

# Technology-Enabled Trials: Transforming Medical Evidence Generation

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**Duke** Clinical Research Institute

FROM THOUGHT LEADERSHIP  
TO CLINICAL PRACTICE

# Conflict of Interest Statement – Matthew T. Roe, MD, MHS

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- **Research Funding:**

- *American College of Cardiology, American Heart Association, Amgen, AstraZeneca, Bayer, Familial Hypercholesterolemia Foundation, Ferring Pharmaceuticals, Myokardia, Patient Centered Outcomes Research Institute, Sanofi-Aventis.*

- **Consulting/Honoraria:**

- *Astra Zeneca, Amgen, Cytokinetics, Eli Lilly, Roche-Genentech, Janssen Pharmaceuticals, Regeneron, Novo Nordisk, Pfizer, Sanofi-Aventis, Signal Path, Elsevier Publishers.*

*Publicly listed on [www.dcri.org/about-us/conflict-of-interest](http://www.dcri.org/about-us/conflict-of-interest)*

# DCRI Think Tanks Mission

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## 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



Technology-Enabled Clinical Trials—Innovations in Trial Design and Conduct  
October 3–4, 2018

The lightning speed of innovation in both scientific research and technology over the past few years have quickly compounded to create a dramatic paradigm shift in clinical research. While the clinical research industry has been traditionally slow to adopt and embrace change, new players in healthcare technology have created a more competitive and collaborative environment helping to drive a faster pace. Regulators have also spurred change by embracing and encouraging innovation and technological development, specifically with the promising trial efficiencies offered by pragmatic trials.

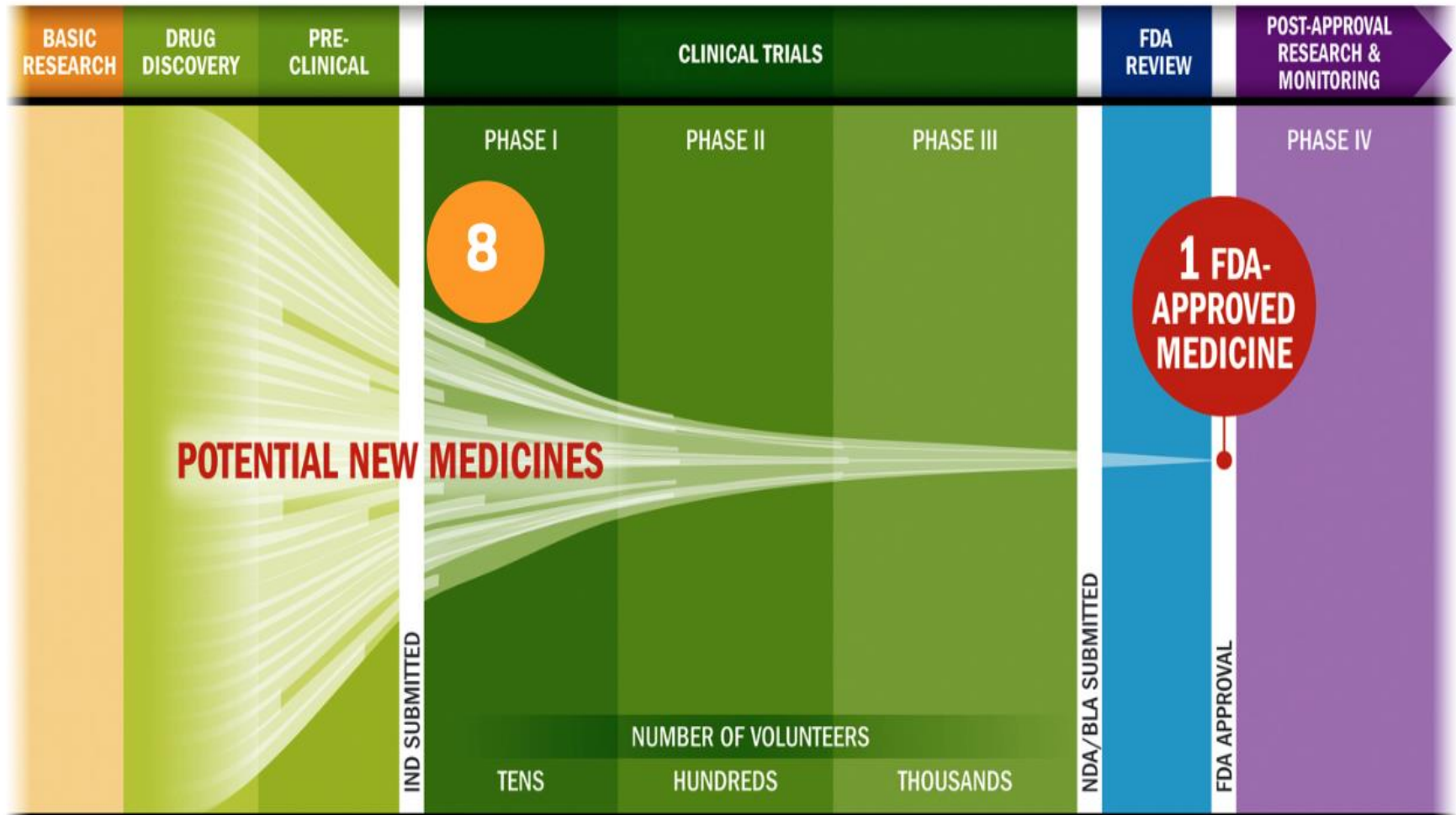
This shift is creating a “clinical trial renaissance” in which all clinical trial stakeholders—investigators, patients, pharmaceutical and device industry partners, academic thought leaders, and regulatory authorities—are all considering how to leverage these new scientific breakthroughs and new technologies into the clinical trial continuum for faster, less expensive, and more applicable clinical trials in the future.

Amidst all of the change, regulators are tasked with providing regulations and guidance that balance the leeway and flexibility needed for disruptive change while also continuing to protect quality, safety, and patient privacy.

The emergence of virtual clinical trials that bypass traditional clinical trial sites by recruiting and following patients directly through electronic approaches is an example of how new technologies have challenged the traditional clinical trial model and dogma.



# Cost and Complexity of Clinical Trials Limit Drug Development



Tufts Center for the Study of Drug Development  
(<https://www.sciencedirect.com/science/article/pii/S0167629616000291><https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3241518/>)

Transforming Clinical Research in the US <https://www.ncbi.nlm.nih.gov/books/NBK50895/>



# Private Investment in Digital Health Steadily Increasing

TOTAL VENTURE FUNDING

# OF DEALS



# Evaluating and Leveraging Technology (Software) Solutions for Clinical Trial Execution

## Protocol design and review



VITAL CROWD

ProofPilot

trials.ai

HealthVibe

+ AllTrials



## Site Selection & Start-Up<sup>1</sup>

DrugDev  
do more trials

QuintilesIMS

WIRB

CenterWatch

COVANCE  
SOLUTIONS MADE REAL

goBalto

ERT

TriNetX

trifecta

teckro.  
FIRECREST

mytrus.  
HEALTH

## Patient Recruitment

Mendel.ai

Driver

Trialx

antidote

Clara

QuintilesIMS

mprove  
HEALTH

D E P 6

ePatientFinder

SubjectWell

ClinicalConnection

patientslikeme

myHealthTeams

VITALTRAX STUDYKIK

langland

seeker  
HEALTH

Be the Partner

trialsark

FindMeCure

myTomorrows

## Virtual Trials Science 37

MEDABLE

Sage  
BIONETWORKS

evidation

aces  
HEALTH

CLINPAL

THREAD

aparito

EmpiraMed

monARC  
BIONETWORKS  
Empowered Patients. Faster Cures.

mytrus.

# Evaluating and Leveraging Technology (Software) Solutions for Clinical Trial Execution

## Conduct Study

### Manage Operations<sup>2</sup>



### Drug & Supply Logistics



## Collect and Analyze Patient-Level Data

### Patient Data Management (e.g., EDC, eCOA, Digital Biomarkers)<sup>3</sup>





# CTTI



CLINICAL  
TRIALS  
**TRANSFORMATION**  
INITIATIVE

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

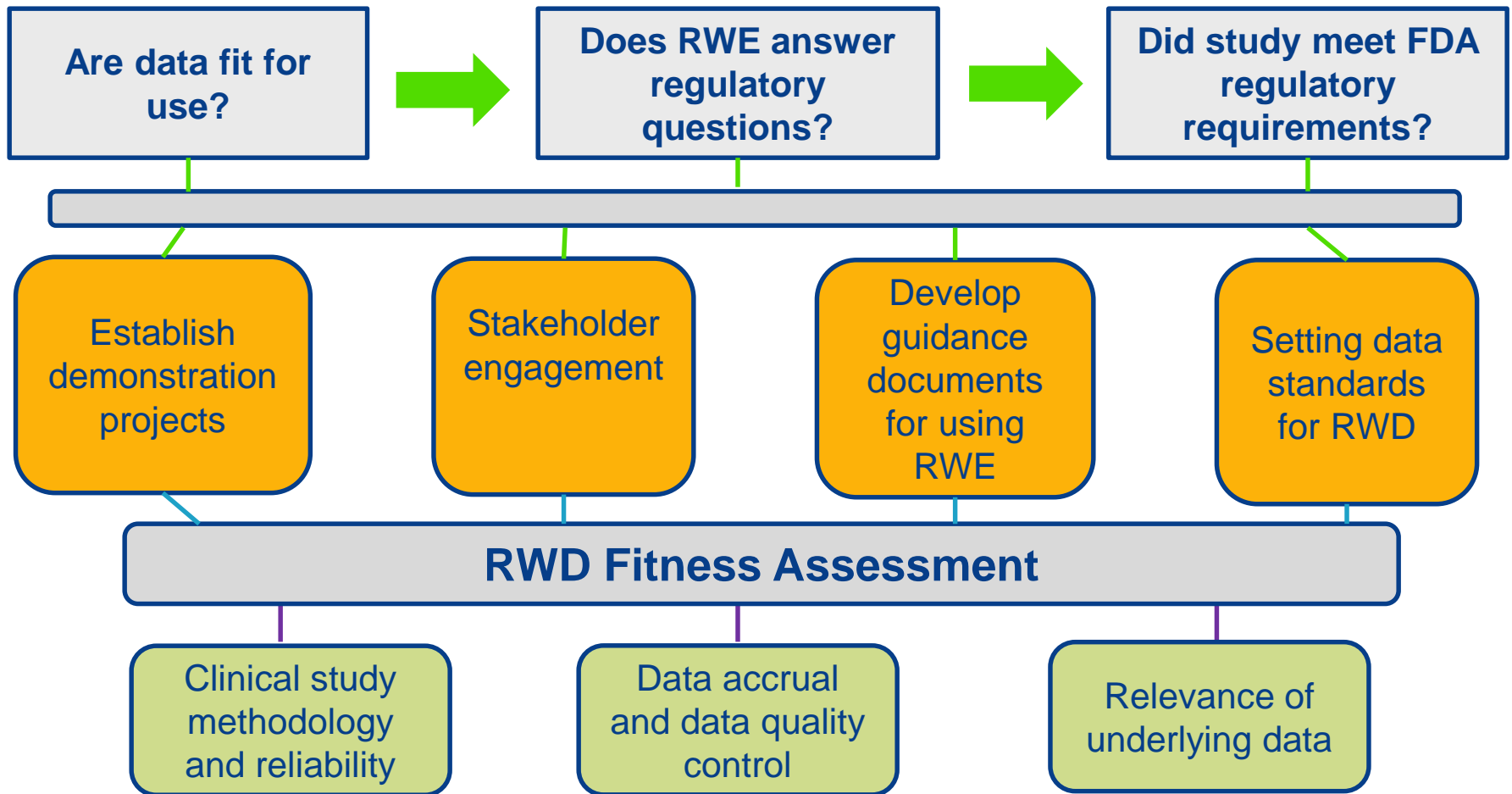
- ▶ Real World Evidence
- ▶ Registry Trials
- ▶ Antibacterial Drug Development
- ▶ Sentinel IMPACT-Afib trial
- ▶ Large Simple Trials
- ▶ Using FDA Sentinel for Trials

## 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



# Regulatory Interest and Oversight of Digital Health Products

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.”*

## Digital Health

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[Email Digital Health and 21st Century Cures Act Questions to the FDA](#) 



### Read Our Digital Health Innovation Action Plan

The [Digital Health Innovation Action Plan](#) outlines our efforts to reimagine the FDA’s approach to ensuring all Americans have timely access to high-quality, safe and effective digital health products. As part of this plan, we committed to several key goals, including [increasing the number and expertise of digital health staff at the FDA](#), [launching the digital health software precertification pilot program \(“Pre-Cert”\)](#) and [issuing guidance to modernize our policies](#).

Commissioner’s Statement: [Advancing new digital health policies to encourage innovation, bring efficiency and modernization to regulation](#)

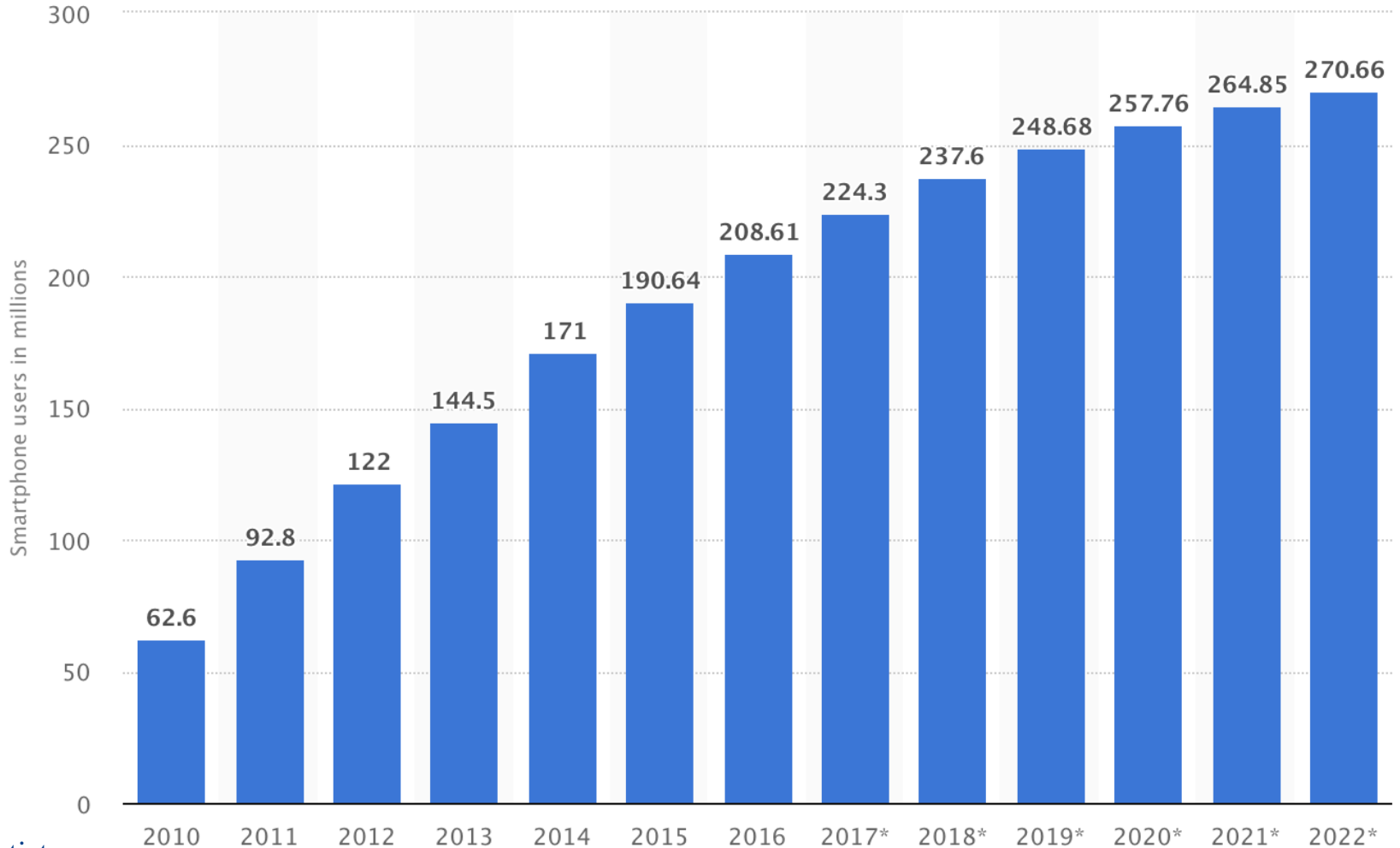
# Mobile/Digital Health Applications, Biosensors, and Wearables to Streamline Trial Conduct



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# Smartphone Ownership Across the United States



Statista.com



## Eye

Glucose-sensing lens  
Digital fundoscope  
Smartphone visual-acuity tracking  
Automated refractive error  
Noninvasive intraocular pressure

## Ear

Smart hearing aids  
Digital otoscope

## Lung

Home spirometry  
Pulse oximetry  
Inhaler use  
Breath-based diagnostics  
Breathing sounds  
Environmental exposure

## Blood

Continuous glucose  
Transdermal Hb  
Pathogens (genomics-based)  
PoC blood tests

## Skin

Temperature  
Gross lesions  
Pressure sensor (wound care)  
Sweat chemistry  
Cutaneous blood flow

## Other sensors and monitors

Pill-box and -bottle  
Posture  
Body position  
Activity  
Sleep

## Bladder and urine

Comprehensive urinalysis  
STDs (genomic detection)  
Diaper-based sensors

## Brain and emotion

Wireless mobile EEG  
Seizure  
Autonomic nervous activity  
Head-impact sensor  
Intracranial pressure (noninvasive)  
Stress recognition (voice, respiration)

## Heart and vascular

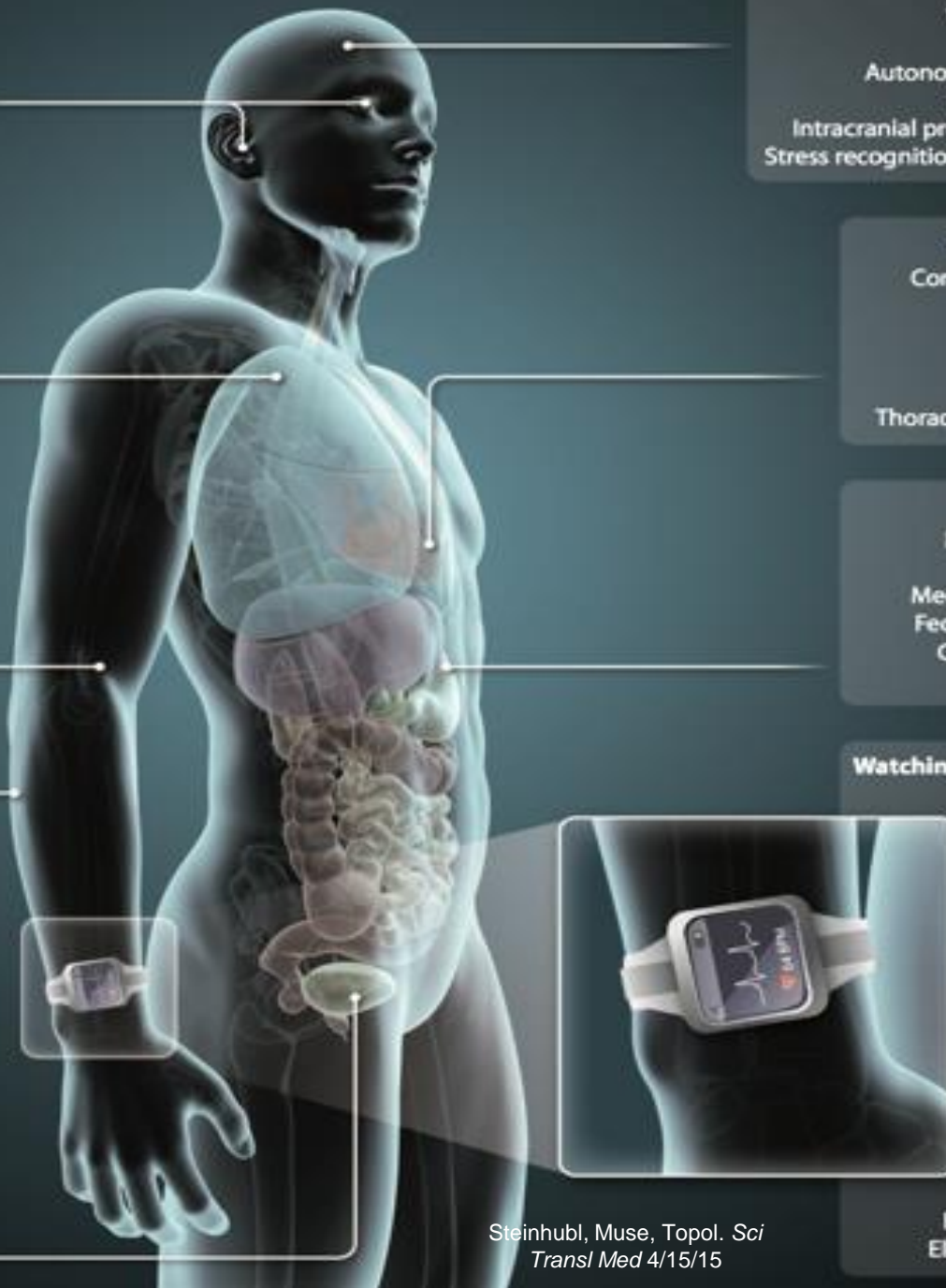
Continuous BP tracking  
Handheld ECG  
Heart rhythm  
Cardiac output  
Stroke volume  
Thoracic impedance (fluid)

## Gastrointestinal

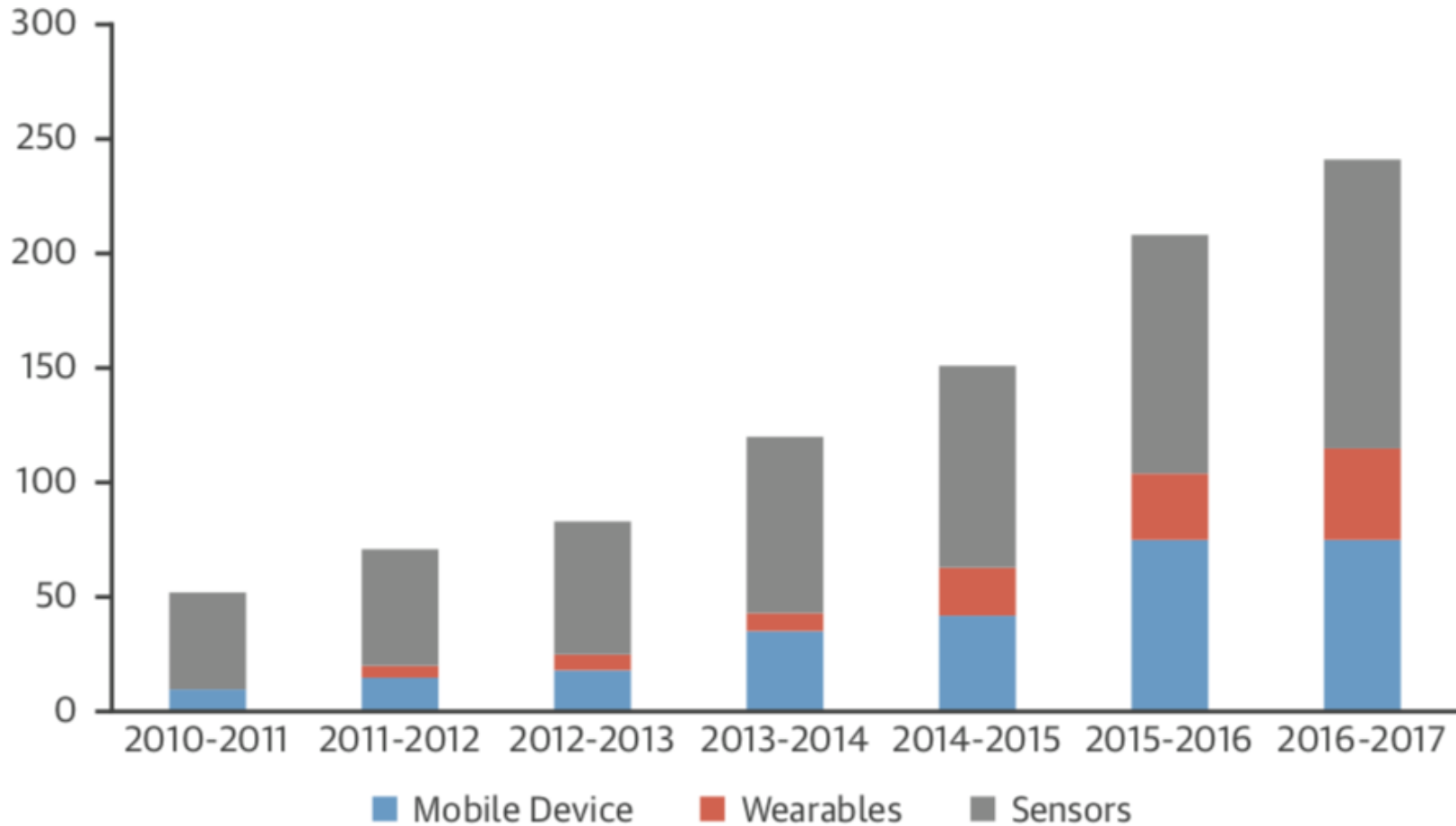
Endoscopic imaging  
Esophageal pH  
Medication compliance  
Fecal blood or bilirubin  
Gut electrical activity  
Chewing

## Watching over one's health

Pulse  
BP  
Temperature  
Activity  
Hydration  
Sleep stages  
Seizure  
Respiration rate  
O<sub>2</sub> saturation  
Blood CO<sub>2</sub>  
Blood glucose  
ECG (single-lead)  
Cardiac output  
Stroke volume  
Stress:  
Heart-rate variability  
Electrodermal activity



# 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



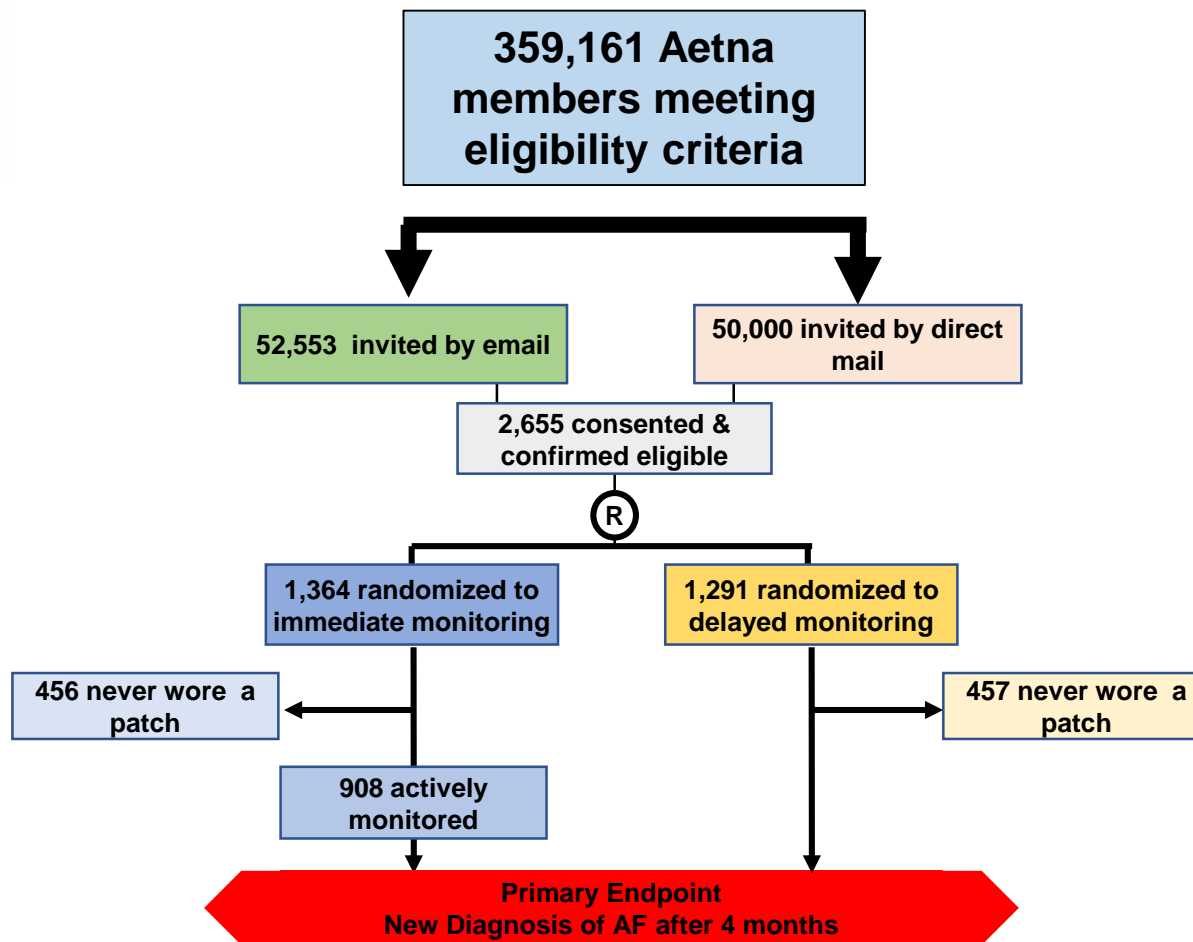
- Remote screening and enrollment enabled with digital devices
- Broader and faster access to patient populations representing routine clinical practice
- Direct collection of data from patients via digital devices and from biosensors

# Overview



aetna<sup>®</sup> Members

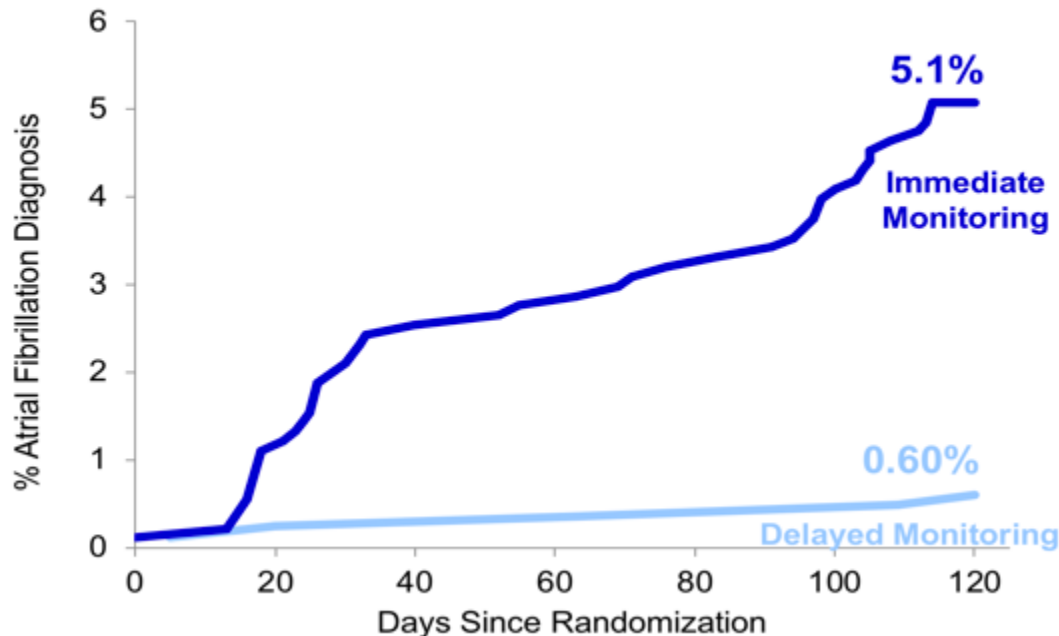




# Primary 4-Month Endpoint – New Diagnosis AF

## 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)



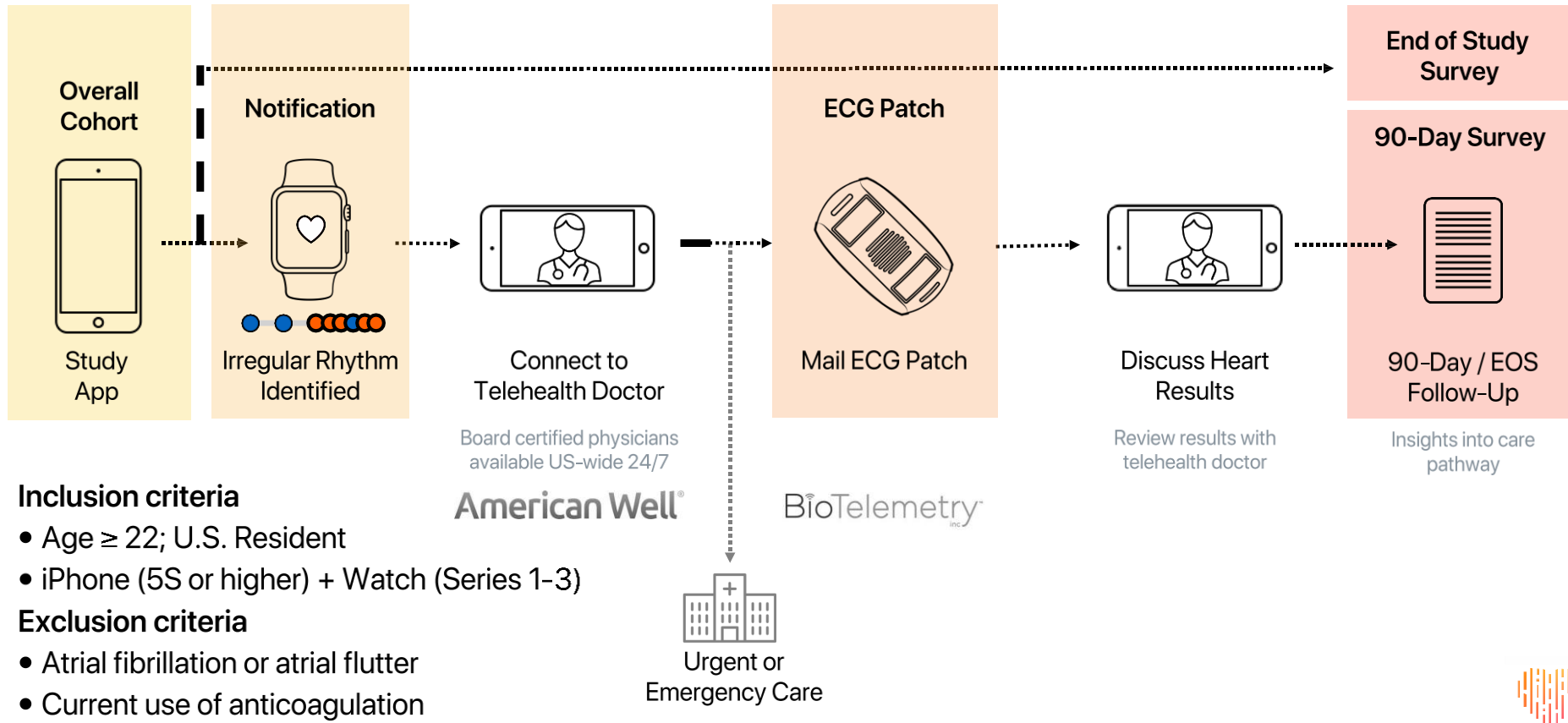
**OR 8.8**  
**95%CI 3.5-22.4**  
**P<0.0001**

### 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  $\geq 22$ ; U.S. Resident
- iPhone (5S or higher) + Watch (Series 1-3)

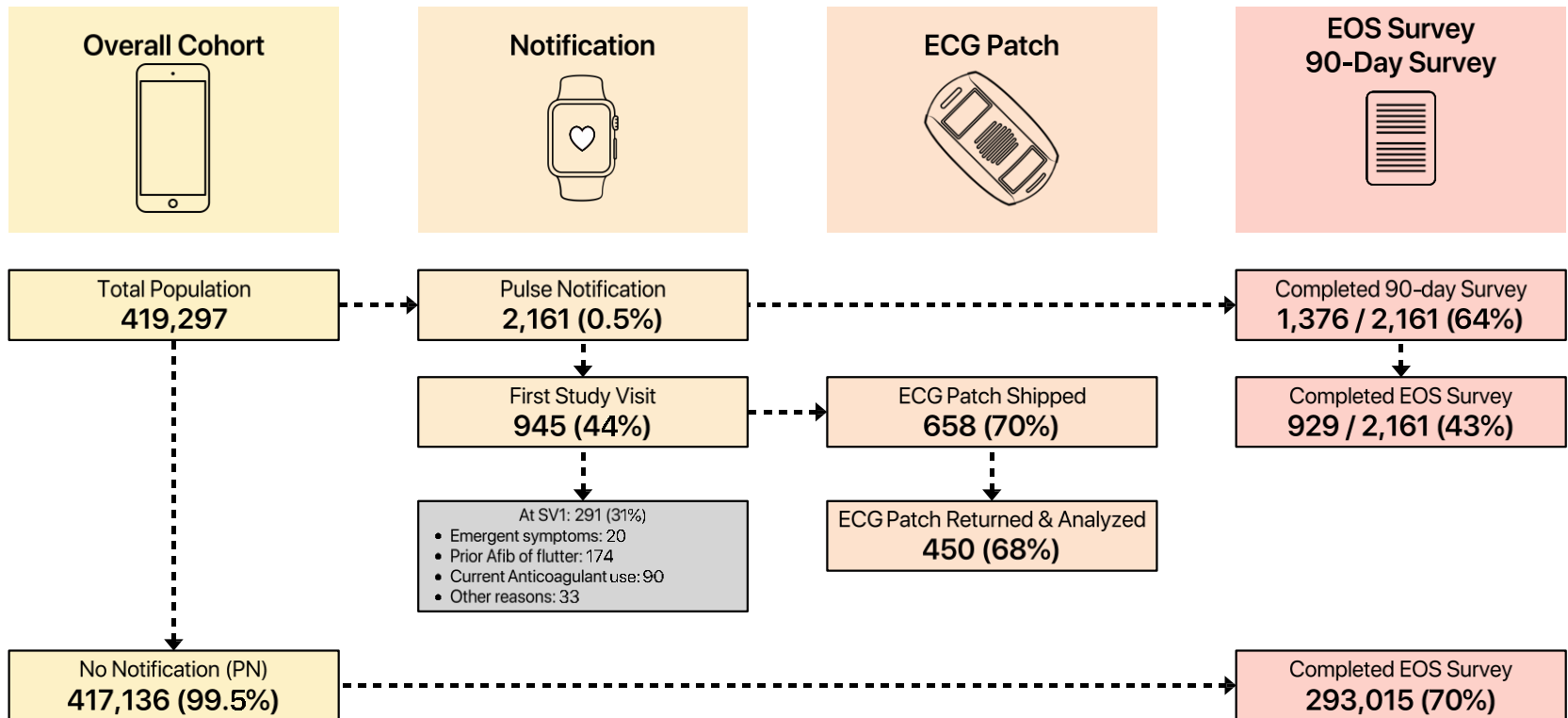
### Exclusion criteria

- Atrial fibrillation or atrial flutter
- Current use of anticoagulation



# Apple Heart Study

## Consort Diagram



# Development and Validation of Novel Digital Endpoints

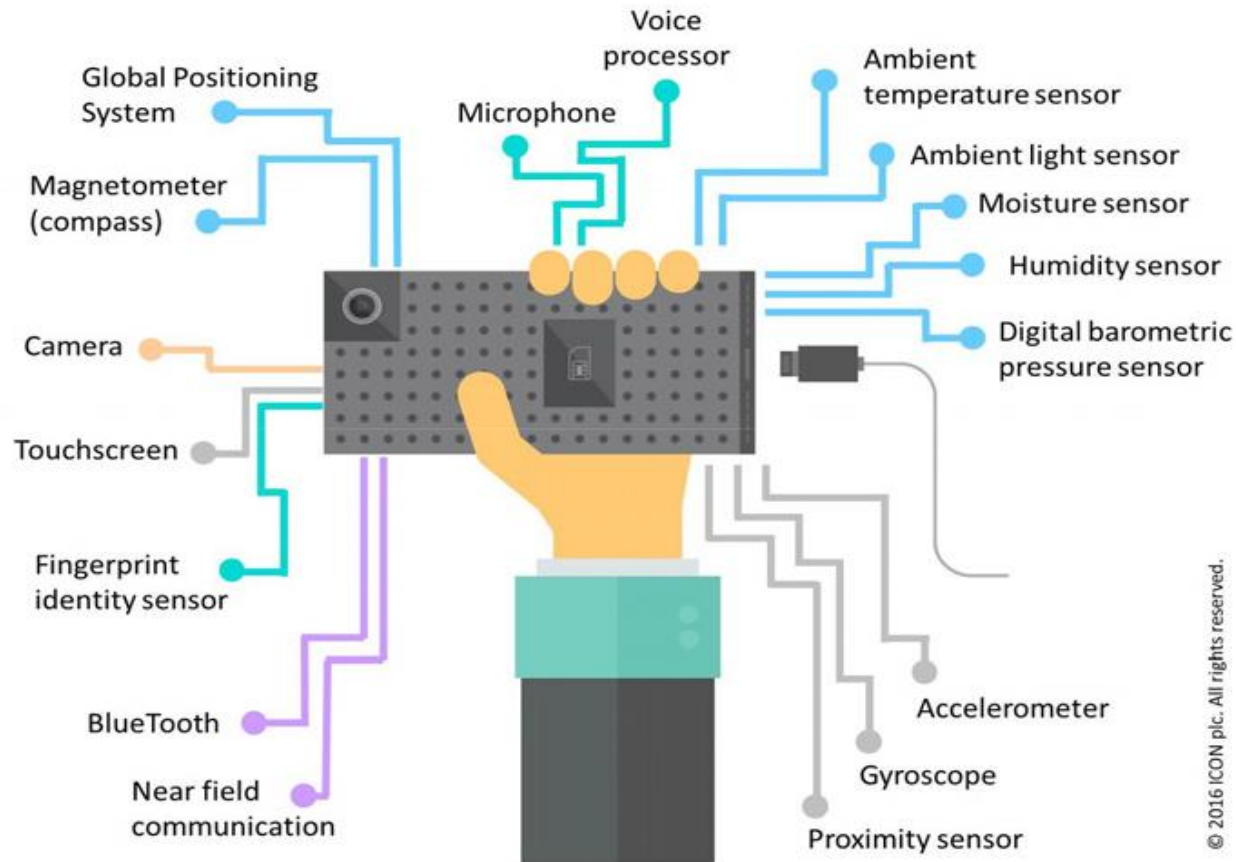
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- Data collection and patient interfaces with digital health applications
  - *Collected in real-time, directly from patients to minimize recall bias*
  - *Embedded trial-specific interventions can be delivered via digital applications*
  - *PROs,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

 Duke Mobile App Gateway



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# Challenges with Digital Health-Enabled Trials

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- 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



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# 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

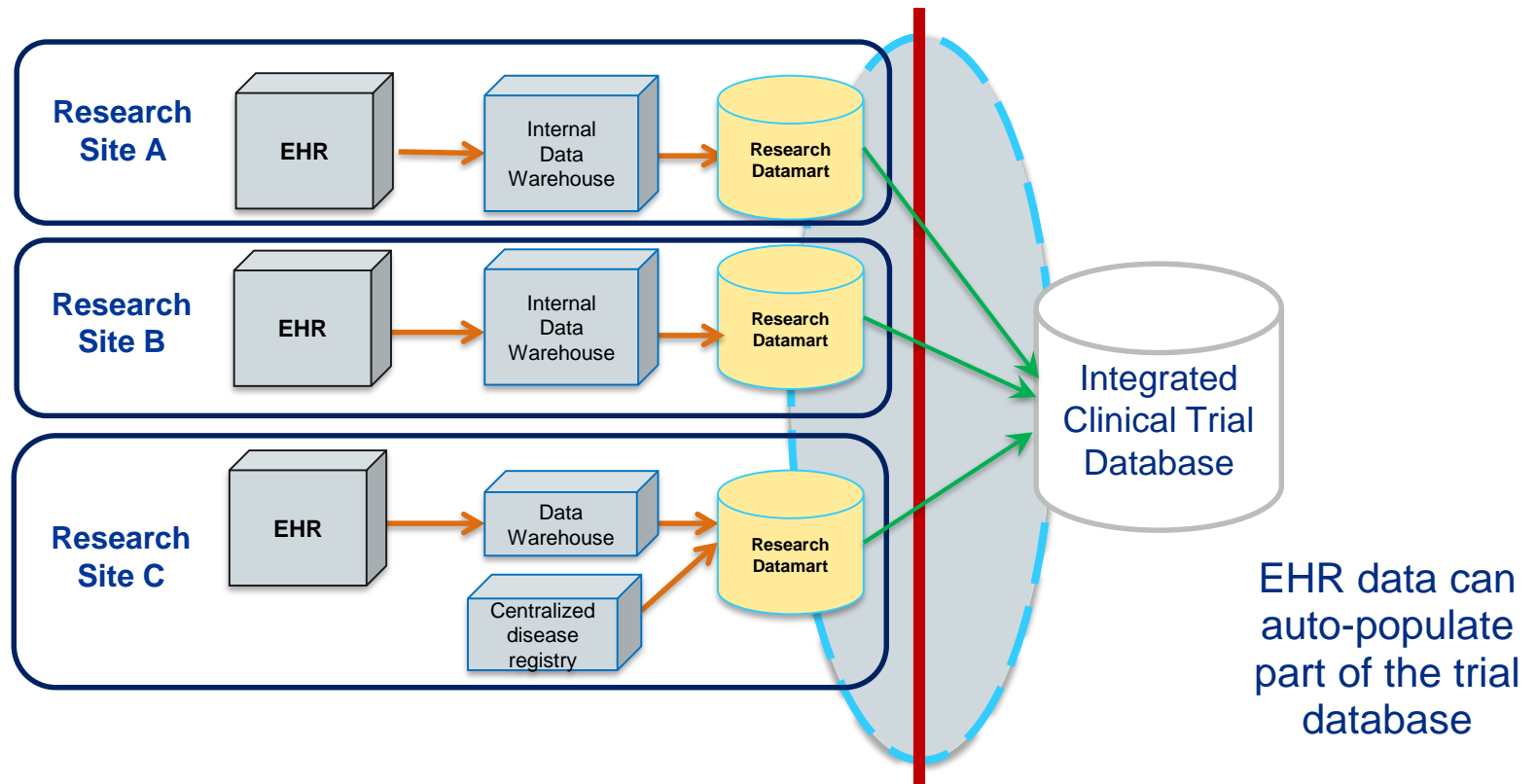
# Real World Data Characterization to Design Trials

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- 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

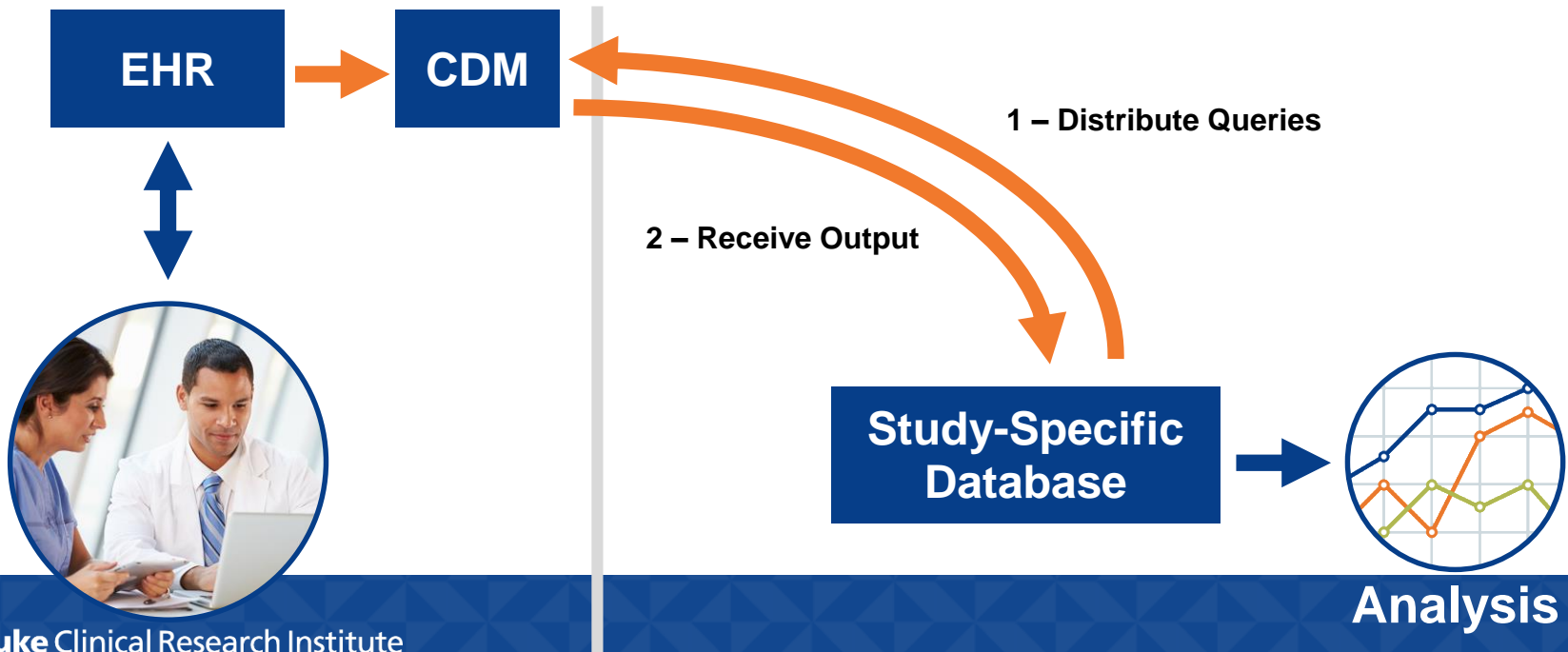
## Trial-Specific Clinical Research Network



# Approaches for Obtaining EHR Data for Trials (1)

## ▪ Distributed Research Network

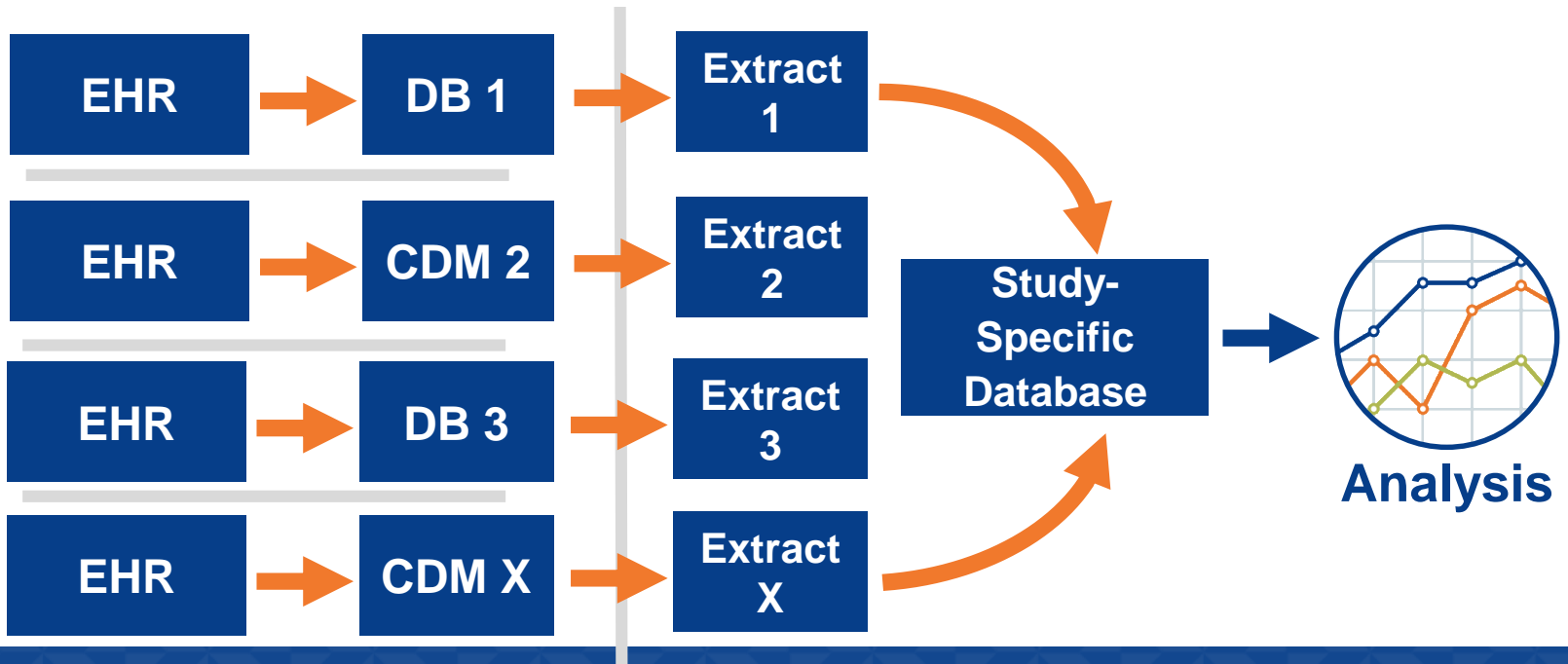
- Send query to sites who have data in pre-existing format (common data model)
- Sites return results (e.g., aggregate counts, summary statistics, patient-level records)



# 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

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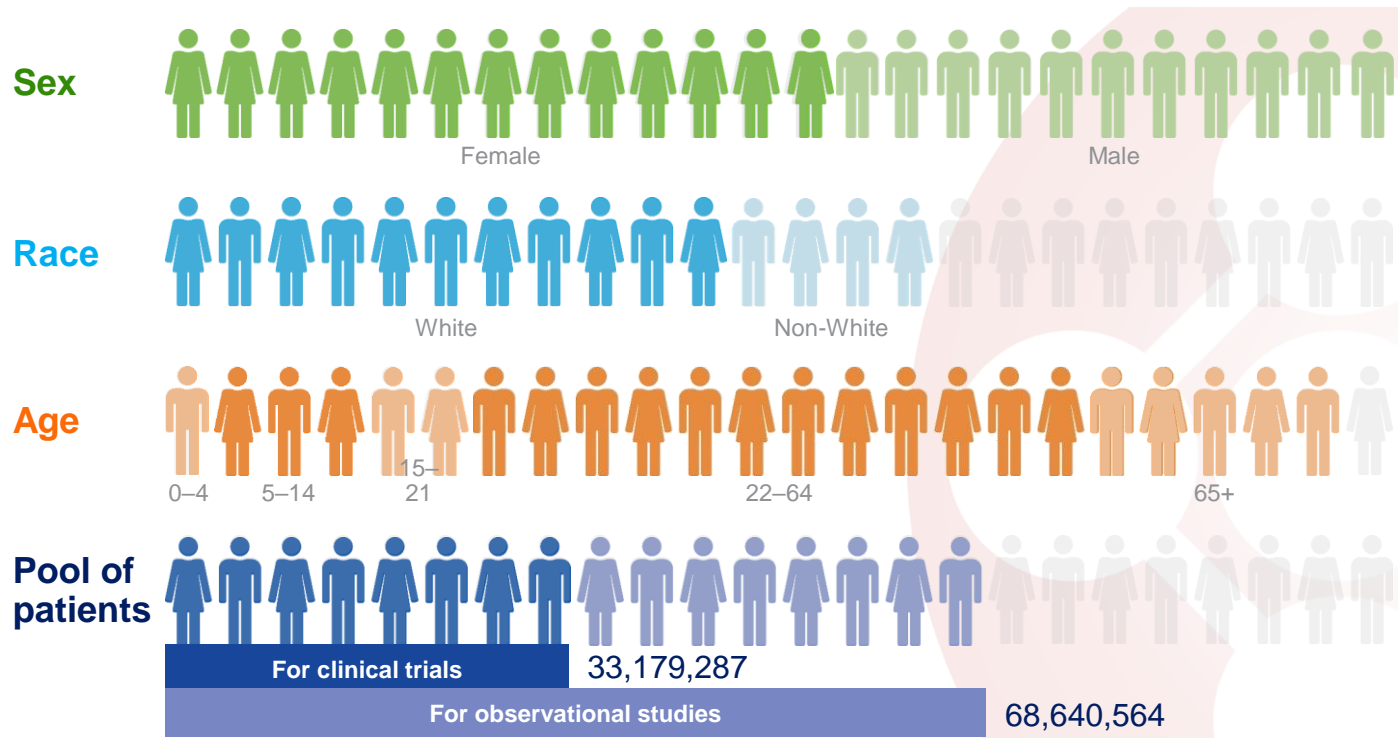
- When receiving data from the EHR (or claims or any other source), important to continuously monitor the quality of the incoming data
- EHR data quality domains ascertained:
  - *Conformance* – are EHR data formatted correctly?
  - *Completeness* – are EHR data present when we expect them to be?
  - *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**





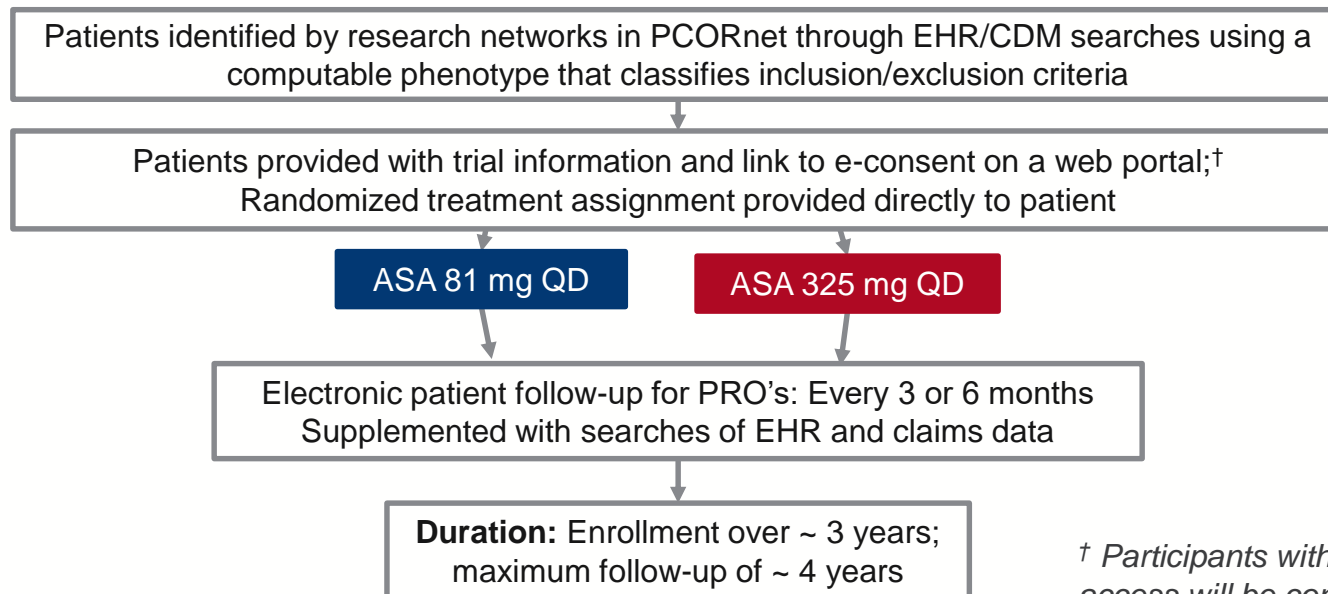
# Case Study: the APAPTABLE Trial Conducted Within PCORnet

## 110 Million patients in 64 Health System Data Marts



# ADAPTABLE Study Design

**15,000 patients with known ASCVD +  $\geq 1$  Enrichment Factor**

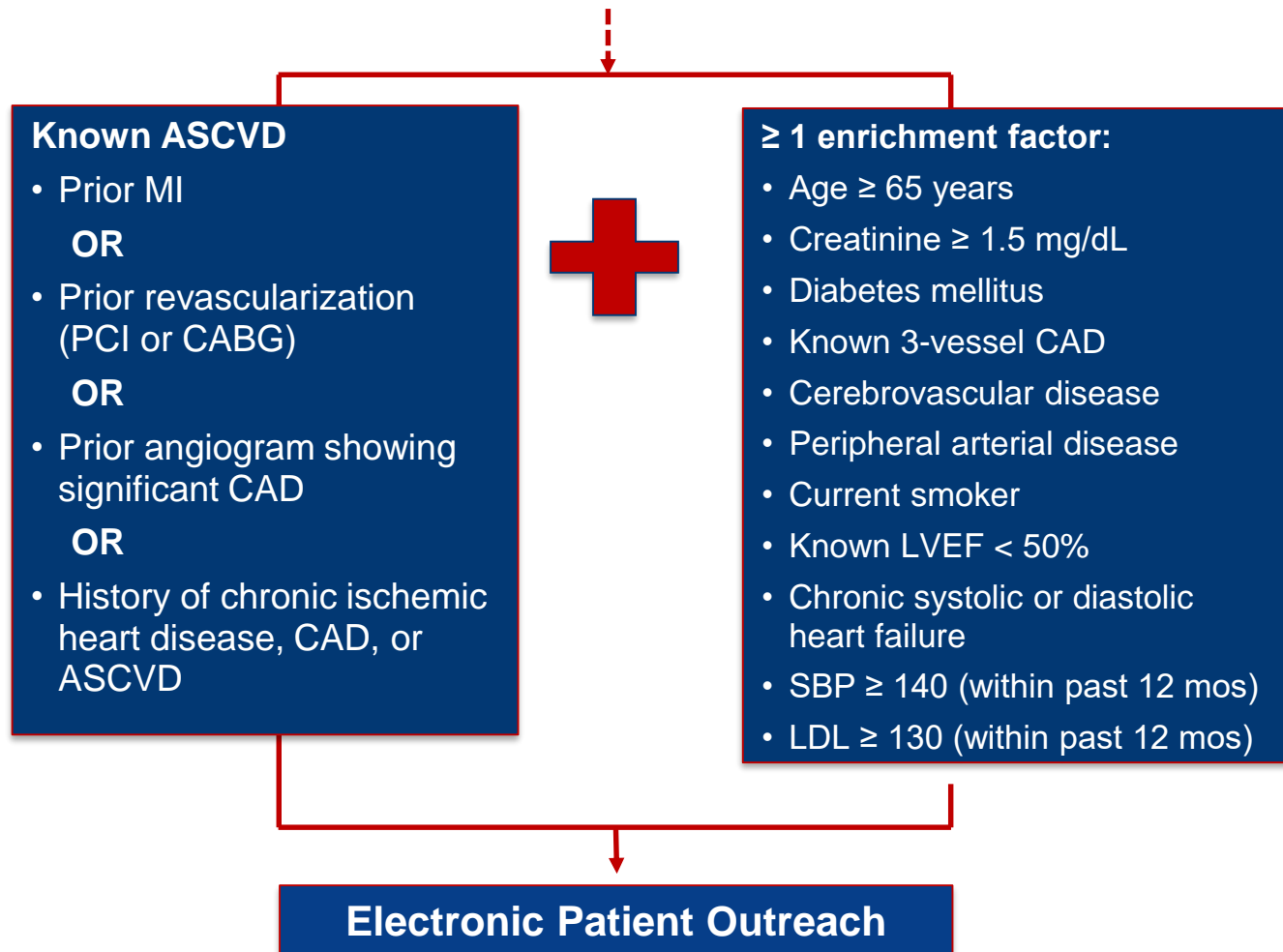


*† Participants without internet access will be consented and followed via a parallel system.*

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

**Primary Safety Endpoint:**  
Hospitalization for major bleeding

# ADAPTABLE Inclusion Criteria – Computable Phenotype



# 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

# 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

The screenshot shows the Adaptable web portal interface. At the top, the Adaptable logo and 'The Aspirin Study' are displayed. The user's name, Allison Smith, is shown in the top right corner. A 'TEXT SIZE' control is visible. The main content area features a welcome message: 'Hi, Allison! Welcome back.' Below this, a prompt asks the user to complete forms, noting that there are no time limits. Four interactive cards are presented: 'Info' (Contact & insurance information, 5 min), 'History' (Past history, 5 min), 'Medications' (Have your current medications handy, 5 min), and 'Hospitalization' (Let us know about any hospitalizations, 3 min). A green 'LET'S GET STARTED' button is prominently displayed. Below the cards, a timeline shows the user's progress: 'Start Date 10/7/15', '1 week 10/14/15' (marked 'TODAY'), '3 mo 1/7/16', and '6 mo 4/7/16'. At the bottom, a section titled 'Your assigned aspirin dosage' shows a 325 mg Aspirin tablet and states: 'You have been assigned the daily dosage of 325 mg of aspirin each day for participation in the ADAPTABLE study.' Links for 'Re-watch video' and 'Re-read documents' are at the bottom.

# 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

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- 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



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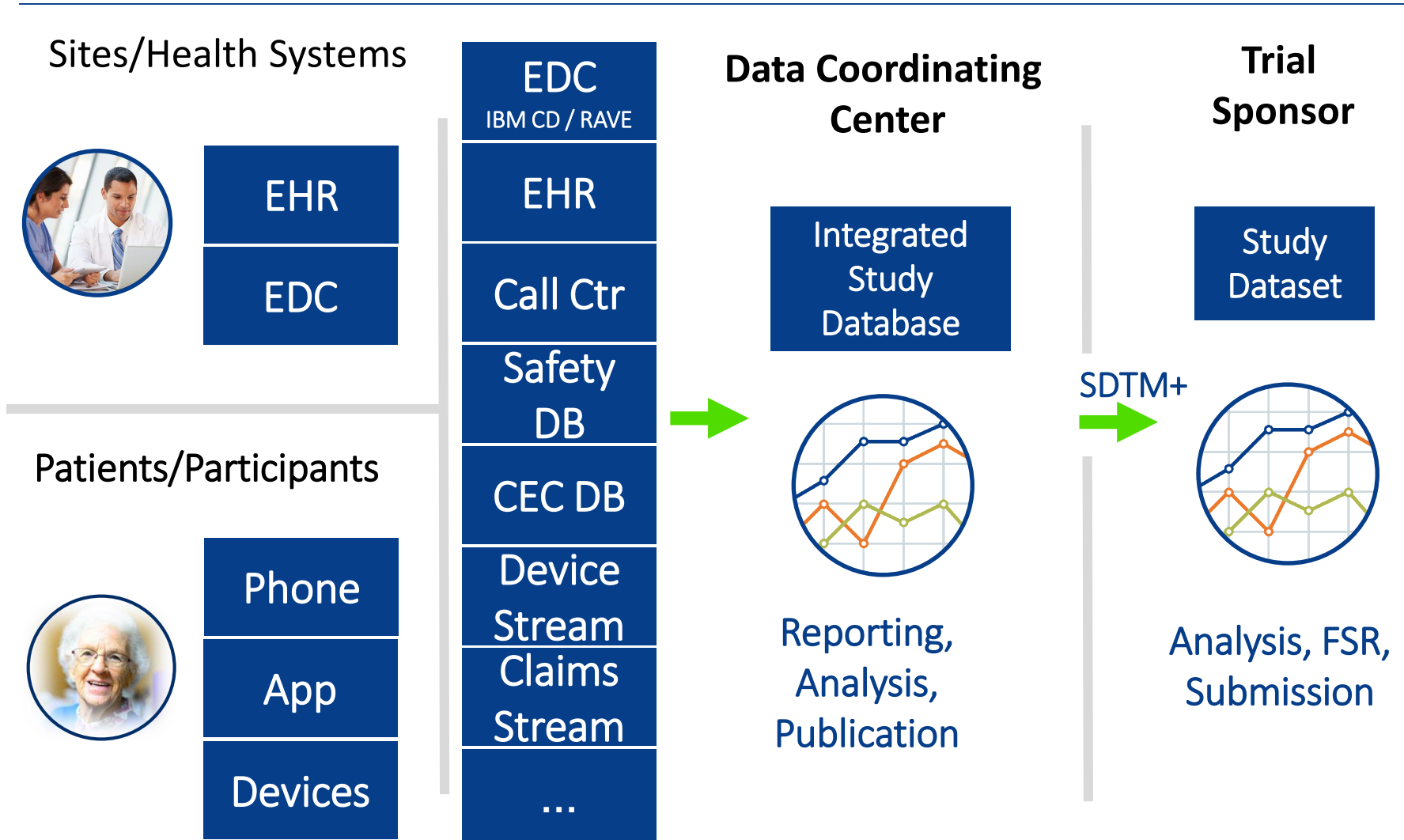
# Pragmatic Data Collection

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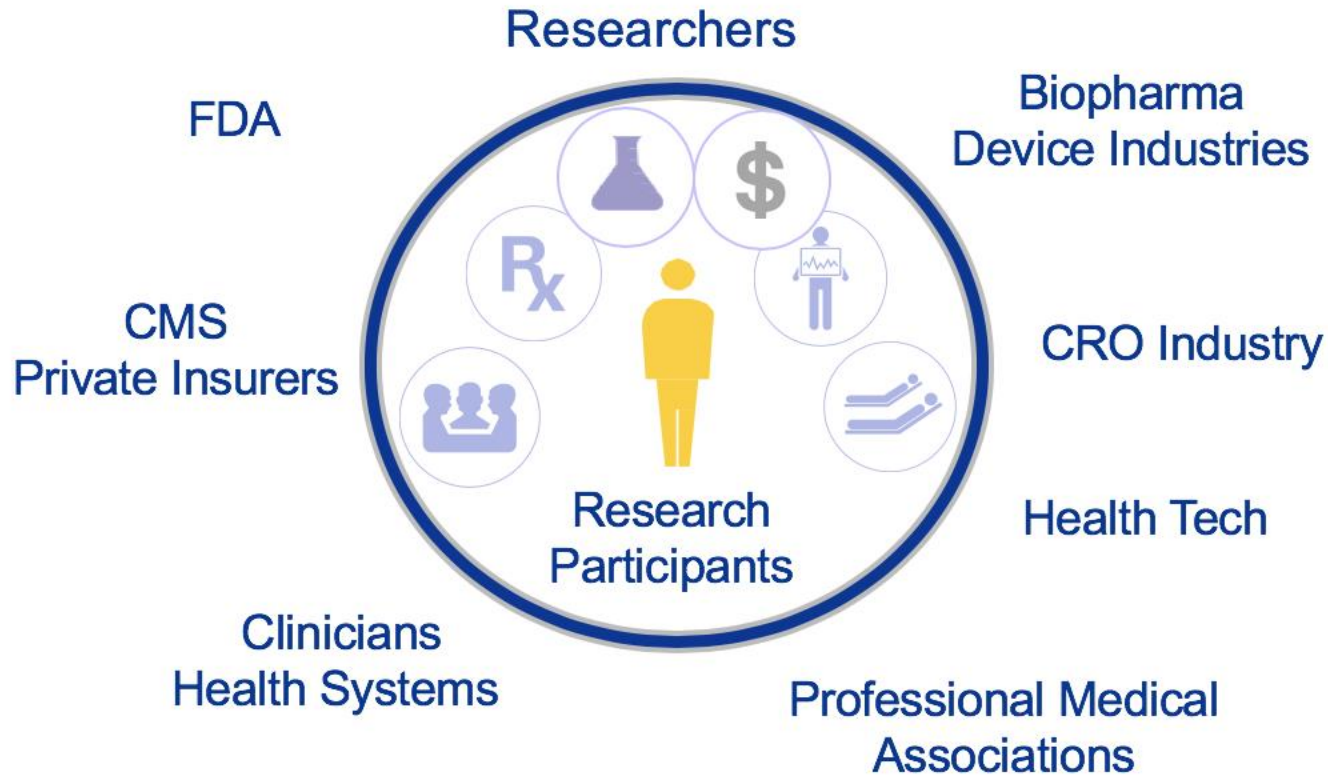
- Goal is to substantially reduce data collection burden for trial sites
- Novel approaches for mechanisms of data capture, endpoint ascertainment, and safety reporting
  - *Some data (clinical characteristics, medications, labs) from local EHR data sources could be directly imported into trial database*
  - *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



# Cross-Sectional Stakeholder Partnerships Needed



# Conclusions

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- 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

