Technology-Enabled Trials: Transforming Medical Evidence Generation

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Conflict of Interest Statement –
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- **Research Funding:**
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- **Consulting/Honoraria:**

Publicly listed on www.dcri.org/about-us/conflict-of-interest
DCRI Think Tanks Mission

MISSION
To address the most critical gaps in clinical research by convening leaders across healthcare industry to map the way forward in designing, conducting and implementing high-quality, evidence-based research.

SAME CONCEPT…
with renewed focus on impact and sense of urgency
Technology-Enabled Clinical Trials Think Tank — Innovations in Trial Design and Conduct

MEETING OBJECTIVES

✓ Review value-added implications for new technological advances that enhance clinical trial efficiency and streamline trial conduct

✓ Discuss the emerging perspectives of clinical trial stakeholders on technology infiltration

✓ Delineate innovative trial designs and options facilitated by technological advances and potential barriers to implementation of innovative trials

✓ Determine the optimal framework for regulatory oversight and partnerships needed to guide the role of technology in changing clinical research paradigms
Cost and Complexity of Clinical Trials Limit Drug Development

Tufts Center for the Study of Drug Development

Transforming Clinical Research in the US
https://www.ncbi.nlm.nih.gov/books/NBK50895/
Private Investment in Digital Health Steadily Increasing

**TOTAL VENTURE FUNDING**

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<th>Year</th>
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# OF DEALS

- 2011: 92
- 2012: 143
- 2013: 198
- 2014: 291
- 2015: 320
- 2016: 334
- 2017: 359
- 2018: 368

Source: [Rock Health](https://rockhealth.com/reports/2018-year-end-funding-report-is-digital-health-in-a-bubble/)
Evaluating and Leveraging Technology (Software) Solutions for Clinical Trial Execution

Conduct Study

Manage Operations
- PAREXEL
- BIOCLINICA
- PERCEPTIVE
- ORACLE
- SIEBEL
- TRIALSPARK
- ClinPay
- CluePoints
- greenphire
- COMPARE
- Cognizant
- Velos

Drug & Supply Logistics
- medidata
- Covance
- Covara
- LORUS
- RealTime
- SimpleTrials
- NextGen
- Comprehend
- health cloud
- eclinical
- clinical research.io

Collect and Analyze Patient-Level Data

Patient Data Management (e.g., EDC, eCOA, Digital Biomarkers)
- REDCap
- medidata
- IBM
- Watson Health
- QuintilesIMS
- evperation
- MedNet
- Altavoz

2017 by @AndreaCoravos
Public-Private Partnership
Co-founded by Duke University & FDA
Involves all trials stakeholders
Approximately 80 member organizations

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials
# CTTI Projects by Topic

## Quality
- Quality by Design
- Informing ICH E6 Renovation
- Analysis of ClinicalTrials.gov
- Recruitment
- Planning for Pregnancy Testing
- State of Clinical Trials Report
- Monitoring

## Patient Engagement
- Patient Groups & Clinical Trials
- Patient Engagement Collaborative

## Investigators & Sites
- Investigator Sustainability
- Investigator Qualification
- GCP Training
- Site Metrics

## Mobile Clinical Trials
- Novel Endpoints
- Mobile Technologies
- Decentralized Clinical Trials
- Engaging Patients and Sites

## Novel Clinical Trial Designs
- Real World Evidence
- Registry Trials
- Antibacterial Drug Development
- Sentinel IMPACT-Afib trial
- Large Simple Trials
- Using FDA Sentinel for Trials

## Ethics & Human Research Protection
- Single IRB
- Data Monitoring Committees
- Informed Consent
- Safety Reporting

Details available at [www.ctti-clinicaltrials.org](http://www.ctti-clinicaltrials.org)
FDA Real World Evidence Framework and Transformation

- Are data fit for use?
  - Establish demonstration projects
- Does RWE answer regulatory questions?
  - Stakeholder engagement
- Did study meet FDA regulatory requirements?
  - Develop guidance documents for using RWE
    - Setting data standards for RWD

RWD Fitness Assessment
- Clinical study methodology and reliability
- Data accrual and data quality control
- Relevance of underlying data

Released by FDA in December, 2018
FDA recently created the Center of Excellence for Digital Health with the goal of “modernizing the regulatory approach to help this industry grow and reach its full potential, while protecting patients.”
Mobile/Digital Health Applications, Biosensors, and Wearables to Streamline Trial Conduct
Smartphone Ownership Across the United States

![Bar chart showing smartphone ownership across the United States from 2010 to 2022.](image_url)
Use of Digital Technologies in Clinical Trials Increasing
Traditional Site-Centric Trial for Chronic Trials

- Screening and enrollment at point-of-care during scheduled outpatient clinical encounters
- Excludes patient populations from underserved geographic areas and from locations without clinical investigators
- Limits patient participation due to requirements for multiple return visits to sites (clinics, hospitals)

Digital Health-Enabled Patient-Centric Chronic Trials

- Remote screening and enrollment enabled with digital devices
- Broader and faster access to patient populations representing routine clinical practice
- Direct collection of data from patients via digital devices and from biosensors
359,161 Aetna members meeting eligibility criteria

- 52,553 invited by email
- 50,000 invited by direct mail
- 2,655 consented & confirmed eligible

1,364 randomized to immediate monitoring
- 456 never wore a patch
- 908 actively monitored

1,291 randomized to delayed monitoring
- 457 never wore a patch

Primary Endpoint
New Diagnosis of AF after 4 months

JAMA. 2018;320(2):146-155.
Primary 4-Month Endpoint – New Diagnosis AF

Definition of Atrial Fibrillation

- > 30 consecutive seconds of AF by ECG. (CEC adjudicated), or
- A new diagnosis of AF through claims data. (A single new ICD9 or ICD10 code)

OR 8.8
95%CI 3.5-22.4
P<0.0001

For ITT population

OR 9.0
95%CI 3.6-22.7
P<0.0001
Apple Heart Study
Prospective, Single Arm, Open Label Study

Inclusion criteria
• Age ≥ 22; U.S. Resident
• iPhone (5S or higher) + Watch (Series 1-3)

Exclusion criteria
• Atrial fibrillation or atrial flutter
• Current use of anticoagulation

American College of Cardiology LBCT, March, 2019
Apple Heart Study

Consort Diagram

Overall Cohort
Total Population 419,297

Notification
Pulse Notification 2,161 (0.5%)
First Study Visit 945 (44%)

ECG Patch
ECG Patch Shipped 658 (70%)
ECG Patch Returned & Analyzed 450 (68%)

EOS Survey 90-Day Survey
Completed 90-day Survey 1,376 / 2,161 (64%)

No Notification (PN) 417,136 (99.5%)

Completed EOS Survey 929 / 2,161 (43%)

American College of Cardiology LBCT, March, 2019
Development and Validation of Novel Digital Endpoints

- Data collection and patient interfaces with digital health applications
  - Collected in real-time, directly from patients to minimize recall bias
  - Embedded trial-specific interventions can be delivered via digital applications
  - PROs, QOL assessments, symptom scores

- Development of novel digital endpoints
  - Continuous data collection from biosensors and activity monitors
  - Apple Watch® AliveCor® KardiaBand to detect arrhythmias

- Geofencing to augment surveillance for hospitalizations
Capturing and Incorporating Digital Health Data Into Clinical Trial Databases
Challenges with Digital Health-Enabled Trials

- Enrollment biases based upon internet connectivity and technical awareness and capabilities
- “Bring your own device” vs. provided devices
- Inadequate confirmation of “end user” identities during data entry
- Technical failure of digital devices and biosensors
- Data privacy and security with consumer-grade devices
- Scientific validity and patient-centeredness of novel digital endpoints
Electronic Health Records to Streamline Trial Conduct
Using RWD (EHRs) to Enable Clinical Trials

Pre-Study (S1)

Protocol Design
- Characterize RWD-based outcomes & endpoints

Cohort Identification
- RWD-compatible inclusion/exclusion criteria (computable phenotype)
- Understand patient cohorts; interactions with health systems

Site Selection
- Experience using RWD to facilitate research
- Feasibility and recruitment plans

Study Setup (S1-S2)

Site Onboarding
- Translate inclusion/exclusion criteria into an EHR-based reporting program (to identify eligible patients)
- Feasibility dashboards
- Embed encounter instructions into sites’ EHR systems
- Pre-consent and study-specific consent
- Model potential outcomes

Recruitment (S2)

Participant Enrollment
- Develop EHR-based screening reports – contact potential participants or identify & recruit during clinics
- Deploy provider-specific EHR alerts to identify eligible patients during care delivery
- Use of patient portals (EHR-based and stand-alone) for patient outreach and electronic consent

Study Conduct (S3)

Data Collection
- Trial-specific data capture embedded within EHR workflows
- CRFs auto-populated with data from EHRs
- Algorithms to identify RWD-based efficacy and safety outcomes

Rules, Alerts & Checks
- Data quality and completeness
- Hospitalization/SAEs
- Event rates

Participant Retention & Contact
- Use of patient portals to collect PRO’s, share trial progress reports, and enhance retention
Real World Data Characterization to Design Trials

- Characterize patient populations of interest in several diverse RWD sources to inform protocol development
  - Duke Health System EHR Data Warehouse (750,000 patients)
  - EHR Data Warehouses from other US health systems with harmonized/standardized data systems
    - PCORnet/PCRF – Distributed Data Network
    - Health Systems Data Network (in development)

- Results from analyses can be used to develop programming code that simulates expected trial inclusion/exclusion criteria (computable phenotype – CP)
  - Initial results confirmed with chart validation in Duke Health System and other partnering health systems
Informatics Solutions for Pragmatic Trials: EHR-Based Clinical Research Networks

Trial-Specific Clinical Research Network

- Research Site A
  - EHR
  - Internal Data Warehouse
  - Research Datamart

- Research Site B
  - EHR
  - Internal Data Warehouse
  - Research Datamart

- Research Site C
  - EHR
  - Data Warehouse
  - Research Datamart
  - Centralized disease registry

Integrated Clinical Trial Database

EHR data can auto-populate part of the trial database
Approaches for Obtaining EHR Data for Trials (1)

- Distributed Research Network
  - Send query to sites who have data in pre-existing format (common data model)
  - Sites return results (e.g., aggregate counts, summary statistics, patient-level records)
Approaches for Obtaining EHR Data for Trials (2)

- Centralized Transformation
  - Sites send “raw” EHR data to central coordinating center from their local EHR databases or common data models
  - Study coordinating center transforms raw EHR data into target format and runs analyses
Assessing EHR Data Quality

- When receiving data from the EHR (or claims or any other source), important to continuously monitor the quality of the incoming data.

- EHR data quality domains ascertained:
  - Conformance – are EHR data formatted correctly?
  - Completeness – are EHR data present when we expect them to be?
  - Plausibility – do the values of the data elements make sense?

- Data checks should be based on use-case scenarios
  - Need to consider point-in-time metrics as well as rates over time
  - Compare within-site metrics, as well as across-site metrics

- Essential to connect back to sites/health systems on a regular basis to improve EHR data quality and address questions.
**Case Study: the APAPTABLE Trial Conducted Within PCORnet**

110 Million patients in 64 Health System Data Marts

### Sex

- Female
- Male

### Race

- White
- Non-White

### Age

- 0–4
- 5–14
- 15–21
- 22–64
- 65+

### Pool of patients

- For clinical trials: 33,179,287
- For observational studies: 68,640,564
ADAPTABLE Study Design

15,000 patients with known ASCVD + ≥ 1 Enrichment Factor

Patients identified by research networks in PCORnet through EHR/CDM searches using a computable phenotype that classifies inclusion/exclusion criteria

Patients provided with trial information and link to e-consent on a web portal; Randomized treatment assignment provided directly to patient

ASA 81 mg QD
ASA 325 mg QD

Electronic patient follow-up for PRO’s: Every 3 or 6 months Supplemented with searches of EHR and claims data

Duration: Enrollment over ~ 3 years; maximum follow-up of ~ 4 years

Primary Efficacy Endpoint:
Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

Primary Safety Endpoint:
Hospitalization for major bleeding

† Participants without internet access will be consented and followed via a parallel system.

ClinicalTrials.gov: NCT02697916
ADAPTABLE Inclusion Criteria –
Computable Phenotype

Known ASCVD
• Prior MI
  OR
  • Prior revascularization (PCI or CABG)
  OR
  • Prior angiogram showing significant CAD
  OR
  • History of chronic ischemic heart disease, CAD, or ASCVD

≥ 1 enrichment factor:
• Age ≥ 65 years
• Creatinine ≥ 1.5 mg/dL
• Diabetes mellitus
• Known 3-vessel CAD
• Cerebrovascular disease
• Peripheral arterial disease
• Current smoker
• Known LVEF < 50%
• Chronic systolic or diastolic heart failure
• SBP ≥ 140 (within past 12 mos)
• LDL ≥ 130 (within past 12 mos)

Electronic Patient Outreach

ClinicalTrials.gov: NCT02697916
Electronic-Facilitated Recruitment Approaches Utilized in ADAPTABLE

Electronic, computable phenotype deployed to participating sites/health systems to query local EHR databases and to facilitate widespread screening of large numbers of potentially eligible patients identified in this manner.

Patient Outreach and Recruitment Approaches (~500,000 patients approached):

- Direct Mail and Email (messages locally customized with input from patient representatives)
- Via health system patient portals such as “MyChart”
- “In-Clinic” Recruitment (EHR Alerts to clinic providers, Tablet-based recruitment during clinic encounters, promotion of trial during clinic)

Potential patients given Golden Ticket numbers and directed to the Adaptable web portal for confirmatory screening and electronic, web-based informed consent.

ClinicalTrials.gov: NCT02697916
Direct-to-Patient Follow-Up

Patients receive email reminders to visit web portal for regular contacts every 3 vs. 6 months

Central DCRI Call Center performs telephone contacts when needed
  - Non-internet participants (20%)
  - Participants who miss at least 2 scheduled electronic contacts
Longitudinal Endpoint Ascertainment

Quarterly queries of the local data marts via the PCORnet common data model (CDM) to capture and classify endpoints

- Hospitalizations for MI, stroke, and bleeding confirmed as endpoints via standardized, validated coding algorithms developed centrally and applied to the CDM

ADAPTABLE web portal will be used to collect data on hospitalizations that are possible endpoints during patient electronic or telephone contacts (every 3–6 months)

- Patient-reported outcomes (PRO’s) are cross-checked and verified with the CDM-generated hospitalization data
- Surveillance of CMS and private health plan data for potential “out-of-network” hospitalizations reported via patient contact
- Medical records obtained for PRO’s not classified through other means

Death ascertainment via CDM, Social Security Administration (Medicare beneficiaries), and Call Center contacts for patients with missed visits
Challenges with EHR-Enabled Trials

- Accuracy, timeliness, and completeness of EHR data sources
- Lack of interoperability of EHR systems requiring multiple different technical approaches to aggregate data from diverse sources
- Lack of widespread implementation and updating of data standards
- Data provenance and security concerns within and across countries
- Highly variable site/health system expertise with leveraging local EHR data for purposeful pragmatic clinical research activities
Envisioning the Future
Pragmatic Data Collection

- Goal is to substantially reduce data collection burden for trial sites

- Novel approaches for mechanisms of data capture, endpoint ascertainment, and safety reporting
  - *Some data (clinical characteristics, medications, labs) from local EHR data sources could be directly imported into trial database*
  - *Patient reported outcomes, including hospitalizations – via web-based portals, digital apps, or telephone contact*
  - *Digital health data – wearables, biosensors, mHealth apps*
  - *EHR data warehouse queries and surveillance of administrative claims databases for hospitalizations*

- Streamlined Electronic Data Capture (EDC) system for trial-specific data
  - *Disciplined, succinct electronic case report form (e-CRF) embedded within EHR workflows, whenever possible*
Data Flow and Data Integration with Multiple, Novel Electronic Data Sources

Sites/Health Systems
- EHR
- EDC

Patients/Participants
- Phone
- App
- Devices

EDC
- IBM CD / RAVE
- EHR
- Call Ctr
- Safety DB
- CEC DB
- Device Stream
- Claims Stream
- ...

Data Coordinating Center
- Integrated Study Database

Trial Sponsor
- Study Dataset
- SDTM+
- Analysis, FSR, Submission
Cross-Sectional Stakeholder Partnerships Needed
Conclusions

- Technological innovations rapidly transforming all aspects of clinical trials from start to finish
- Digital health applications and EHRs provide tremendous opportunities for improving trial efficiencies and broadening patient participation with great potential for cost reductions
- Integrated and creative data solutions needed to leverage and optimize technology options
- Future is bright, but new partnerships and collaboration models must be nurtured, developed, and realized