Disrupting Clinical Research: Transforming a System

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Vice Chancellor for Clinical and Translational Research
Duke University
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Conflicts

• All of my “industry relationships” can be found at www.dcri.org/about-us/conflict-of-interest/Califf-COI_2013

• I work as an official in an academic health and science system that depends on a margin from the current reimbursement system that rewards behaviors that may not be good for your health!
The Best of Times, the Worst of Times

Fundamental science unprecedentedly advanced, but:

- Poor transition of basic or clinical observations into interventions that tangibly improve human health
- Drug/device/diagnostic development system in crisis
- Clinical trials system in crisis
- Poor adoption of demonstrably useful interventions

People unhealthier and funders of biomedical research enterprise (public and private) impatient
PHARMACEUTICAL INDUSTRY
RECENT TRENDS AND CHALLENGES

+ $1.1 TRILLION BY 2014. WORLDWIDE PHARMACEUTICAL SALES ARE EXPECTED TO INCREASE AT A COMPOUND ANNUAL GROWTH RATE OF 5–8%. FUELING THESE GAINS ARE PROJECTED DOUBLE-DIGIT GROWTH RATES IN EMERGING ECONOMIES.

THE CHALLENGES

EXPIRING PATENTS

2011 $142 billion

2015

AS PRODUCTS COME OFF PATENT PROTECTION, MANY LARGE FIRMS ARE AT RISK OF REVENUE REDUCTION OF UP TO 30–40%.

GROWTH OF GENERICS

THE US GENERIC MARKET IS ANTICIPATED TO GROW 10% ANNUALLY DURING 2010–2013, FUELED BY THE PRESSURE TO REDUCE COSTS IN HEALTHCARE, THE EXPIRATION OF PATENTS AND THE ESTABLISHMENT OF AN APPROVAL PATHWAY FOR BIOSIMILARS.

DRUG RECALLS

↑ 309% IN 2009

CONCERNS OVER SAFETY AND SUPPLY CHAIN QUALITY HAVE SURGED.

THE OPPORTUNITIES

HEALTHCARE REFORM

32 MILLION+

ADDITIONAL PEOPLE WILL HAVE HEALTH INSURANCE AND ACCESS TO PRESCRIPTION DRUGS UNDER THE NEW HEALTH PLAN.

OUTSOURCING, COLLABORATIVE PARTNERSHIPS AND STRATEGIC ALLIANCES WITHIN THE INDUSTRY ARE FORGING NEW BUSINESS MODELS.

2x

THE 65+ SEGMENT OF THE POPULATION WILL NEARLY DOUBLE BETWEEN 2010 AND 2030. ON AVERAGE, THOSE OVER 65 YEARS OLD TAKE BETWEEN 5 TO 6 PRESCRIPTION MEDICINES.

Progressive pharmaceutical companies are realizing that in order to respond to these pressures and command a competitive position in the marketplace, they must take a new approach to their overall workforce strategy, finding new strategies for accessing and deploying critical talent where and when they need it.
Eroom’s Law

The number of new drugs approved by the FDA per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years since 1950.

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
  - Unreliable
  - 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.

The Clinical Trials Transformation Initiative

- Public private partnership co-founded by Duke and FDA in late 2007
- All stakeholders involved
- Through a MOU with FDA, Duke convenes the initiative

**Mission**
To identify and promote practices that will increase the quality and efficiency of clinical trials

**Vision**
A high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options
CTTI Member Organizations

- 17 Academia
- 17 Patient Reps
- 12 Pharmaceutical
- 10 Government US
- 5 Biotech
- 4 Clinical Research Organization
- 4 Device/Diagnostics
- 4 Institutional Review Boards
- 4 Professional Societies
- 4 Other
- 3 Clinical Investigators
- 2 Professional Services
How does CTTI seek to effect change?

- Identify and eliminate activities in the conduct of trials that do not add value
- Understand incentives to maintain non-value-added activities
- Develop solutions that are mindful of the needs of patients and all sectors in the clinical research enterprise
- Maintain an open and respectful dialogue across sectors
- Involve all sectors in selection, conduct, and interpretation of projects
CTTI Strategy

1. Identify and shape potential **TRANSFORMATIONAL** changes to the system

2. Seek **INCREMENTAL** improvements to current system

3. Consider **PORTFOLIO** improvements of clinical trials being done relative to public health needs
## Portfolio of CTTI Projects

<table>
<thead>
<tr>
<th></th>
<th>Investigational Plan</th>
<th>Study Start-Up</th>
<th>Study Conduct</th>
<th>Analysis &amp; Dissemination</th>
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</thead>
<tbody>
<tr>
<td><strong>Completed</strong></td>
<td>Long-Term Opioid Data Uses of Electronic Data</td>
<td><strong>Central IRB</strong></td>
<td>Adverse Event Reporting IND Safety Monitoring</td>
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<tr>
<td></td>
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<td>Site Metrics</td>
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<tr>
<td><strong>2014</strong></td>
<td>Trials based on registries</td>
<td></td>
<td>Site Quality and Performance</td>
<td>DMCs</td>
</tr>
</tbody>
</table>

[www.ctti-clinicaltrials.org](http://www.ctti-clinicaltrials.org)
CTTI Projects

Current State Of Clinical Trials

Transformed Clinical Trials System

A high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.
Every day, patients and doctors face questions for which evidence is lacking to guide answers

- “Does ibuprofen cause heart attacks or strokes? If so, how much does it increase my risk?”
- “For ‘short cervix,’ does bed rest prevent early labor?”
- “Should my daily blood pressure medicine be taken in the morning or at night?”
- “What should I do about the new guidelines for prescribing statins for people with high cholesterol, but no symptoms?”
- “How can I help my 87-year-old patient with multiple myeloma decide which chemotherapy option is best?”
- “My child has been diagnosed with ADHD. What are the benefits and risks of giving him medication?”
Historical model of clinical research: Many recruitment sites and a coordinating center

- Hub & spoke model
- Top-down decision-making
- Sites operate independently
Both researchers and funders now recognize the value in integrating clinical research networks

- Linking existing networks means clinical research can be conducted more effectively
- Ensures that patients, providers, and scientists form true “communities of research”
- Creates “interoperability” – networks can share sites and data
The missing link: An agile and efficient infrastructure to support rapid, reliable studies
Health Care Systems Research Collaboratory

A Virtual Home for Knowledge about Pragmatic Clinical Trials using Health Systems: www.theresearchcollaboratory.org
Health Care Systems Research Collaboratory

1. Pragmatic trial design
2. Electronic health record as core data collection instrument
3. At least 2 integrated health systems collaborating to answer the question
   * Over 80 applications—7 funded to go forward with planning phase
NIH Health Care System Collaboratory

- Collaboratory Coordinating Center
- Nighttime Dose of Anti-Hypertensive Medications
- Prevent Suicide Attempt
- Reduce Mortality in End Stage Renal Disease (sites to be selected from units across all 50 states)

- Stop Colon Cancer in Priority Populations
- Chronic Pain in Primary Care
- Reduce Infections and Readmissions
- Lumbar Image Reporting and Epidemiology

Additional sites to be determined
PRAGMATIC TRIALS IN HEMODIALYSIS

Demonstration Project:
The Time to Reduce Mortality in Endstage Renal Disease (TiME) Trial

Principal Investigator:
Laura M. Dember, MD
University of Pennsylvania
TiME Trial Design

• **Hypothesis:**
  – extending dialysis sessions improves health outcomes

• **Interventions:**
  – extended dialysis sessions vs usual care

• **Cluster Randomization:**
  – by dialysis facility

• **Eligibility:**
  – all patients starting chronic hemodialysis

• **Outcomes:**
  – mortality, hospitalizations, HRQoL
Introducing PCORnet: The National Patient-Centered Clinical Research Network
PCORnet’s goal

PCORnet seeks to improve the nation’s capacity to conduct clinical research by creating a large, highly representative, national patient-centered network that supports more efficient clinical trials and observational studies.
PCORnet’s vision

PCORnet will support widespread capability for the US healthcare system to learn from research, meaning that large-scale research can be conducted with greater speed and accuracy within real-world care delivery systems.
**Overall objectives of PCORnet: achieving a single functional research network**

- **Create** a secure national research resource that will enable teams of health researchers, patients, and their partners to work together on researching questions of shared interest
- **Utilize** multiple rich data sources to support research, such as electronic health records, insurance claims data, and data reported directly by patients
- **Engage** patients, clinicians & health system leaders throughout the research cycle from idea generation to implementation
- **Support** observational and interventional research studies that compare how well different treatment options work for different people
- **Enable** external partners to collaborate with PCORI-funded networks
- **Sustain** PCORnet resources for a range of research activities supported by PCORI and other sponsors
29 CDRN and PPRN awards were approved on December 17th by PCORI’s Board of Governors.

This map depicts the number of PCORI-funded Patient-Powered or Clinical Data Research Networks that have coverage in each state.
Purposeful composition of the Steering Committee will help ensure that PCORnet influences research funded or conducted by others (PCORI Strategic Goal #3)
Goals for each Clinical Data Research Network (CDRN)

- Create a research-ready dataset of at least 1 million patients that is:
  - **Secure** and does not identify individual patients
  - **Comprehensive**, using data from EHRs to describe patients’ care experience over time and in different care settings

- Involve patients, clinicians, and health system leaders in all aspects of creating and running the network

- Develop the ability to run a clinical trial in the participating systems that fits seamlessly into healthcare operations

- Identify at least 3 cohorts of patients who have a condition in common, and who can be characterized and surveyed
CDRN highlights

• Networks of academic health centers, hospitals & clinical practices
• Networks of non-profit integrated health systems
• Networks of Federally Qualified Health Centers (FQHCs) serving low-income communities
• Networks leveraging NIH and AHRQ investments (CTSAs)
• Inclusion of Health Information Exchanges
• Wide geographical spread
• Inclusion of under-served populations
• Range from 1M covered lives to 28M
# CDRNs organizations and leadership

<table>
<thead>
<tr>
<th>CDRN Name</th>
<th>Lead Organization</th>
<th>Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE</td>
<td>Oregon Community Health Information Network</td>
<td>Jennifer DeVoe</td>
</tr>
<tr>
<td>CAPriCORN</td>
<td>The Chicago Community Trust</td>
<td>Terry Mazany</td>
</tr>
<tr>
<td>Greater Plains Collaborative</td>
<td>University of Kansas Medical Center</td>
<td>Russ Waitman</td>
</tr>
<tr>
<td>Louisiana Clinical Data Research Network</td>
<td>Louisiana Public Health Institute</td>
<td>Thomas Carton</td>
</tr>
<tr>
<td>Mid-South CDRN</td>
<td>Vanderbilt University</td>
<td>Russell Rothman</td>
</tr>
<tr>
<td>NYC-CDRN</td>
<td>Weill Medical College of Cornell University</td>
<td>Rainu Kaushal</td>
</tr>
<tr>
<td>PEDSNet</td>
<td>The Children’s Hospital of Philadelphia</td>
<td>Christopher Forrest</td>
</tr>
<tr>
<td>PORTAL</td>
<td>Kaiser Foundation Research Institute</td>
<td>Elizabeth McGlynn</td>
</tr>
<tr>
<td>pSCANNER</td>
<td>University of California, San Diego</td>
<td>Lucila Ohno-Machado</td>
</tr>
<tr>
<td>PaTH</td>
<td>University of Pittsburgh</td>
<td>Rachel Hess</td>
</tr>
<tr>
<td>SCIHLS</td>
<td>Harvard University</td>
<td>Kenneth Mandl</td>
</tr>
</tbody>
</table>
## CDRNs: disease cohorts

<table>
<thead>
<tr>
<th>Organization</th>
<th>Common Cohort</th>
<th>Rare Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE</td>
<td>Diabetes</td>
<td>HIV &amp; hepatitis C virus co-infection</td>
</tr>
<tr>
<td>CAPriCORN</td>
<td>Anemia; asthma</td>
<td>Sickle cell disease; recurrent <em>C. difficile</em> colitis</td>
</tr>
<tr>
<td>Great Plains Collaborative</td>
<td>Breast cancer</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>Louisiana Clinical Data Research Network</td>
<td>Diabetes</td>
<td>Sickle cell disease; rare cancers</td>
</tr>
<tr>
<td>NYC-CDRN</td>
<td>Diabetes</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Mid-South CDRN</td>
<td>Coronary heart disease</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>PEDSNet</td>
<td>Inflammatory bowel disease</td>
<td>Hypoplastic left heart syndrome</td>
</tr>
<tr>
<td>PORTAL</td>
<td>Colorectal cancer</td>
<td>Severe congenital heart disease</td>
</tr>
<tr>
<td>pSCANNER</td>
<td>Congestive heart failure</td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td>P2ATH</td>
<td>Atrial fibrillation</td>
<td>Idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>SCIHLS</td>
<td>Osteoarthritis</td>
<td>Pulmonary arterial hypertension</td>
</tr>
</tbody>
</table>
Goals for each Patient-Powered Research Network (PPRN)

- Establish an activated patient population with a condition of interest (Size >50 patients for rare diseases; >50,000 for common conditions)
- Collect patient-reported data for ≥80% of patients in the network
- Involve patients in network governance
- Create standardized database suitable for sharing with other network members that can be used to respond to “queries” (ideas for possible research studies)
PPRN highlights

- Participating organizations and leadership teams include patients, advocacy groups, clinicians, academic centers, practice-based research networks
- Strong understanding of patient engagement
- Significant range of conditions and diseases
- Variety in populations represented (including pediatrics; under-served populations)
- 50% are focused on rare diseases
- Varying capabilities with respect to developing research data
- Several PPRNs have capacity to work with biospecimens
PPRNs represent a number of conditions...

<table>
<thead>
<tr>
<th>Organization</th>
<th>Principal Investigator</th>
<th>Condition</th>
<th>Population Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated Cure Project for Multiple Sclerosis</td>
<td>Robert McBurney</td>
<td>Multiple sclerosis</td>
<td>20,000</td>
</tr>
<tr>
<td>American Sleep Apnea Association</td>
<td>Susan Redline</td>
<td>Sleep apnea</td>
<td>50,000</td>
</tr>
<tr>
<td>Cincinnati Children's Hospital Medical Center</td>
<td>Peter Margolis</td>
<td>Pediatric Crohn's disease and ulcerative colitis</td>
<td>15,000</td>
</tr>
<tr>
<td>COPD Foundation</td>
<td>Richard Mularski</td>
<td>Chronic obstructive pulmonary disease</td>
<td>50,000</td>
</tr>
<tr>
<td>Crohn’s and Colitis Foundation of America</td>
<td>R. Balfour Sartor</td>
<td>Inflammatory bowel disease (Crohn’s disease and ulcerative colitis)</td>
<td>30,000</td>
</tr>
<tr>
<td>Global Healthy Living Foundation</td>
<td>Seth Ginsberg</td>
<td>Arthritis (rheumatoid arthritis; spondyloarthritis), musculoskeletal disorders (osteoarthritis), and inflammatory conditions (psoriasis)</td>
<td>50,000</td>
</tr>
<tr>
<td>Massachusetts General Hospital</td>
<td>Andrew Nierenberg</td>
<td>Major depressive disorder and bipolar disorder</td>
<td>50,000</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Mark Pletcher</td>
<td>Cardiovascular health</td>
<td>100,000</td>
</tr>
<tr>
<td>University of South Florida</td>
<td>Rebecca Sutphen</td>
<td>Hereditary breast &amp; ovarian cancer</td>
<td>17,000</td>
</tr>
</tbody>
</table>
….including rare diseases

<table>
<thead>
<tr>
<th>Organization</th>
<th>Principal Investigator</th>
<th>Condition</th>
<th>Population Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALD Connect, Inc</td>
<td>Florian Eichler</td>
<td>Adrenoleukodystrophy</td>
<td>3,000</td>
</tr>
<tr>
<td>Arbor Research Collaborative for Health</td>
<td>Bruce Robinson</td>
<td>Primary nephrotic syndrome; focal segmental glomerulosclerosis; minimal change disease; and membranous nephropathy multiple sclerosis</td>
<td>1,250</td>
</tr>
<tr>
<td>Duke University</td>
<td>Laura Schanberg</td>
<td>Juvenile rheumatic disease</td>
<td>9,000</td>
</tr>
<tr>
<td>Epilepsy Foundation</td>
<td>Janice Beulow</td>
<td>Aicardi syndrome; Lennox-Gastaut syndrome; Phelan-McDermid syndrome; hypothalamic hamartoma; Dravet syndrome, tuberous sclerosis</td>
<td>1,500</td>
</tr>
<tr>
<td>Genetic Alliance, Inc</td>
<td>Sharon Terry</td>
<td>Alström syndrome; dyskeratosis congenital; Gaucher disease; hepatitis; inflammatory breast cancer; Joubert syndrome; Klinefelter syndrome &amp; associated conditions; psoriasis; metachromatic leukodystrophy; pseudoxanthoma elasticum</td>
<td>50- 50,000</td>
</tr>
<tr>
<td>Immune Deficiency Foundation</td>
<td>Kathleen Sullivan</td>
<td>Primary immunodeficiency diseases</td>
<td>1,250</td>
</tr>
<tr>
<td>Parent Project Muscular Dystrophy</td>
<td>Holly Peay</td>
<td>Duchenne and Becker muscular dystrophy</td>
<td>4,000</td>
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<tr>
<td>Phelan-McDermid Syndrome Foundation</td>
<td>Megan O’Boyle</td>
<td>Phelan-McDermid syndrome</td>
<td>737</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>Peter Merkel</td>
<td>Vasculitis</td>
<td>500</td>
</tr>
</tbody>
</table>
Innovation: How Markets Respond

- Sustaining technological improvements
- Disruptive Technologies
- New performance trajectory
- Performance that customers can utilize or absorb

Pace of Technological Progress

Adapted from: The Innovator’s Dilemma, Clayton M. Christensen, 2000.
Innovation: How Markets Respond

“...as a rule the new does not grow out of the old but appears alongside of it and eliminates it competitively...”


• In most markets, technology & organizational innovation drive cost and quality improvement
Disruptive Innovation in Health Care

Source: Curtis LH and Schulman KA. Law and Contemporary Problems. Autumn 2006
## Re-engineering the Clinical Research Enterprise

| Plan and start a few demonstration networks | Funding mechanism to sustain national system through consensus of all constituents (“1% solution”) | National Clinical Research System creates effectiveness data that moves rapidly into the community AND data on outcomes and quality of care; sustained efficient infrastructure to rapidly initiate large clinical trials; scientific information for patients, families, advocacy groups |
| Simplify complex regulatory systems – demonstration projects | Simplified regulatory system in place for networks | |
| Plan for networks in place for all institutes | Data standards shared across NIH institutes | ONE medical nomenclature with national data standards (agreed to by NIH, CMS, FDA, DOD, CDC) |
| Establish repositories of biological specimens and standards for collection | Funding mechanisms evaluated to determine which are most efficient | Data standards updated “in real time” through networks |
| Standardize nomenclature, data standards, core data, forms for most major diseases | | National repository of images and samples |
| Start a library of these elements shared between institutes and NLM | | Critical national “problem list” |
| Develop efficient network administration infrastructure at NIH | | Most efficient network funding mechanisms in place across NIH |
| Develop standards for capturing images for research | | |
| Create NIH standards to provide “safe haven” for clinical research | NIH standards for safe haven in place | Participation in research is a professional standard (taught in all health professions schools) |
| Inventory and evaluate existing public-private partnerships, networks, CR institutions, and regulatory systems | Regulations and ethics harmonized with FDA, CMS | Study, evaluation and training regarding clinical research a part of every medical school, nursing school, pharmacy school |
| Establish FORUM(S) of all stakeholders | Public private partnership mechanisms in place | Clinical research practices documented and updated regularly to maintain safe haven |
| Establish standards for and pilot creation of a National Clinical Research Corps | 100,000 members of certified “Clinical Research Corps” | Networks provide detailed training about network specific issues |
| Demonstration/planning grants to enhance/evaluate/develop model networks | Standards shared across NIH | |