponsors and investigators, around clinical trials.

3. Explore successes and failures to identify models of engagement with PGs that have led to more quality driven and efficient trials.

4. Formulate recommendations and opportunities for implementation of best practices with PGs, academia and industry that will lead to more efficient and successful clinical trials.
CONFIRMED BARRIERS TO COLLABORATION

- Mismatched expectations between trial teams & PGs
- Excluding PGs from early stages of trial planning & design
- Lack of sophistication of PGs
- Unsure of how to identify/engage w/ PGs
- Providing PGs w/ only a token seat at the table, not making them full partners in the trials process
- Internal resistance, lack of buy-in
- Perceived difficulty of overcoming legal barriers to industry/patient collaboration
- Lack of best practices for engagement & lack of infrastructure to support patient outreach operations
- Lack of demonstrated value
- Lack of funding
PG Engagement Across the Research & Development Continuum

From Bench to Bedside and Back

- Input re interest of research question to patient community
- Providing data on unmet need & therapeutic burden
- Fundraising and direct funding for research to identify target molecules
- Facilitating collaboration with NIH
- Characterizing the disease & relevant mechanisms of action

Pre-Discovery
- Fundraising and direct funding for research
- Providing translational tools (assays, cell & animal models, biosamples, biomarkers, etc.)
- Helping define study’s eligibility criteria
- Natural history database & patient registry support
- Input on meaningful clinical endpoints
- Assistance re informed consent form
- Working with FDA re benefit-risk and draft guidance
- Accompanying sponsor to Pre-IND FDA mtg to advocate for study

Pre-Clinical
- FDA review & approval
- Providing public testimony at the FDA Advisory Committee & other FDA hearings
- Preparing submission for newborn screening when appropriate

Phase 1/2/3
- PAS/Outcomes
- Serving on post-market surveillance initiatives
- Helping return study results to participants
- Co-presenting results
- Publications/communications re results
- Feedback on how patient community views results
- Natural history database & registry support
- Working with payers re reimbursement

*Adapted from Parkinson’s Disease Foundation materials for CTTI’s Patient Groups & Clinical Trials Project*
Putting in All Together: Impact of Patient Engagement Resulting in Avoiding an Amendment & An Improved Patient Experience

<table>
<thead>
<tr>
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<th>Impact of Patient Engagement*</th>
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<tr>
<td>Started in</td>
<td>Phase 2</td>
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<tr>
<td></td>
<td>Phase 3</td>
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<tr>
<td>Launch Date</td>
<td>9 months earlier</td>
</tr>
<tr>
<td></td>
<td>6 months earlier</td>
</tr>
<tr>
<td>NPV ($MM)</td>
<td>$62</td>
</tr>
<tr>
<td></td>
<td>$65</td>
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<tr>
<td>P(launch)</td>
<td>5%</td>
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<td>6%</td>
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<td>ENPV ($MM)</td>
<td>$35</td>
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<td>$75</td>
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<tr>
<td>Cost to Launch ($MM)</td>
<td>-$0.5</td>
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Phase 2
- 10x benefit in cost
- 700x benefit in ENPV
- 1240x benefit in NPV

Phase 3
- 42x benefit in cost
- 1500x benefit in ENPV
- 1300x benefit in NPV

High benefits retained with sensitivity analyses

*Amendment avoidance and improved patient experience
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell
Balancing Safety and Effectiveness

Conceptual Goal: Not a ratio that can be calculated the same way for every person!
God at His computer
Approaches to Trials

• “Umbrella” trials
  – One medical issue with multiple drugs and predictive biomarkers
  – Participants are matched to drugs based on predictive biomarkers
  – Cooperation among multiple sponsors and hard to pull off
  – Examples: BATTLE, I-SPY, Lung-MAP

• “Basket” or “bucket” trials
  – Multiple medical issues with one drug and a predictive biomarker
  – Intends to gain drug approval in multiple tumor types with a common predictive biomarker under the premise that molecular subtype is more fundamental than histology
  – Single sponsor and easy to pull off
Generating Evidence to Inform Decisions

1. FDA Critical Path
2. NIH Roadmap
3. Data Standards
4. Network Information
5. Empirical Ethics
6. Priorities and Processes
7. Inclusiveness
8. Use for Feedback on Priorities
9. Conflict of Interest Management
10. Evaluation of Speed and Fluency
11. Pay for Performance
12. Transparency to Consumers

Discovery Science

Early Translational Steps

Measurement and Education

Outcomes

Performance Measures

Clinical Trials

Clinical Practice Guidelines
Our National Clinical Research System is Well-intentioned But Flawed

- High percentage of decisions not supported by evidence*
- Health outcomes and disparities are not improving
- Current system is great except:
  - Too slow, too expensive, and not reliable
  - Doesn’t answer questions that matter most to patients
  - Unattractive to clinicians & administrators

We are not generating the evidence we need to support the healthcare decisions that patients and their doctors have to make every day.

* Tricoci P et al. JAMA 2009;301:831-41
Which Treatment is Best for Whom?  
High-Quality Evidence is Scarce  
< 15% of Guideline Recommendations Supported by High Quality Evidence

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD  
Joseph M. Allen, MA  
Judith M. Kramer, MD, MS  
Robert M. Califf, MD  
Sidney C. Smith Jr, MD  

Clinical practice guidelines are systematically developed statements to assist practitioners with decisions about appropriate health care for specific patients.

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.
Trial Hyperinflation

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

Index (1989 = 1.000)

Mean Total Grant Cost per Patient Index

Pooled hedonic index with trial phase, therapeutic area, and year as indicator variables

Biomedical R&D Price Index

Pooled hedonic index with trial phase, therapeutic area, and year as indicator variables and with SWE and LPATIENTS added to base model as regressors.

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

Berndt E, Cockburn I. Monthly Labor Review, June 2014
Learning health care systems

In a learning health care system, research influences practice and practice influences research.

**INTERNAL AND EXTERNAL SCAN**
Identify problems and potentially innovative solutions.

**DESIGN**
Design care and evaluation based on evidence generated here and elsewhere.

**IMPLEMENT**
Apply plan in pilot and control settings.

**EVALUATE**
Collect data and analyze results to show what works and what doesn’t.

**ADJUST**
Use evidence to influence continual improvement.

**DISSEMINATE**
Share results to improve care for everyone.
Historical model of clinical research: Many recruitment sites and a coordinating center

- Hub & spoke model
- Top-down decision-making
- Sites operated independently
Modified Model
Data Shared, Sites owned by Health Systems
Academic medical centers in the US have become academic health and science systems (AHASs!)—they are no longer ivory towers—they are major economic engines and social forces in our society.
The “Biomedical Academic System”

Figure 2: Academic health sciences system (AHSS) as a vertically integrated care-delivery system

Previously Independent Sites now part of large integrated health systems
increasingly sophisticated data warehouses
Nodes are Operational Clusters Using Common Data

KP Colorado
KP Georgia
KP Mid-Atlantic
KP Northwest
KP Northern CA
KP Georgia
KP Southern CA

Kaiser/CESR
Sentinel Distributed Analysis

1- User creates and submits query (a computer program)
2- Data partners retrieve query
3- Data partners review and run query against their local data
4- Data partners review results
5- Data partners return results via secure network
6 Results are aggregated
Sentinel Distributed Database*

- Populations with well-defined person-time for which most medically-attended events are known
  - 193 million members**
  - 351 million person-years of observation time
  - 39 million people currently accruing new data
  - 4.8 billion dispensings
  - 5.5 billion unique encounters
    - 51 million acute inpatient stays
  - 33 million people with >1 laboratory test result

* As of August 2015, excludes HCA and BCBS of Massachusetts
** Double counting exists for individuals who change health plans
Post Market Studies, including comparative effectiveness

PCORnet

Coordinating Center
PCORnet embodies a “network of networks” by uniting people, clinicians & systems

20 Patient-Powered Research Networks (PPRNs) + 13 Clinical Data Research Networks (CDRNs) = PCORnet A national infrastructure for people-centered clinical research
Resulting in a national evidence system with unparalleled research readiness

PCORnet represents:

~110 million patients

who have had a medical encounter in the past 5 years

*some individuals may have visited more than one Network Partner and would be counted more than once

<table>
<thead>
<tr>
<th>Pool of patients</th>
<th>For clinical trials</th>
<th>For observational studies</th>
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<tbody>
<tr>
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<td>42,545,341</td>
<td>83,131,450</td>
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Sex
Race
Age
Pool of patients
Device Surveillance and Trials
National System Paradigm Shift

Passive Surveillance
- Challenging to find right pre/post market balance without confidence in post-market data
- Parallel track to clinical practice

Active Surveillance
- Leverage RWE to support regulatory decisions throughout TPLC

Embedded in Health Care System
- (collect data during routine clinical care)

Shared system to inform the entire Ecosystem
- (patients, clinicians, providers, payers, FDA, Device Firms)

Current
- Inefficient one-off studies

National System
Learning Medical Device Ecosystem

Total Product Life Cycle (TPLC) Framework

- **Learning Medical Device Ecosystem**
- **Total Product Life Cycle (TPLC) Framework**

---

**INFORMATION**

- Benefit-Risk Evidence

---

**INFORMATION**

- Patient Access
- Benefit-Risk

---

**INTERNATIONAL HARMONIZATION**

- Progressive Approval, Safety and Performance
- NEST
- Clinical Research Incorporated Into Routine Clinical Practice

---

**TIME TO MARKET**

- Expedited Access
- Postmarket Surveillance
- National Evaluation System (NEST)

---

**EVOLUTION OF BENEFIT–RISK EVIDENCE**

- Total Product Life Cycle (TPLC) Framework
  - Progressive Approval, Safety and Performance
  - NEST
  - Clinical Research Incorporated Into Routine Clinical Practice

---

**INFORMATION**

- Patient Access
- Benefit-Risk

---

**INTERNATIONAL HARMONIZATION**

- Progressive Approval, Safety and Performance
- NEST
- Clinical Research Incorporated Into Routine Clinical Practice

---

**TIME TO MARKET**

- Expedited Access
- Postmarket Surveillance
- National Evaluation System (NEST)
FDA Safety and Innovation Act

• Section 1136 of FDASIA (Jul 9, 2012) amended the FD&C Act by adding new section 745A, which addresses electronic submissions.

• Starting 24 months after final guidance for a specific submission type, Sponsors must use the standards defined in the data standards catalog (for submissions for NDAs, ANDAs, and BLAs)

• Guidance document for Submissions Under Section 745A(a):
  – Draft published February 2014
  – Final publication December 17, 2014
FDASIA Guidance
Implementation Highlights

How does FDA plan to implement Section 745A(a) of the FD&C Act?

- **FDASIA Guidance**
  - Technical Conformance Guide
    - Provides specifications, recommendations, and general considerations on how to submit standardized study data.

- **eStudy Guidance**
  - Binding Guidance—Requires that studies are compliant with the standards outlined in the FDA Data Standards Catalog
  - What submission types must be electronic?

- **Data Standards Catalog**
  - Lists supported and/or required standards.

- **eCTD Guidance**
  - 24 months after guidance is finalized, content must be submitted to the Agency electronically in the format specified in the guidance.

**FDASIA Guidance**

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Data Activation and Testing Outcomes

What Impacts Behavior?

A
CONTROL

B
VARIATION
Call to Action

• Organize operational systems that bring together research networks embedded in practice
  
  – to enable patients, consumers, clinicians, industry, government, and health care systems to participate in prospective trials and observational studies
  
  – Develop operational/regulatory approaches to facilitate practice-based systems for therapeutic research, safety surveillance, public health, and quality improvement.
  
  – Support adequate time commitment for clinicians to engage with patients to ensure mutual understanding and appropriate consent
  
  – Efficient systems for contracting and liability
  
  – Clinical care and research closely aligned in “learning health system” supported by education and training
  
  – How can delivery systems with their evolving power create a system that encourages participation in an efficient system?
Call to Action

• Establish a robust framework for privacy, confidentiality, and security
  • endorsed by patients and consumers to ensure the trust a learning health system will require,
  • Robust procedures that ensure data security and protect confidentiality
  • Efficient and thorough digital system of education and research permissions for patients
  • Balance of individual autonomy and public health needs
  • Great start: Precision Medicine Initiative: Privacy and Trust Principles
  • How can delivery systems take on a more constructive role to move the system to a participatory learning system?
Call to Action

- Adopt a common approach to configuring, storing, and re-using digital health care data to enable use in care, research, safety surveillance, and public health
  - As called for in the Nationwide Interoperability Roadmap published by the Office of the National Coordinator for Health Information Technology.
  - Common standards and terminology for prospective data collection
  - Continuous effort to curate data to produce high quality data sets for analysis using common data models
  - Leverage existing digital health/healthcare data to create efficiencies (registries, claims data, EHR data, personal devices)
  - Can delivery systems figure out how to share data at the scale needed now that we understand the needed sample sizes?
Call to Action

• Develop and test new methods to reliably answer research questions
  – more efficient RCTs,
  – Novel designs such as cluster-randomized trials, basket trials
  – And more reliable observational studies aimed at assessment of interventions
  – “Meta-knowledge” on which methods are best for which types of questions
  – By leveraging data already collected by health information technology and other electronic sources to answer research questions or facilitate the conduct of new trials.
  – **Will delivery systems value clinical science enough to create the needed work force and reward scholarly activity in this arena?**
Call to Action

• Ensure the development of novel approaches focusing on streamlining and harmonizing processes in ways that eliminate barriers that promote unnecessary complexity, while ensuring safeguards that are truly needed.
  – Streamlined and harmonized processes eliminate barriers to efficient research while ensuring needed safeguards
  – Systems for high quality and efficient ethics review and contracting
  – Development of approaches to assuring quality systems through better use of analytics
  – Can AMCs regard efficiency in research with the same seriousness as they have addressed efficiency in clinical care?
The End Game

• Continuous observational learning
• Broad sharing of data
• Providers and systems
  – Acknowledge uncertainty
  – Benefit from learning as a way of practice
• Patients actively participate
THANK YOU.

www.ctti-clinicaltrials.org