Technology-Enabled Trials: Transforming Medical Evidence Generation

Matthew T. Roe, MD, MHS
Duke Clinical Research Institute

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

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

- **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

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…

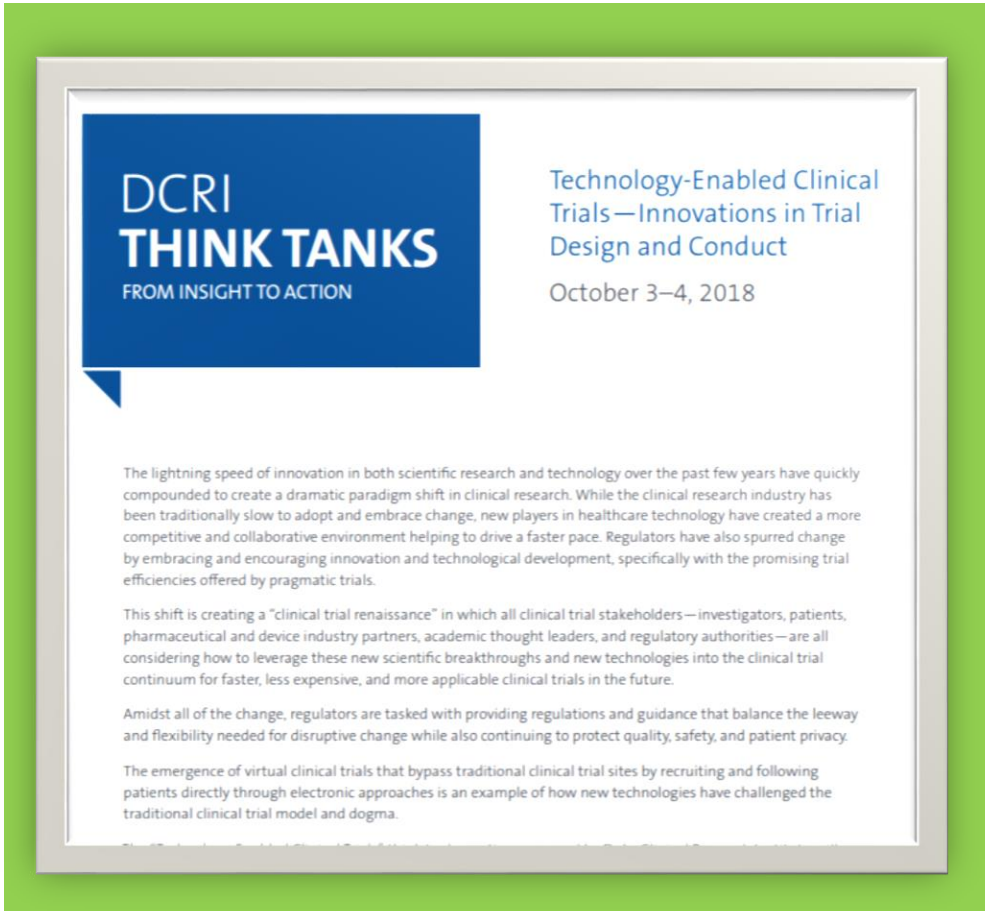
with renewed focus on

impact and sense of urgency

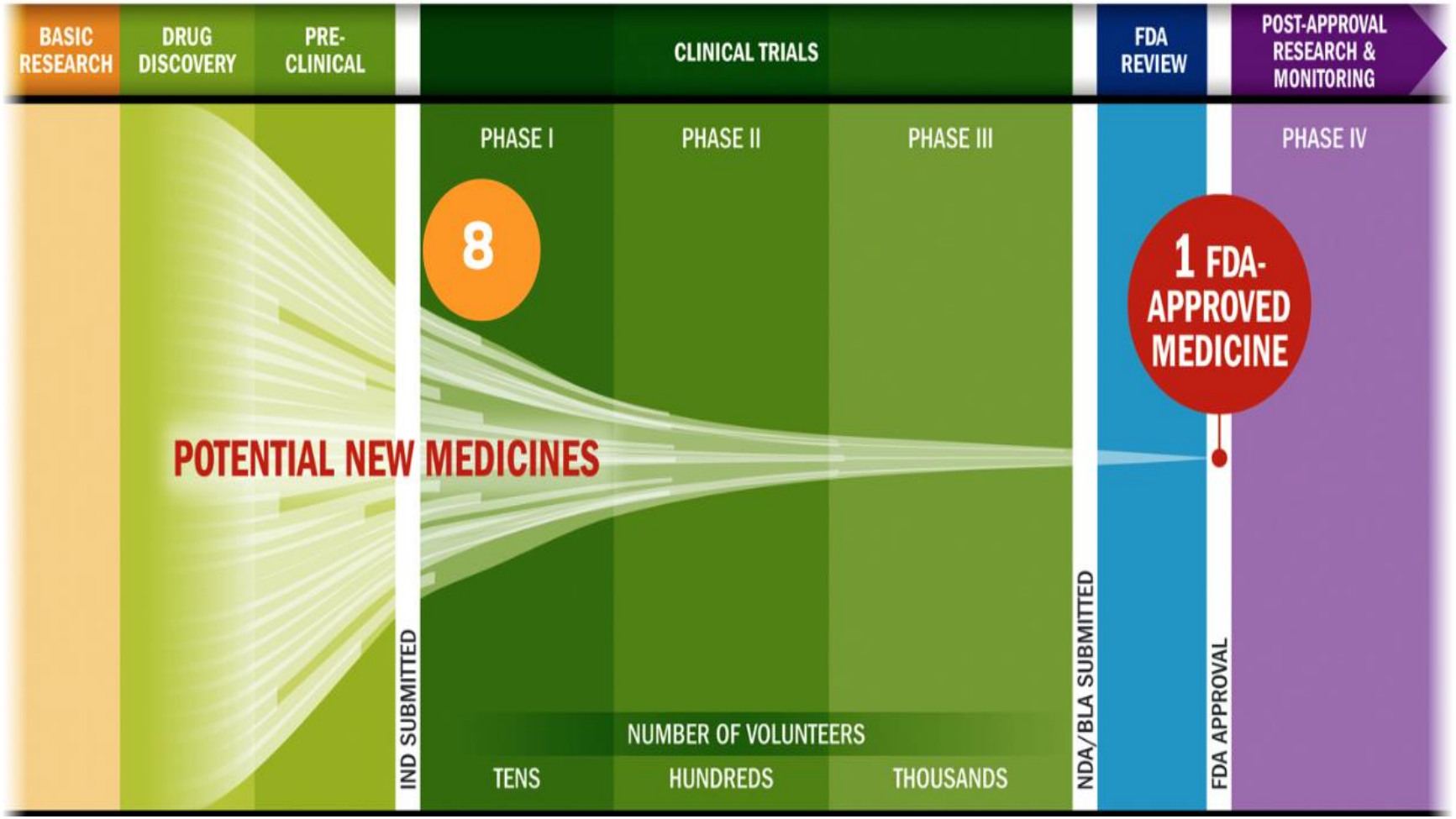
Technology-Enabled Clinical Trials Think Tank — Innovations in Trial Design and Conduct

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



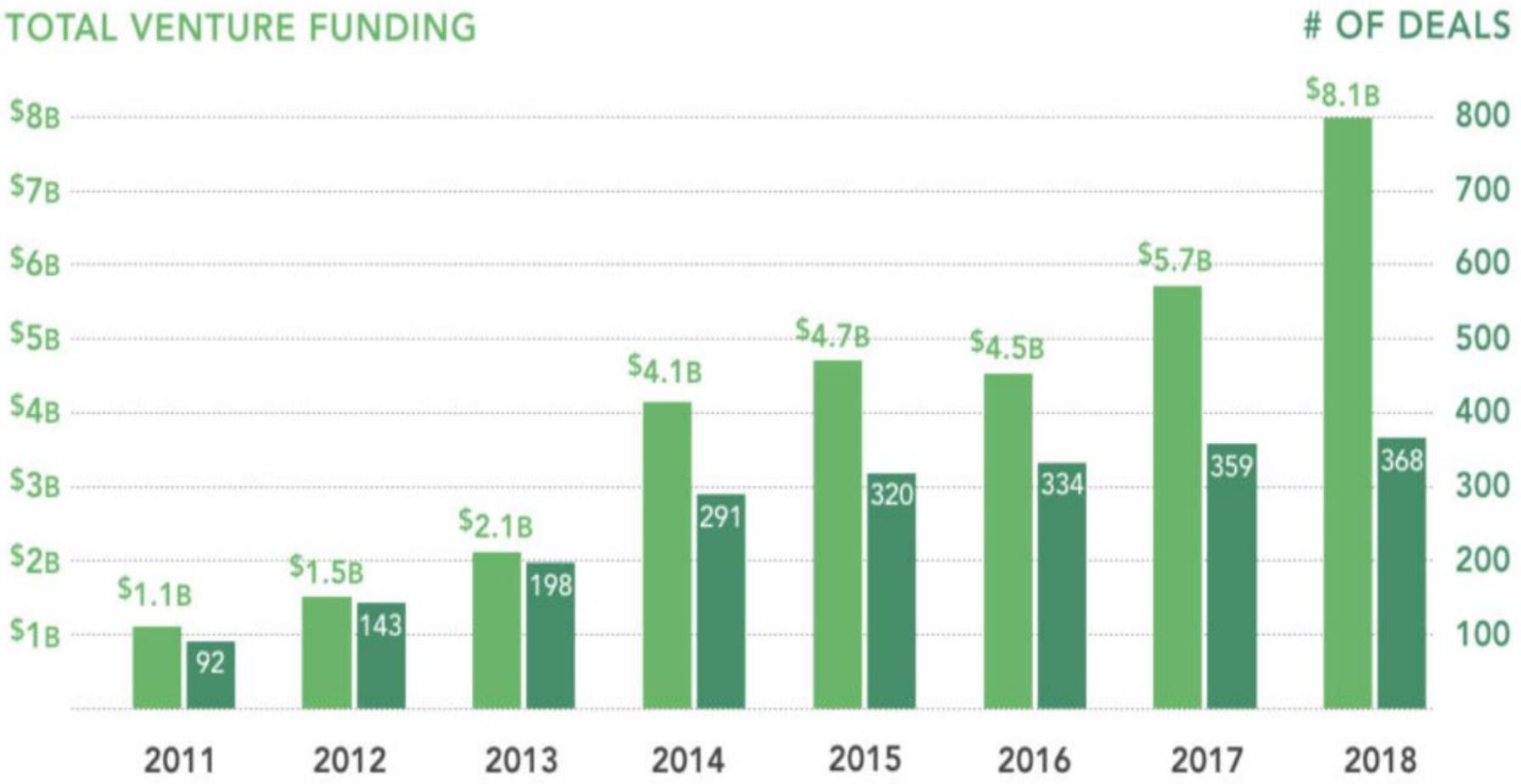
Cost and Complexity of Clinical Trials Limit Drug Development



Tufts Center for the Study of Drug Development (https://www.sciencedirect.com/science/article/pii/S0167629616000291https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3241518/)

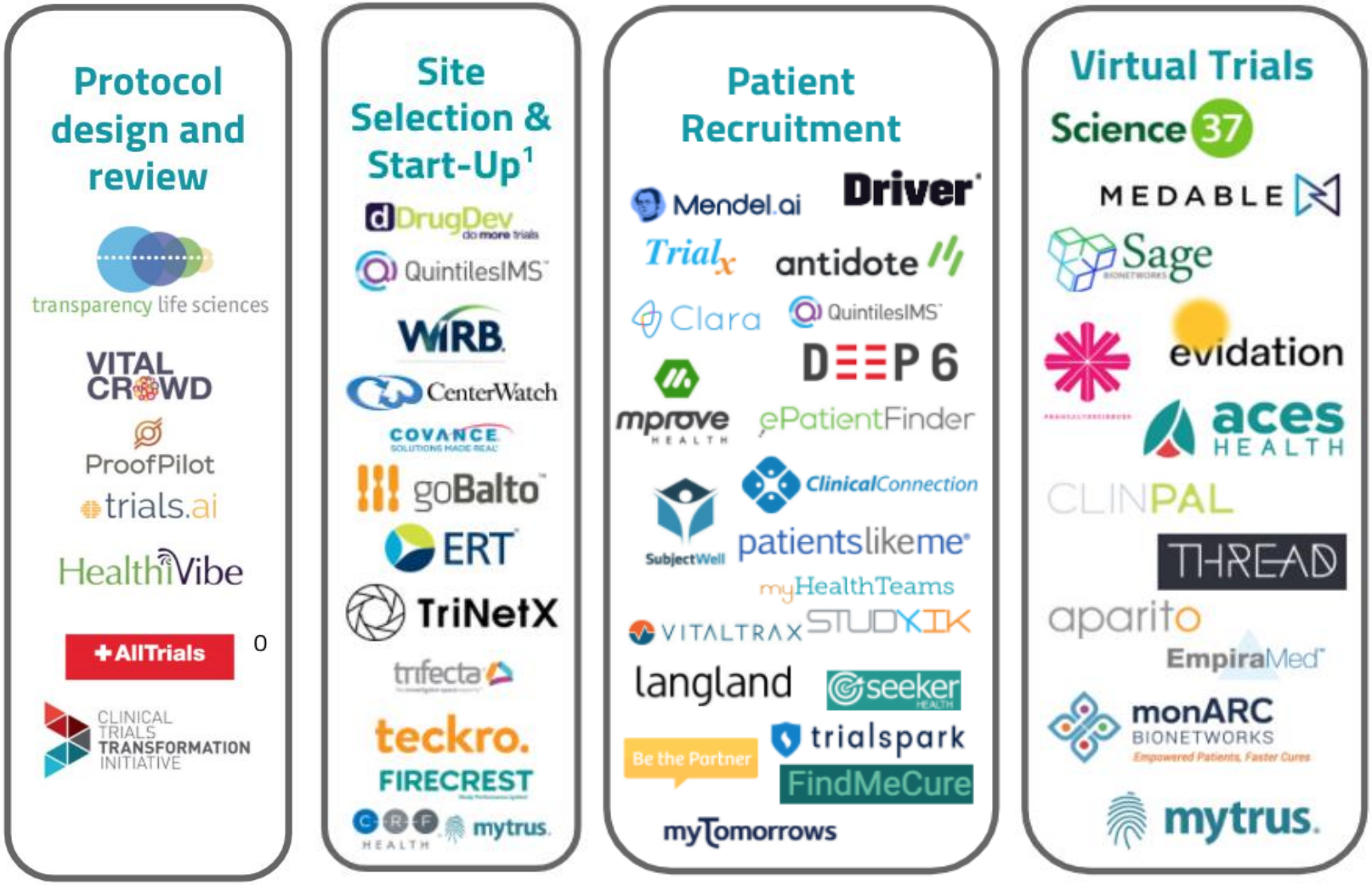
Transforming Clinical Research in the US https://www.ncbi.nlm.nih.gov/books/NBK50895/

Private Investment in Digital Health Steadily Increasing



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



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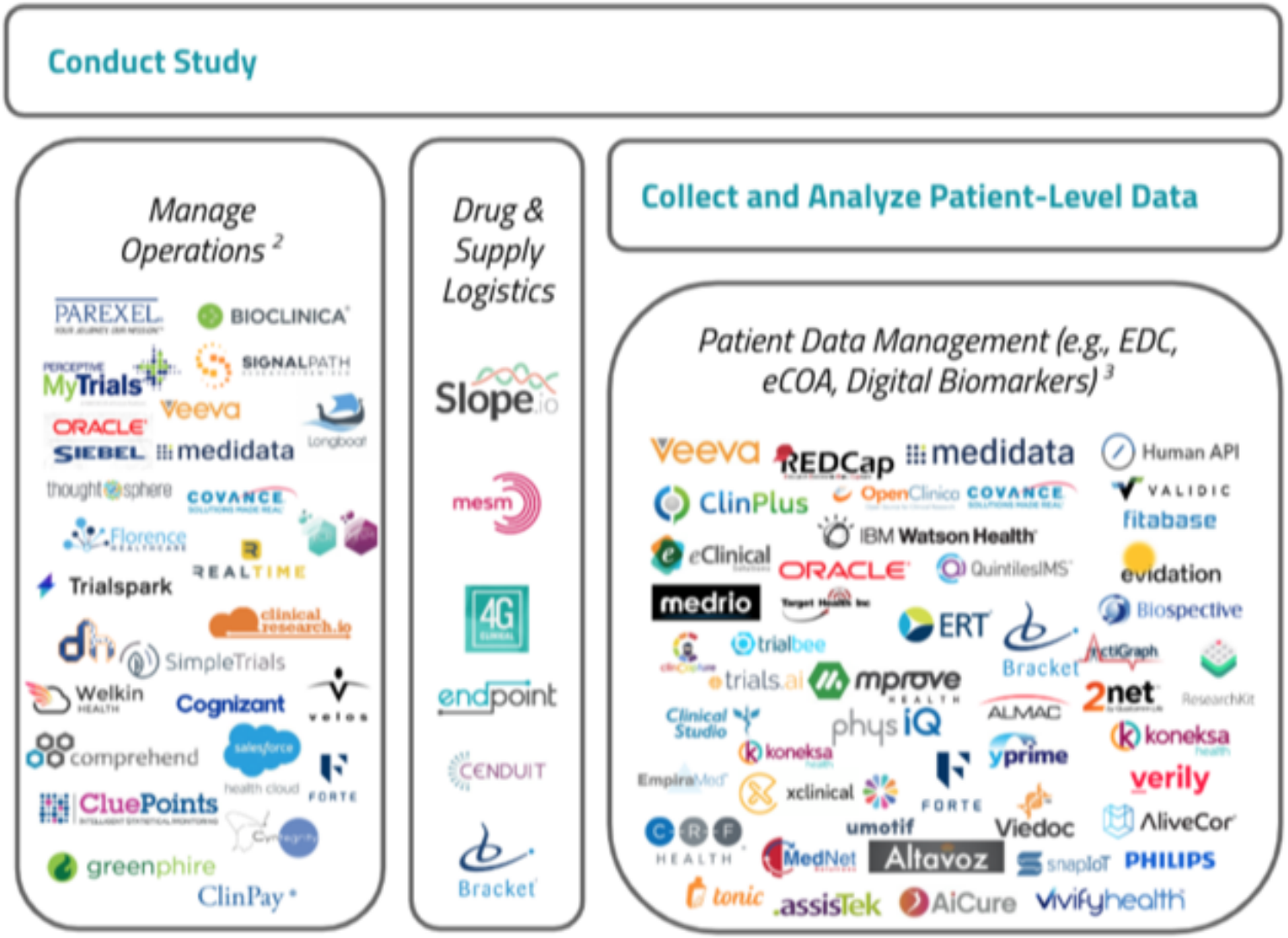


CTTI

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

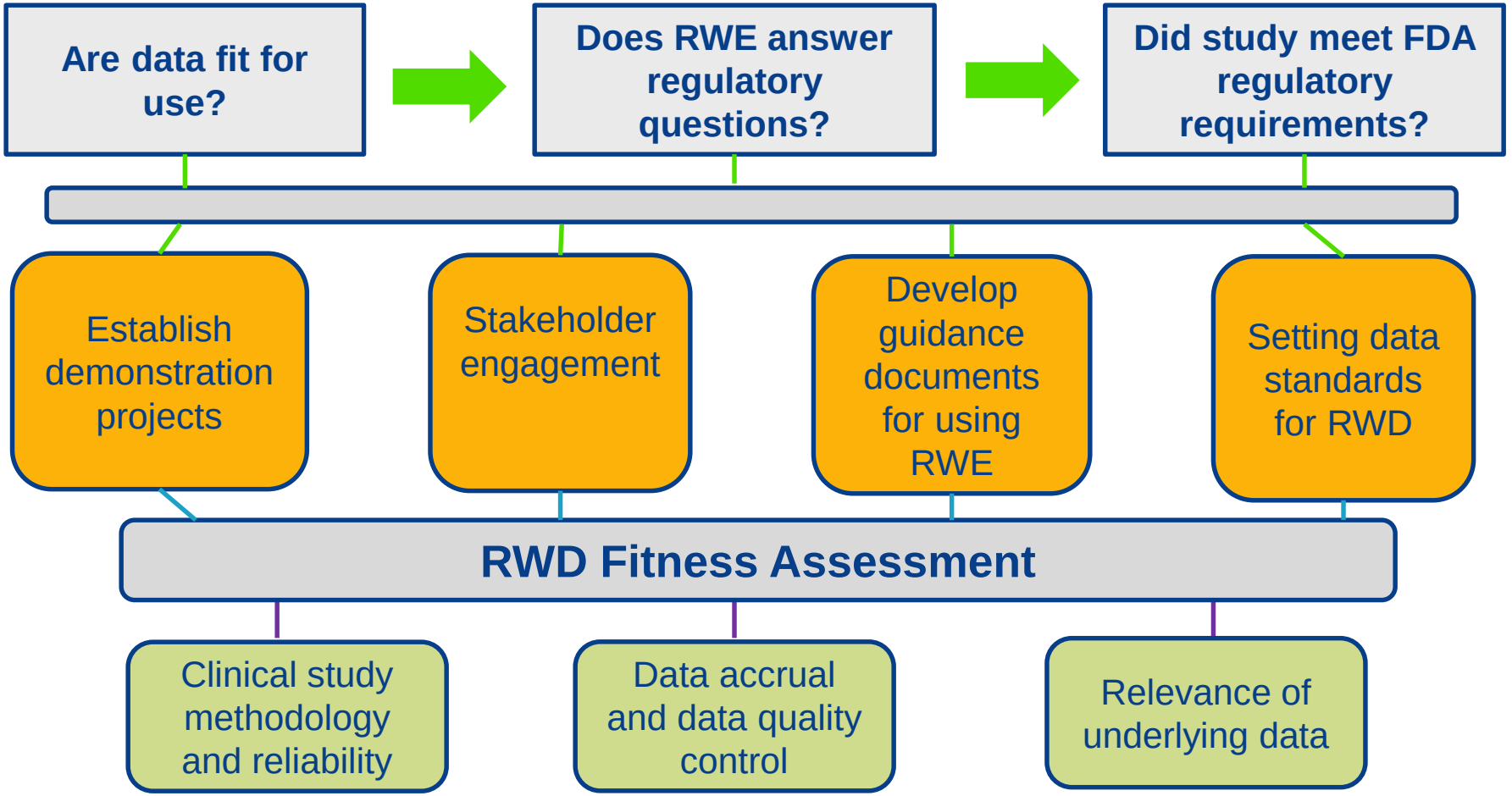
- Real World Evidence
- Registry Trials
- Antibacterial Drug Development
- Sentinel IMPACT-Afib trial
- Large Simple Trials
- Using FDA Sentinel for Trials

Ethics & Human Research Protection

- Single IRB
- Data Monitoring Committees
- Informed Consent
- Safety Reporting

Details available at www.ctti-clinicaltrials.org

FDA Real World Evidence Framework and Transformation



Released by FDA in December, 2018

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

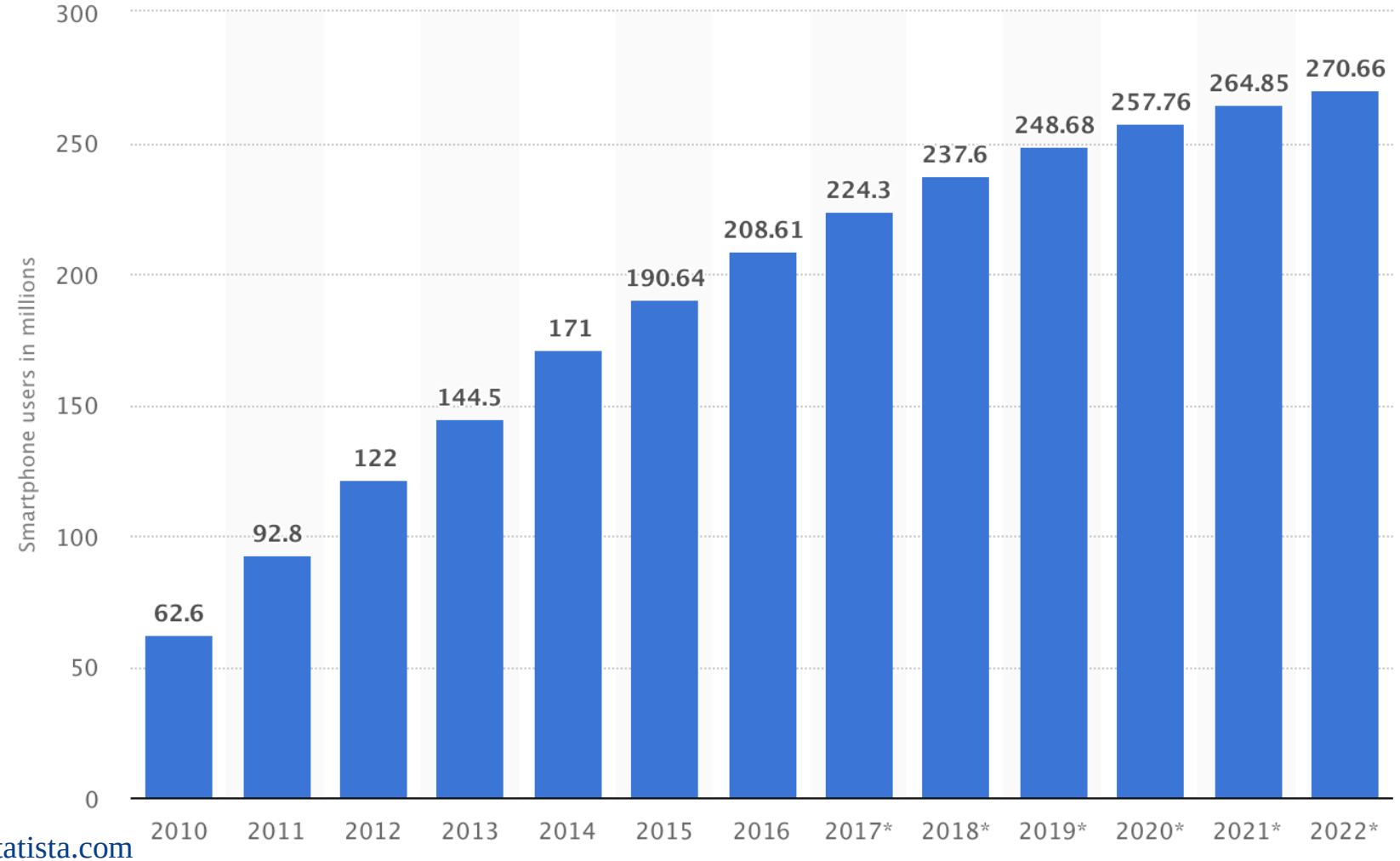
The Digital Health Innovation Action Plan outlines our efforts to reimagine the FDA's approach to ensuring all Americans have timely access to high-quality, safe and effective digital health products. As part of this plan, we committed to several key goals, including increasing the number and expertise 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

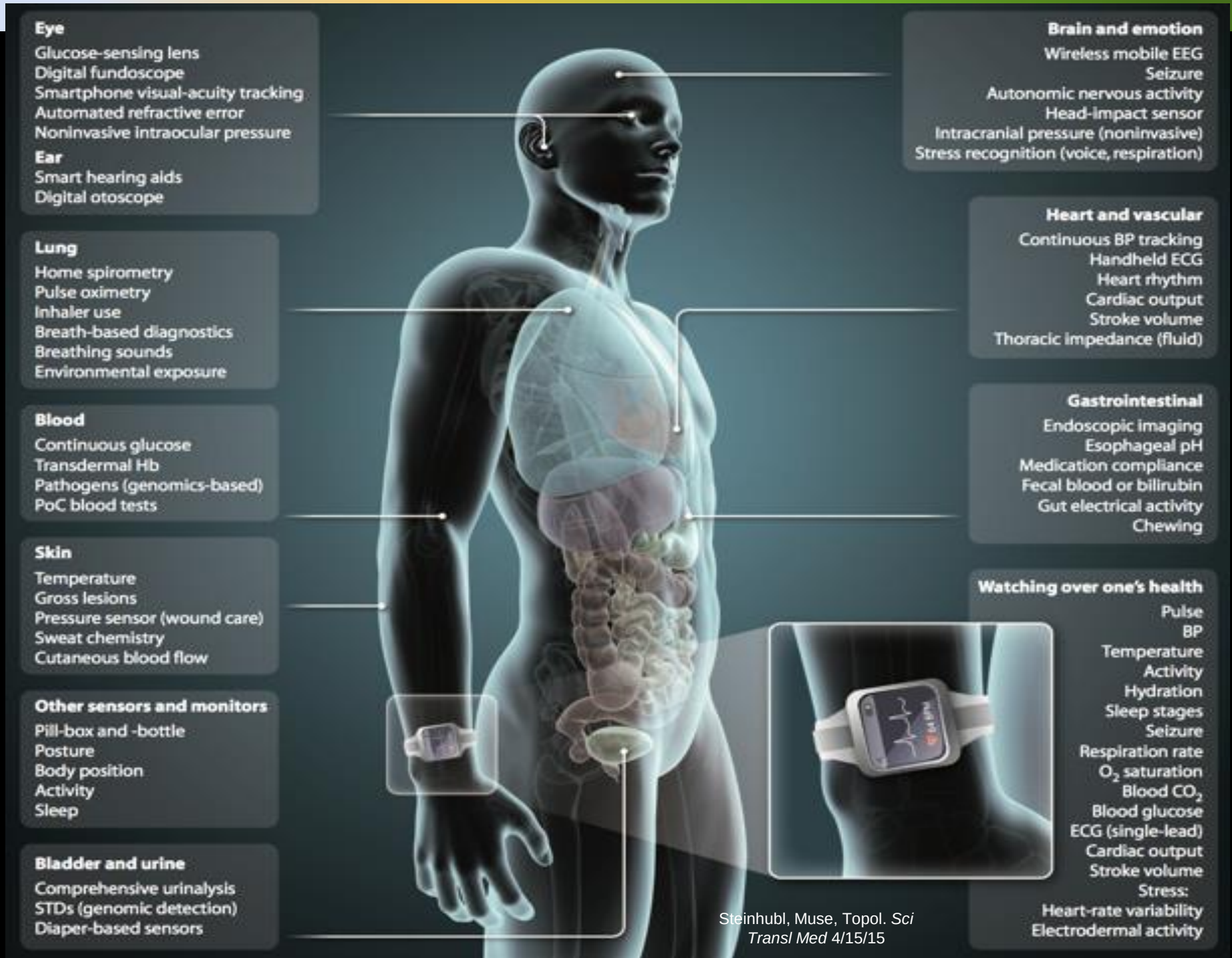
https://www.fda.gov/medical-devices/digital-health

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

Smartphone Ownership Across the United States

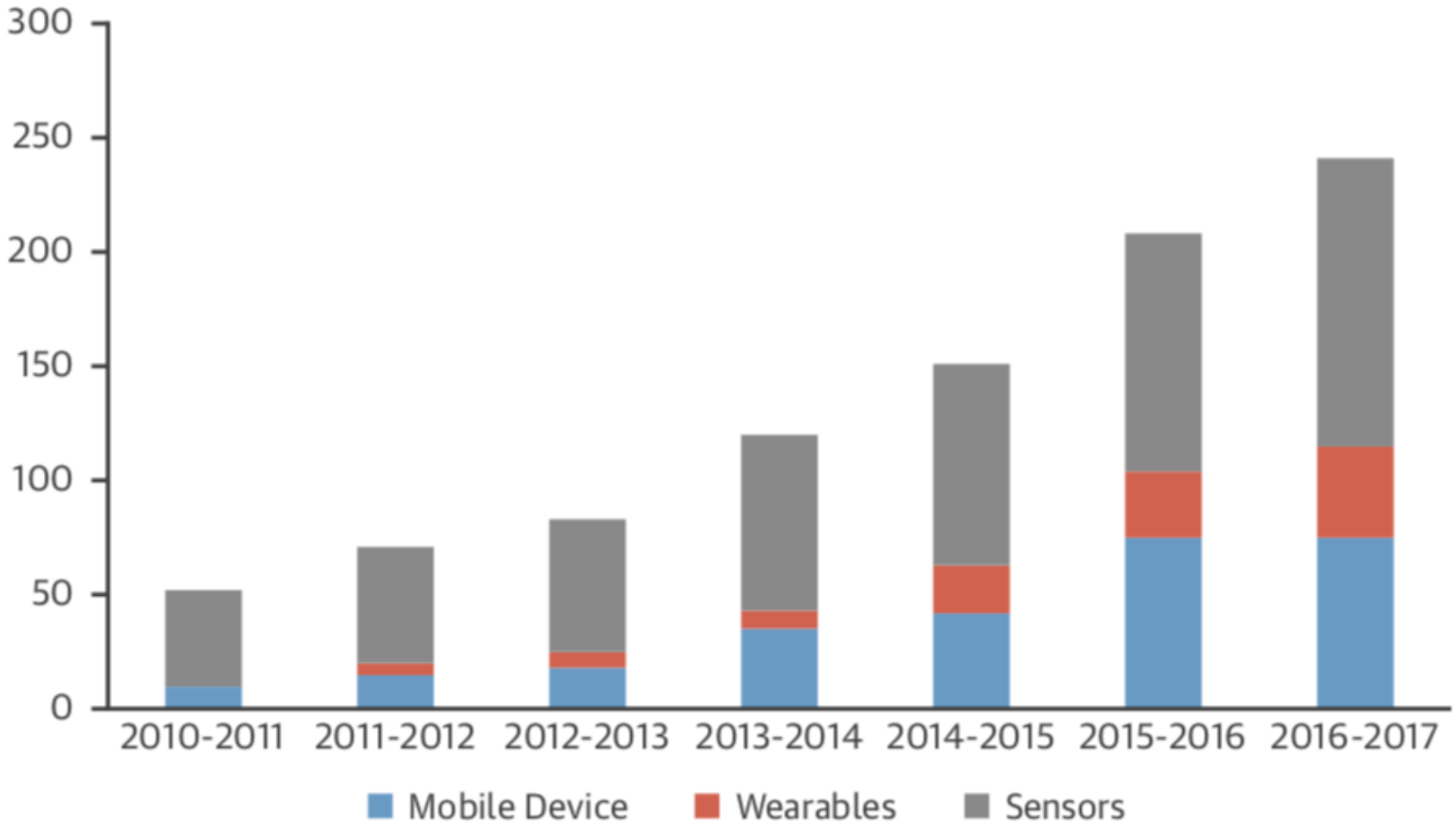


Statista.com



Steinhubl, Muse, Topol. *Sci Transl Med* 4/15/15

Use of Digital Technologies in Clinical Trials Increasing



JACC 2018;71:DOI: 10.1016/j.jacc.2018.03.523

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

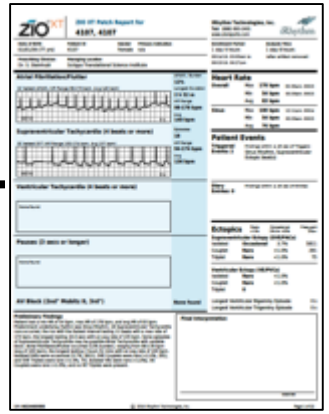
- Remote screening and enrollment enabled with digital devices
- Broader and faster access to patient populations representing routine clinical practice
- Direct collection of data from patients via digital devices and from biosensors

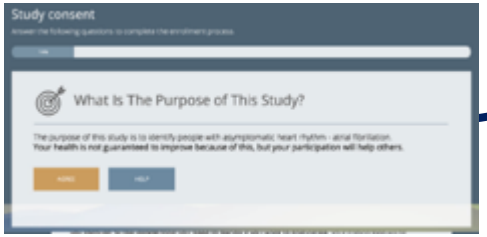
Overview

MSToPS

aetna® Members

Scripps Translational Science Institute

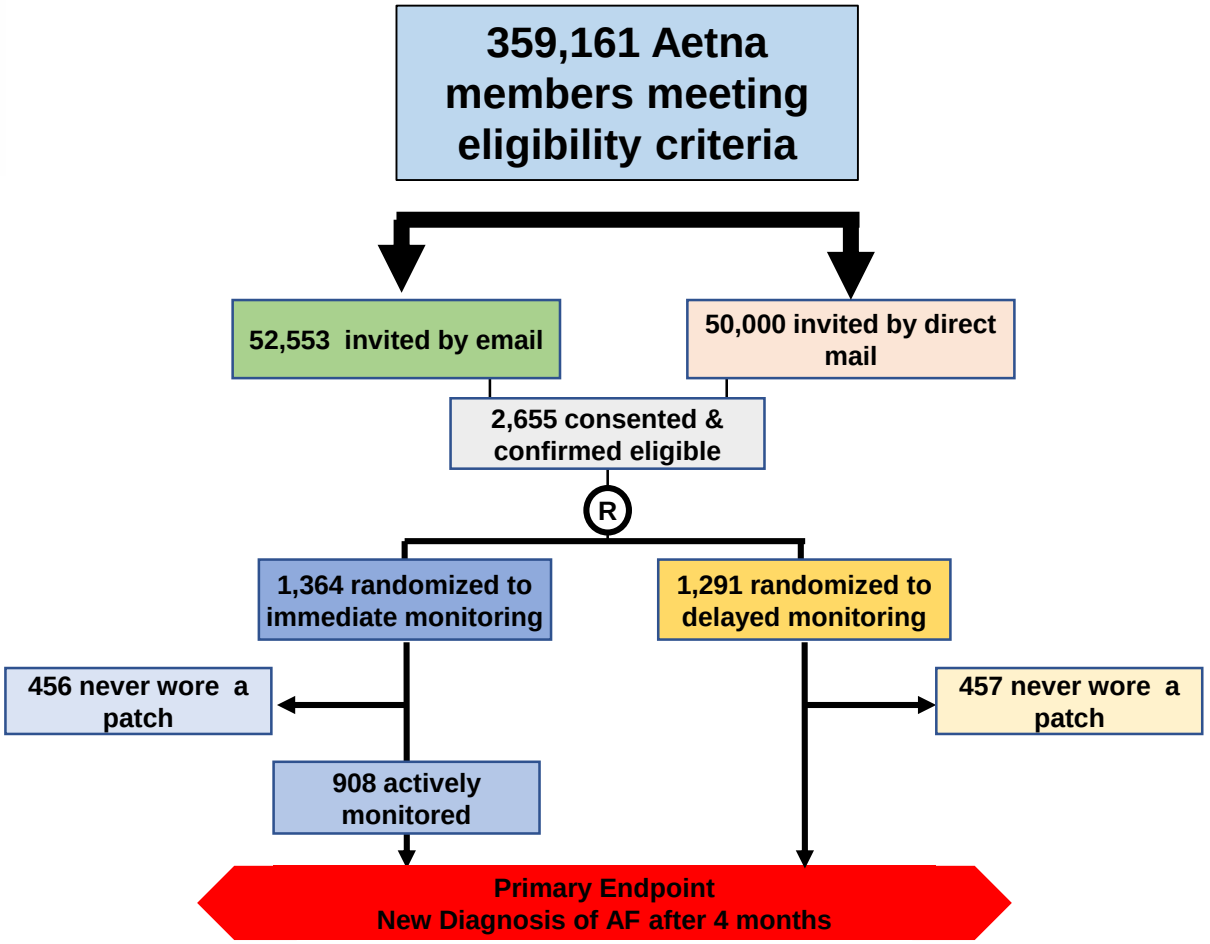




Scripps Research

JAMA. 2018;320(2):146-155.

MSToPS



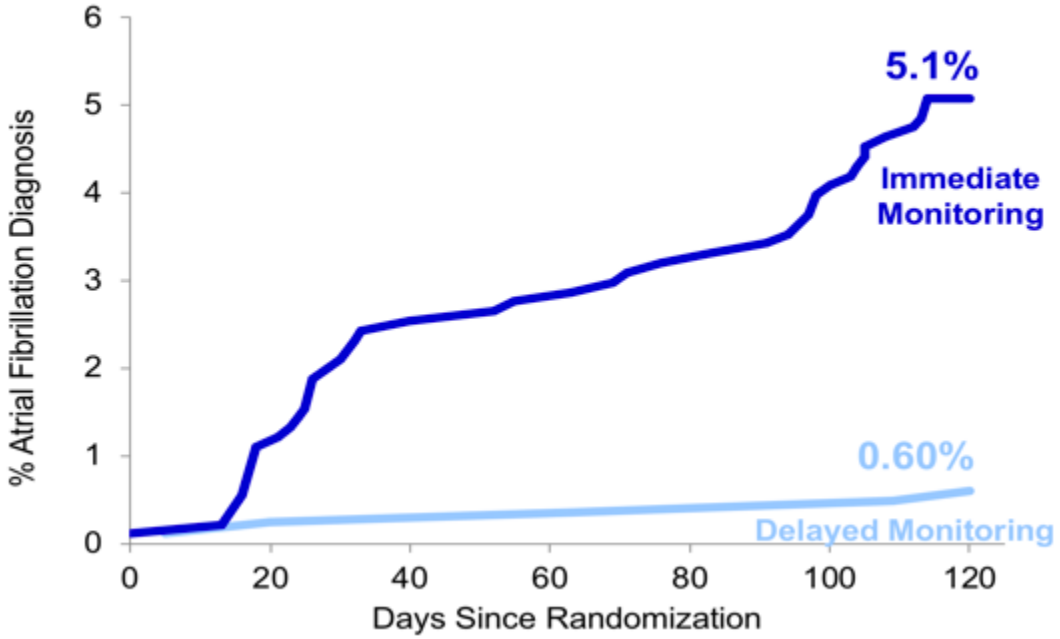
Scripps Research

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

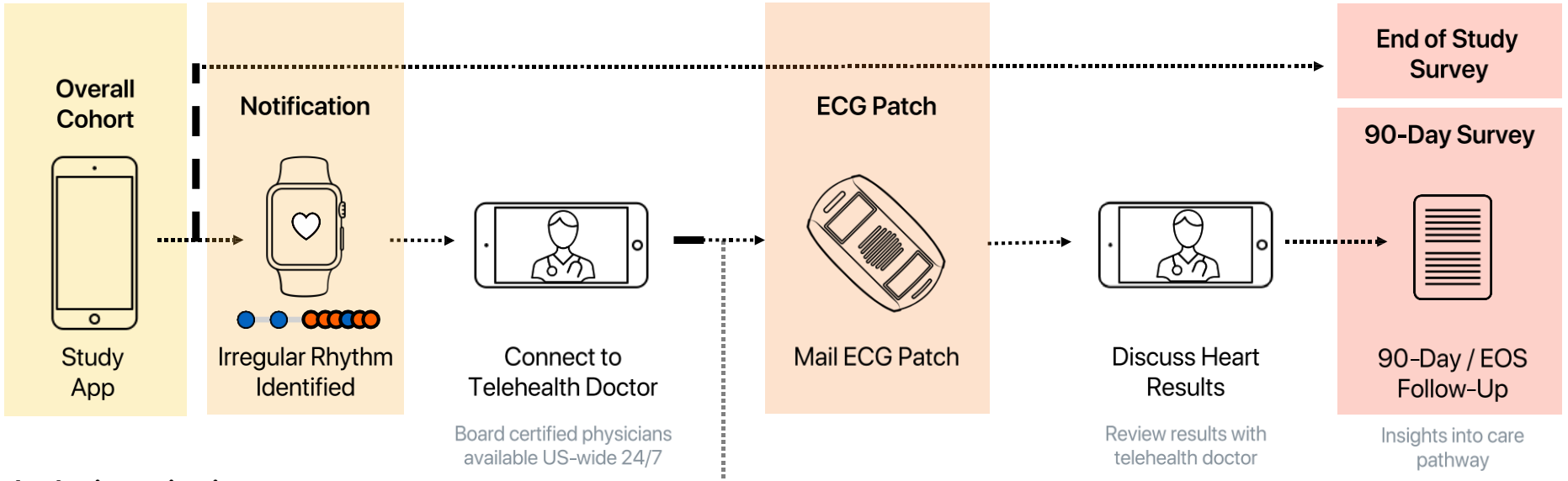
95%CI 3.6-22.7
P<0.0001

Scripps Research

JAMA. 2018;320(2):146-155.

Apple Heart Study

Prospective, Single Arm, Open Label Study



Inclusion criteria

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

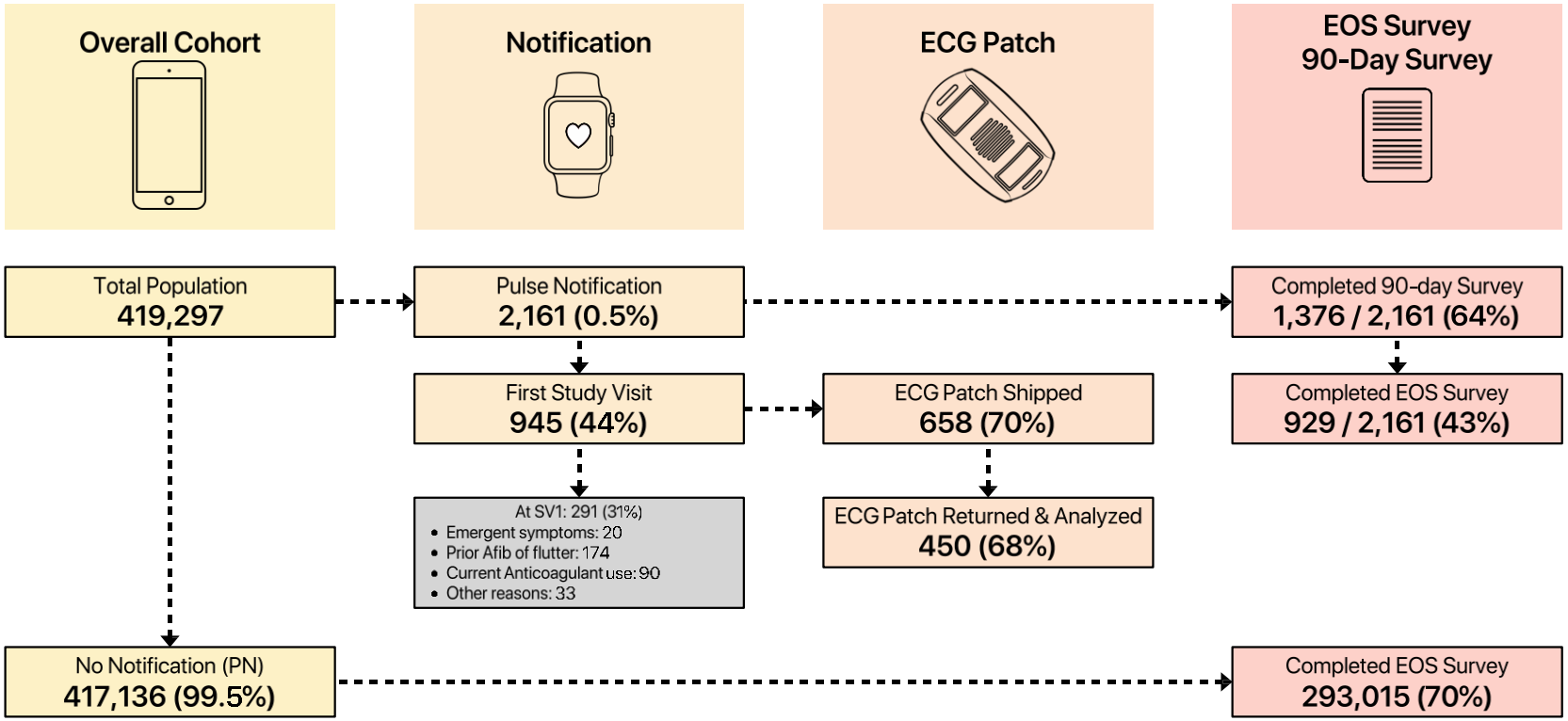
Exclusion criteria

- Atrial fibrillation or atrial flutter
- Current use of anticoagulation

American College of Cardiology LBCT, March, 2019

Apple Heart Study

Consort Diagram



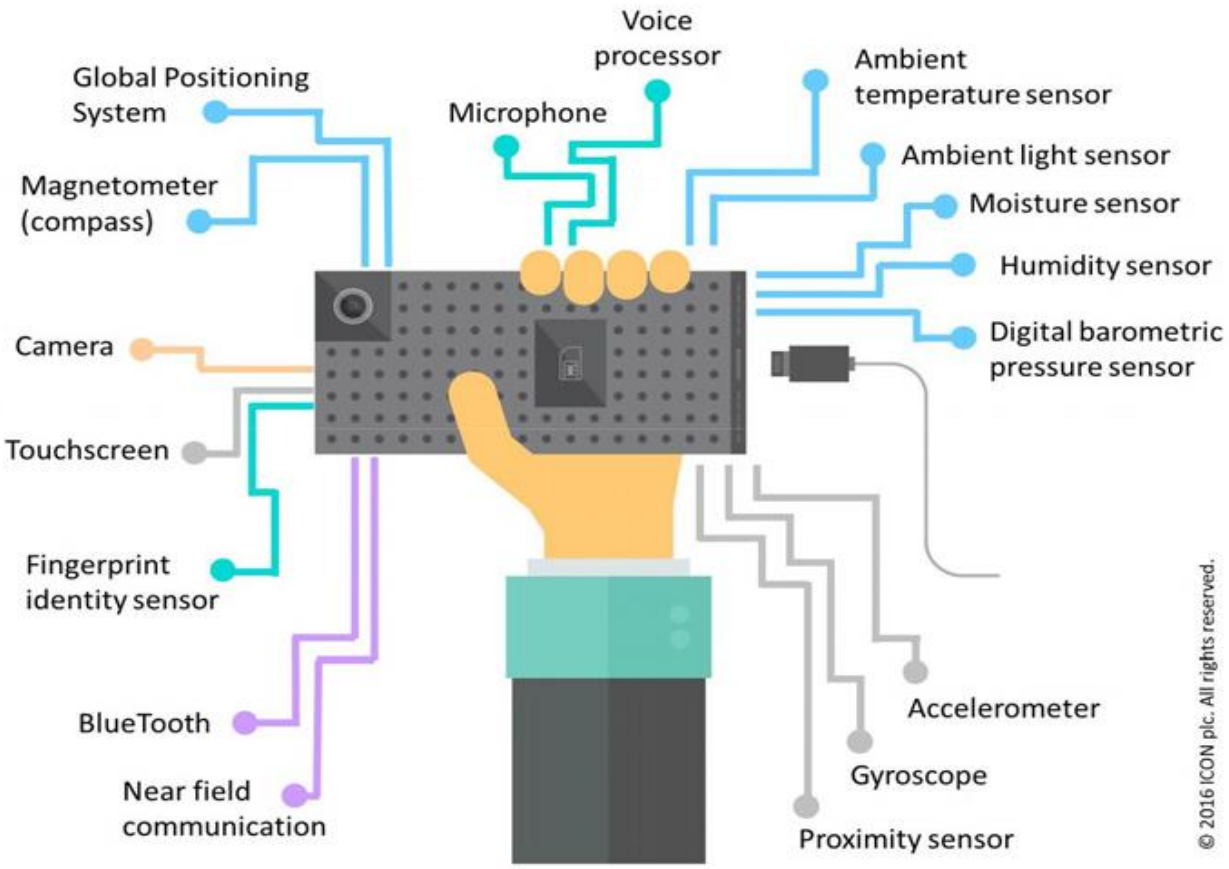
American College of Cardiology LBCT, March, 2019

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

Duke Mobile App Gateway



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

Duke Clinical Research Institute

FROM **THOUGHT LEADERSHIP**
TO **CLINICAL PRACTICE**

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

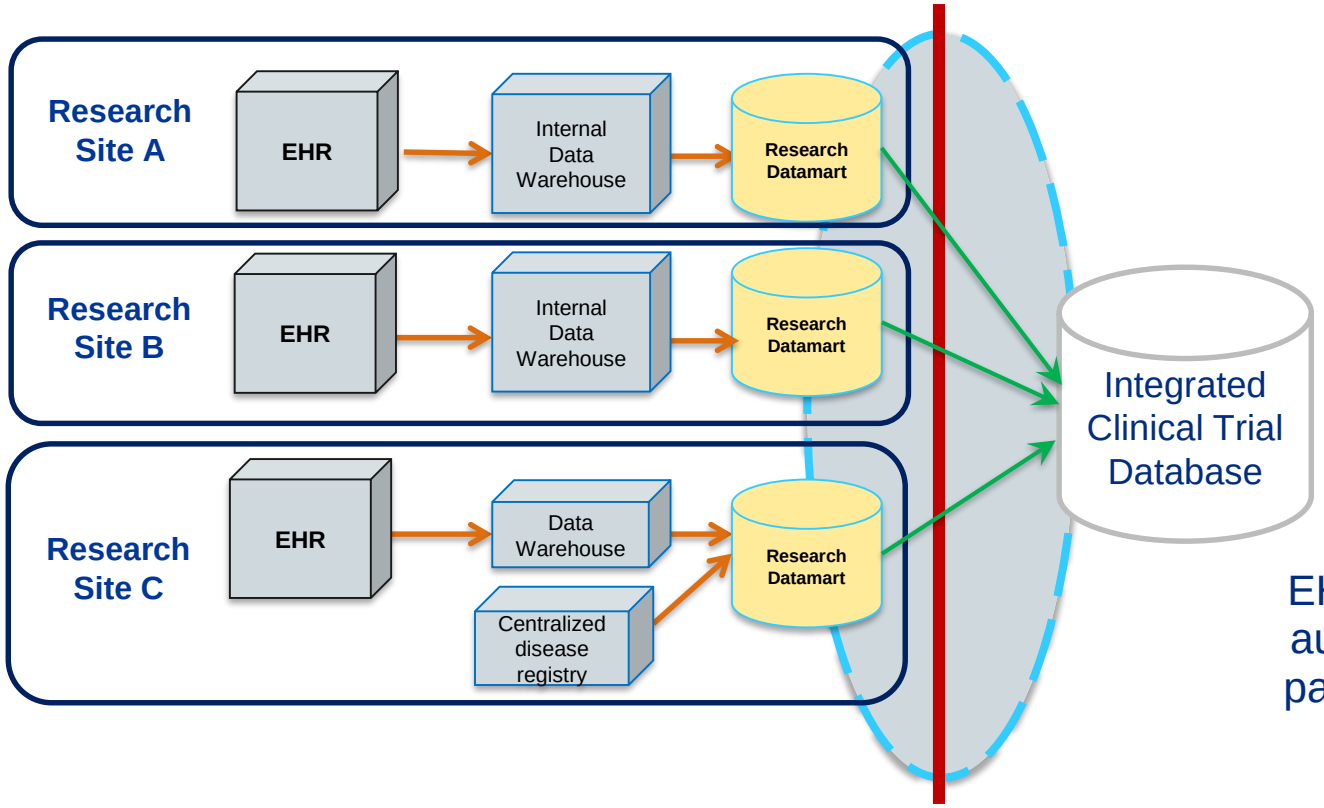
Participant Retention & Contact
- Use of patient portals to collect PRO's, share trial progress reports, and enhance retention

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

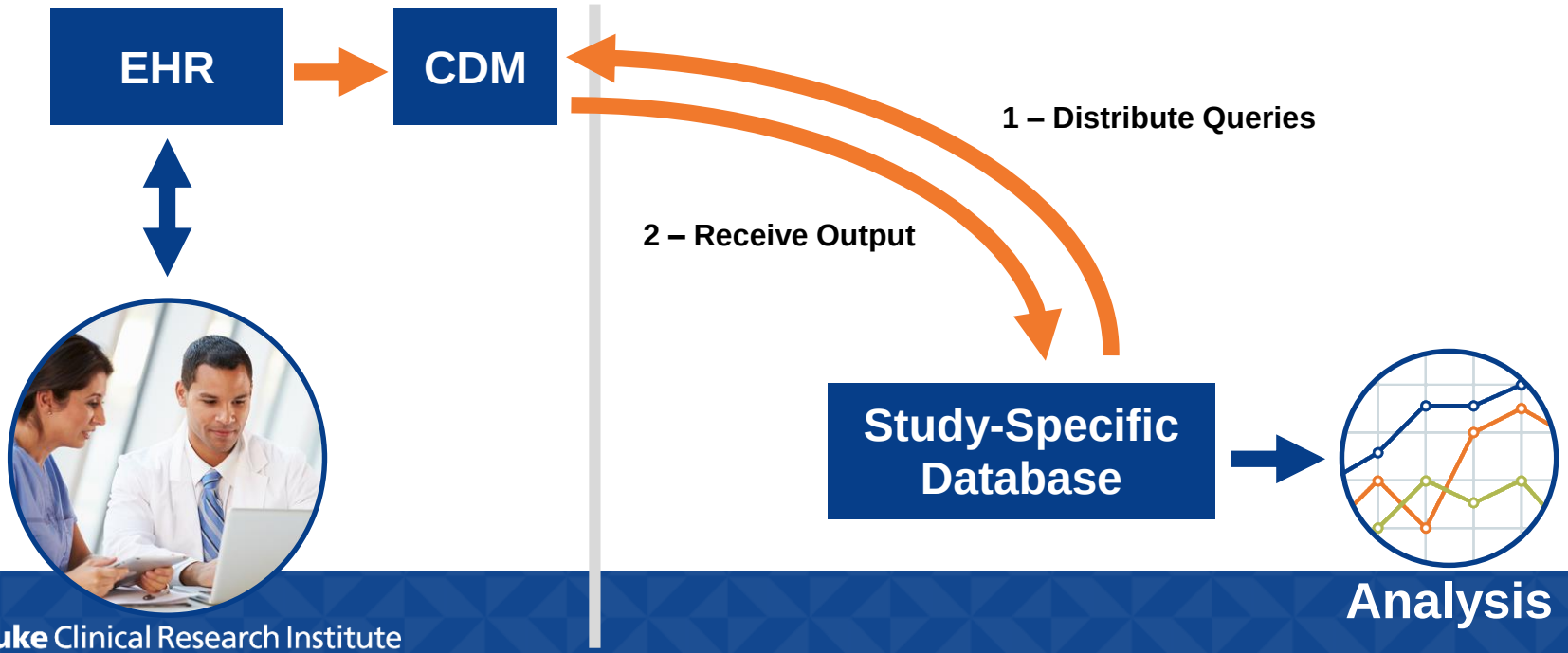
Trial-Specific Clinical Research Network



EHR data can auto-populate part of the trial database

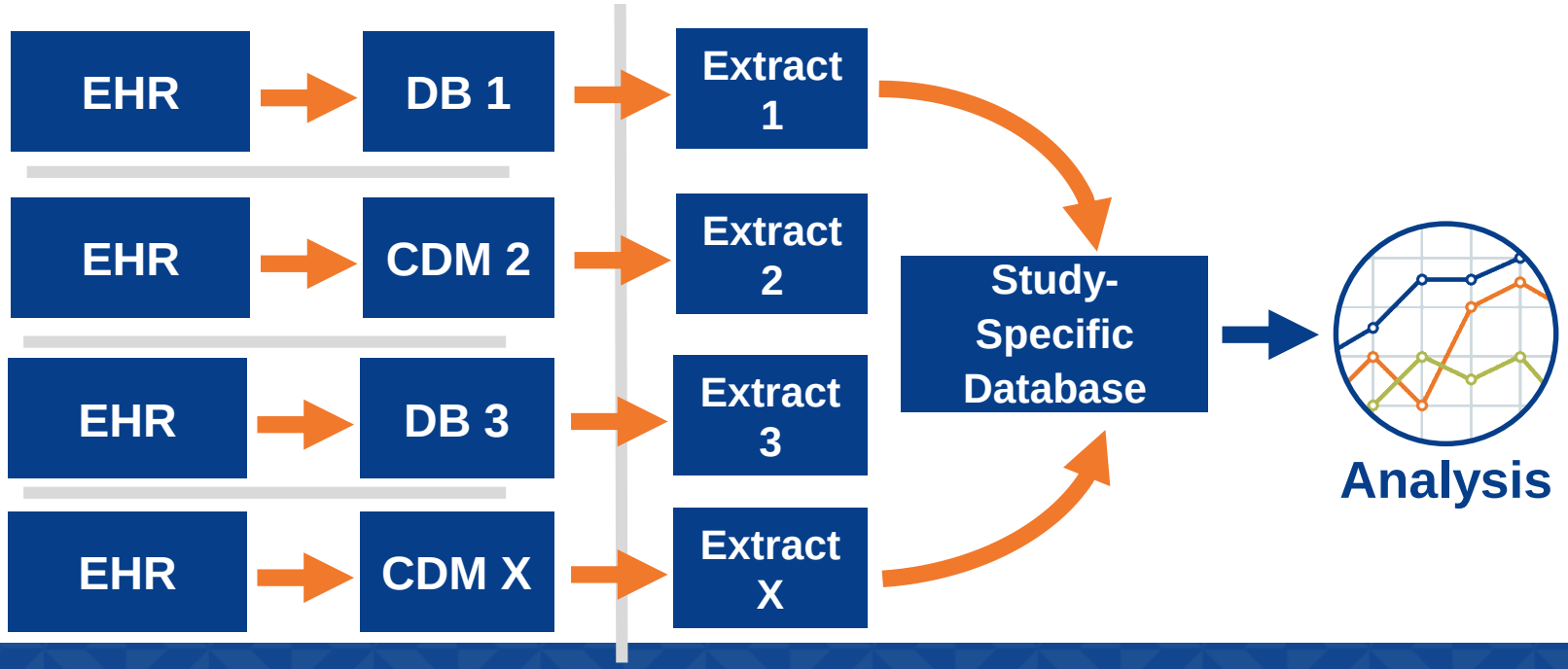
Approaches for Obtaining EHR Data for Trials (1)

- **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

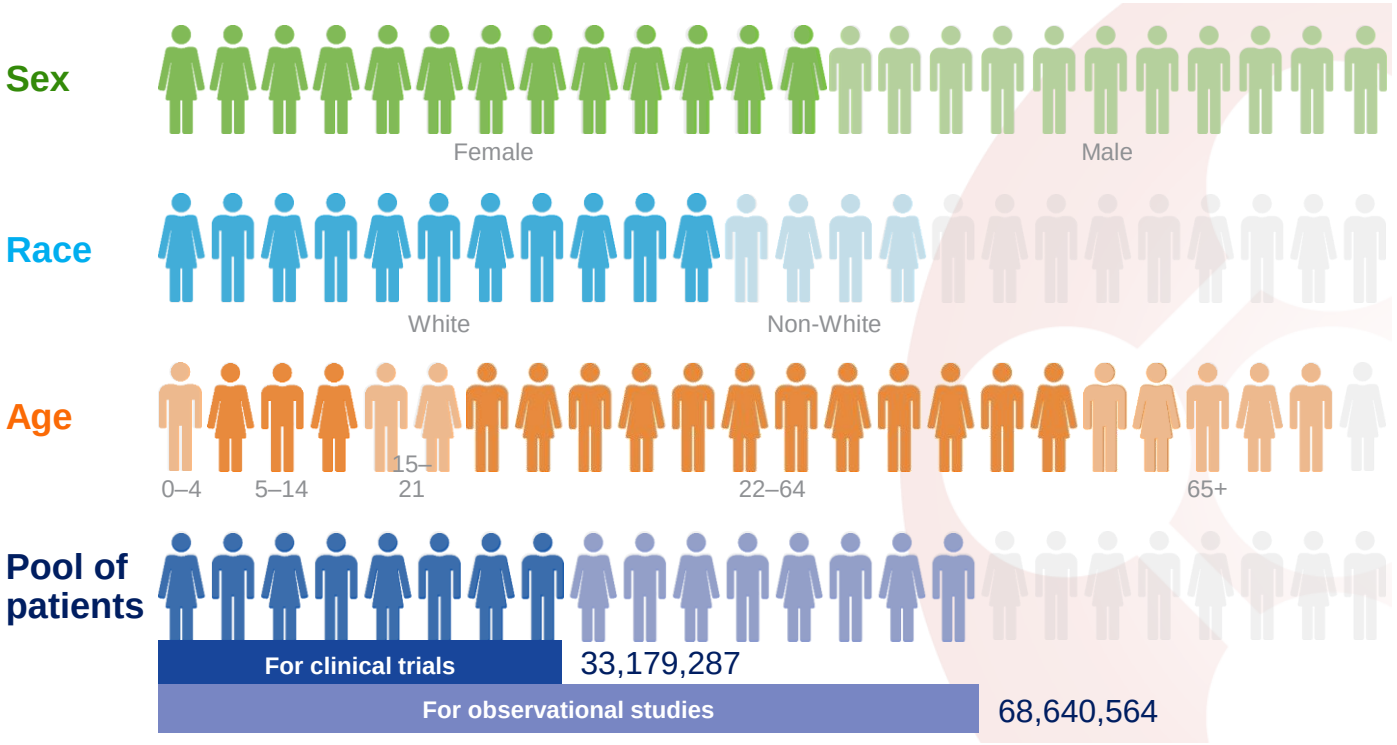


Assessing EHR Data Quality

- 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**

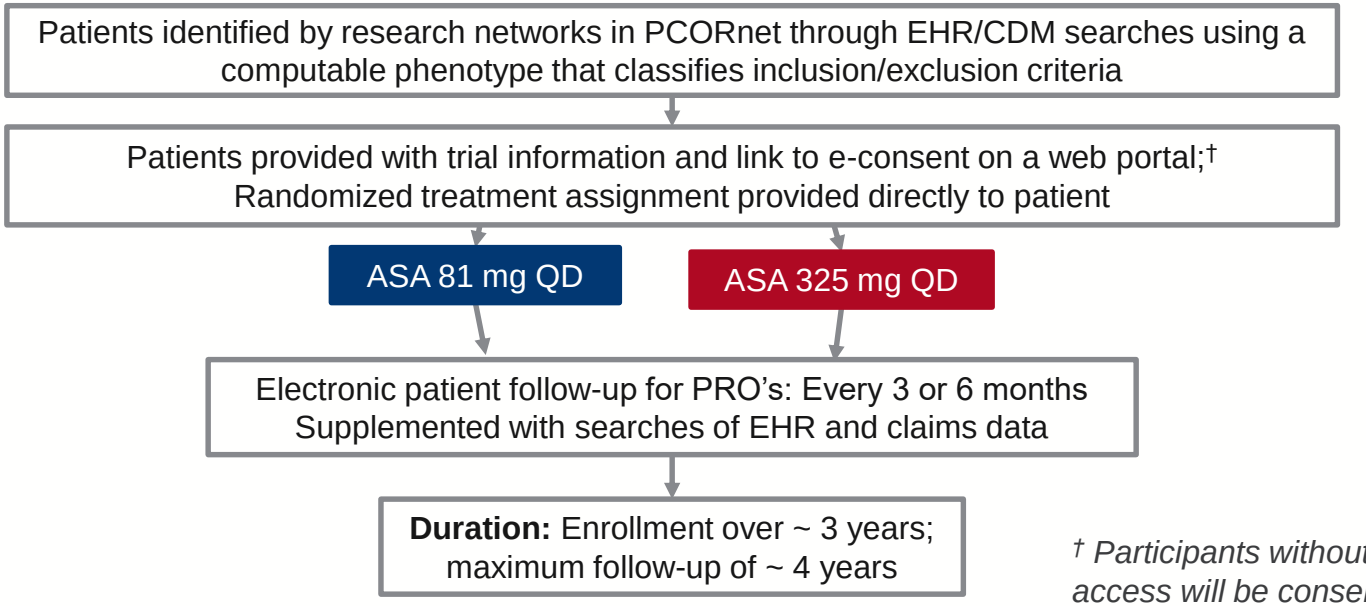
Case Study: the APAPTABLE Trial Conducted Within PCORnet

110 Million patients in 64 Health System Data Marts



ADAPTABLE Study Design

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



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

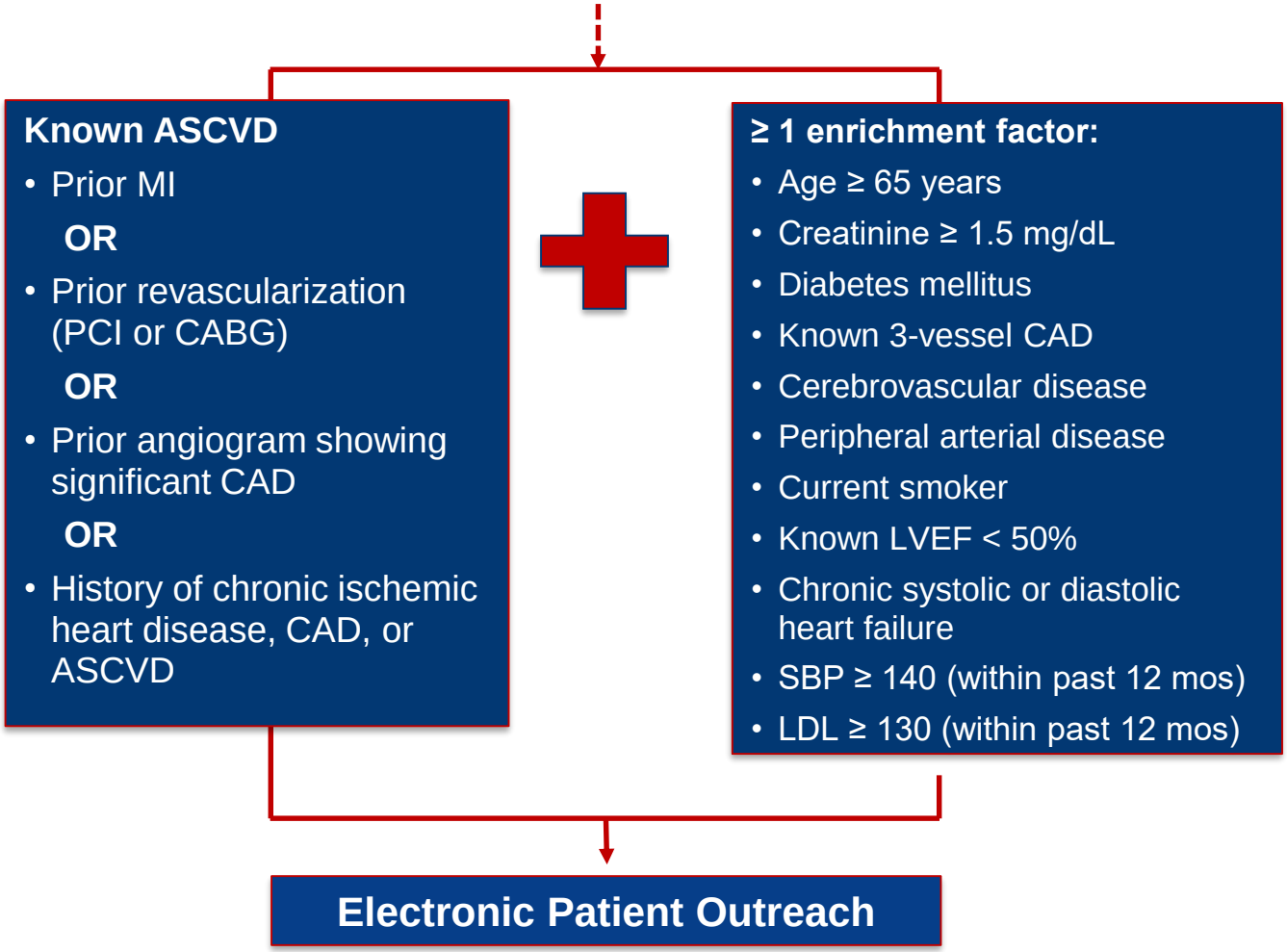
Primary Safety Endpoint:
Hospitalization for major bleeding

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

Adaptable

ClinicalTrials.gov: NCT02697916

ADAPTABLE Inclusion Criteria – Computable Phenotype



ClinicalTrials.gov: NCT02697916

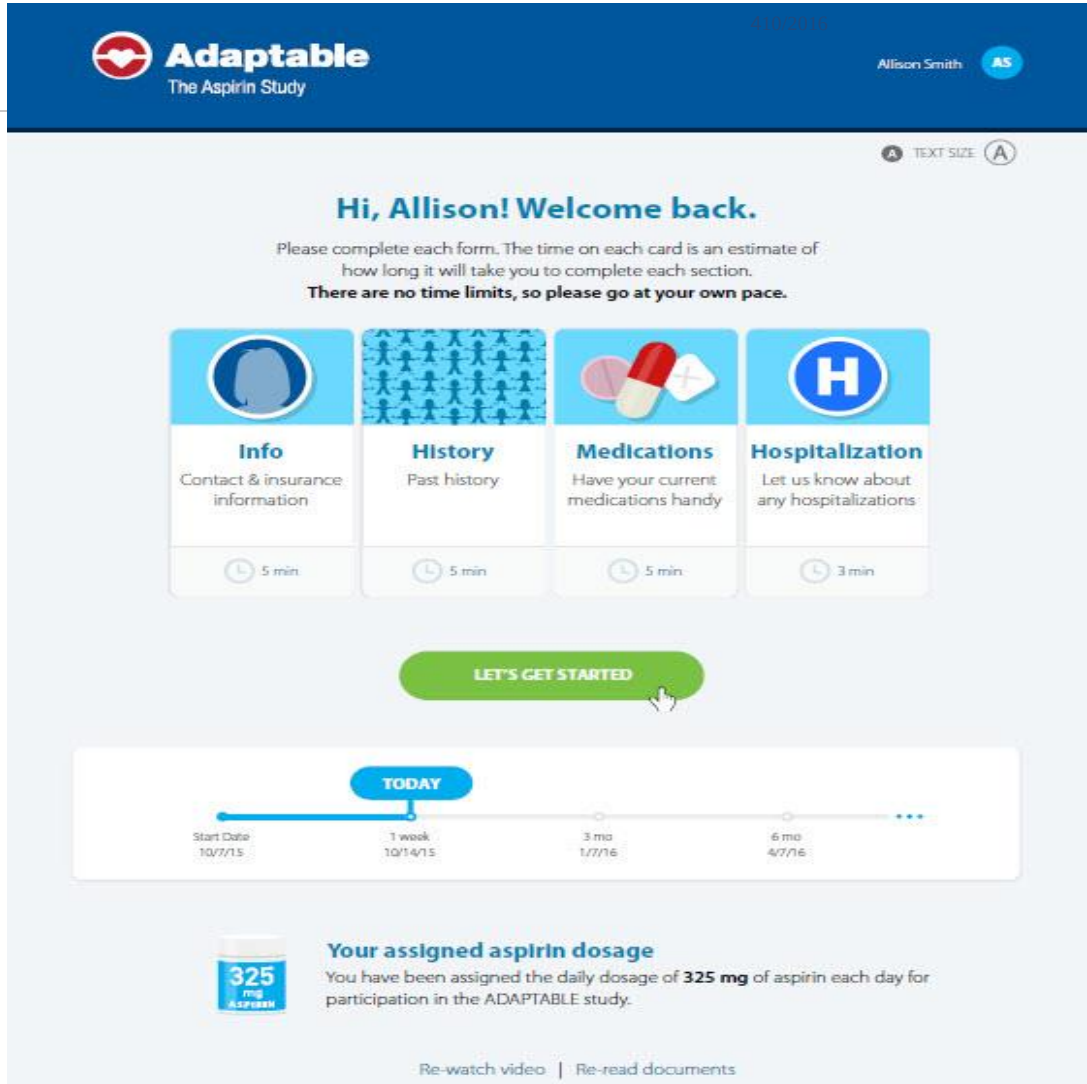
Electronic-Facilitated Recruitment Approaches Utilized in ADAPTABLE

- 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

Reporting, Analysis, Publication

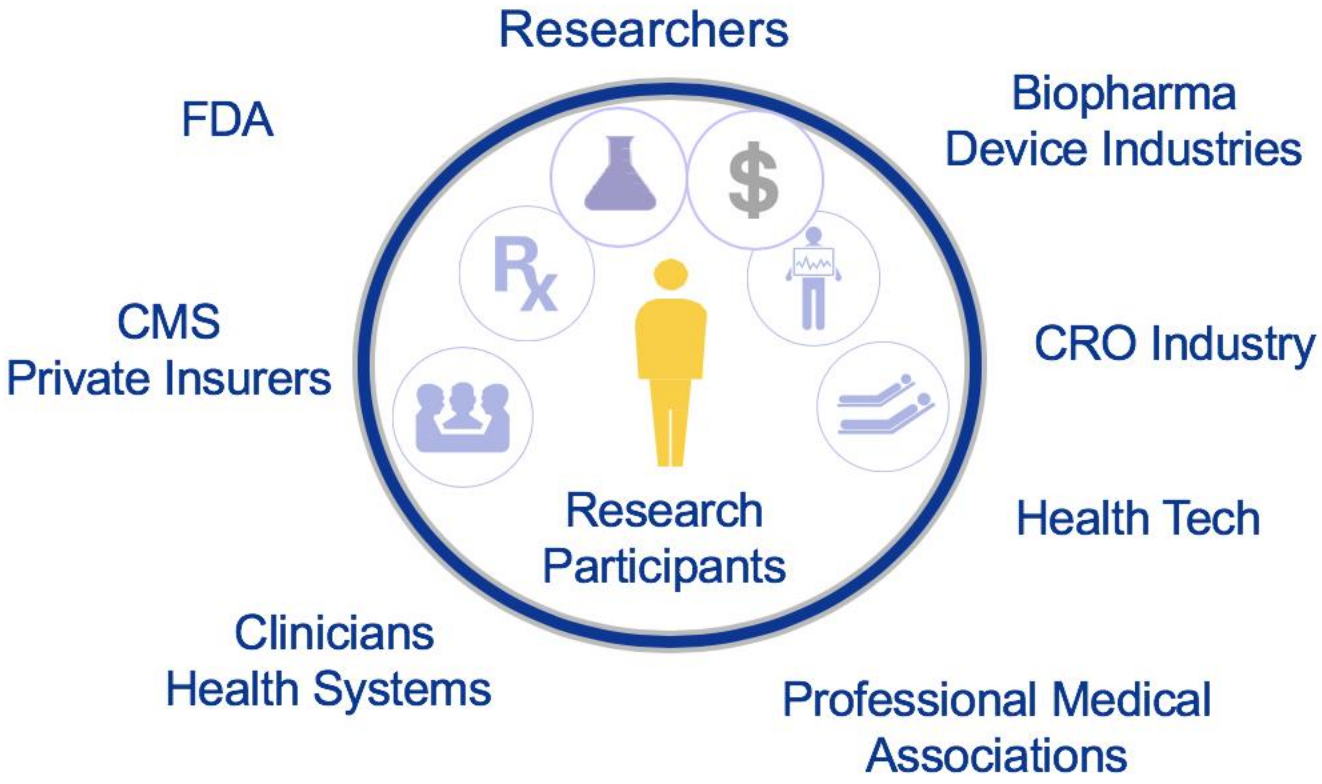
SDTM+

Trial Sponsor

Study Dataset

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