Good Clinical Practice: Considerations for Trials with Pragmatic or Decentralized Features

The public meeting will begin shortly

September 13, 2023, from 7:30-9:30 am ET

REAGAN-UDALL FOUNDATION FOR THE FDA

Housekeeping

REAGAN-UDALL FOUNDATION FOR THE FDA

Due to the meeting size, please keep your microphone and video off during the meeting.

This public meeting is being recorded. The video recording and transcript will be posted on the Foundation website soon after the meeting. Slide are available now. www.ReaganUdall.org.

Please share your questions and comments for the speakers using the Zoom Q&A function.

Agenda

REAGAN-UDALL FOUNDATION FOR THE FDA

7:30 am	Welcome & Overview
7:35 am	Recap of Previous Day
7:45 am	Otavio Berwanger, MD, PhD
8:05 am	Noelle Cocoros, DSc, MPH
8:25 am	Adrian Hernandez, MD, MHS
8:45 am	Moderated Discussion
9:25 am	Closing Remarks & Adjournment

Why Are We Here Today?

REAGAN-UDALL FOUNDATION FOR THE FDA

Understand the opportunities and challenges of conducting trials with innovative design features to help inform the development of responsive policies and guidelines that encourage innovation, while protecting participants and safeguarding the reliability of trial results.

REAGAN-UDALL FOUNDATION FOR THE FDA

Recap of Previous Day

Khair ElZarrad, PhD, MPH

Director, Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

Otavio Berwanger, MD, PhD

Executive Director
The George Institute for Global Health

Chair in Clinical Trials
Imperial College London

Pragmatic & Decentralized Clinical Trials

The George Institute for Global Health UK

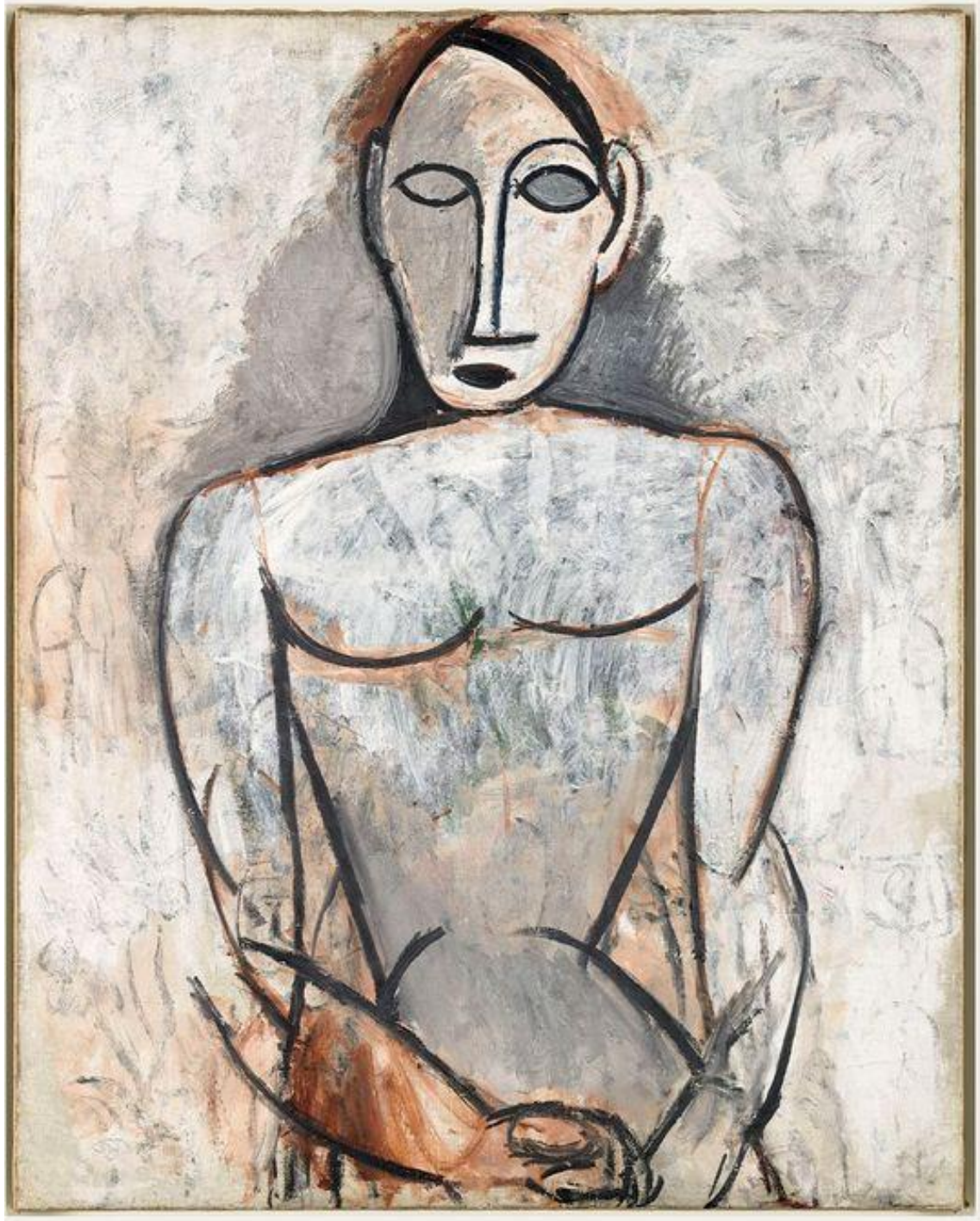
Prof. Otavio Berwanger

Executive Director - The George Institute for Global Health UK

Chair in Clinical Trials, Imperial College London

London, United Kingdom

Imperial College London



MUSÉE DU LUXEMBOURG

13 SEPTEMBRE 2023
28 JANVIER 2024

GERTRUDE STEIN & PABLO PICASSO

L'INVENTION DU LANGAGE

MUSÉE DU LUXEMBOURG SÉNAT

EN COLLABORATION AVEC

Picasso Célébration — 1973.2023

AVEC LE SOUTIEN EXCLUSIF DE

CHANEL

arte RATP Le Parisien TRANSFUGE mac Insert Public Sénat

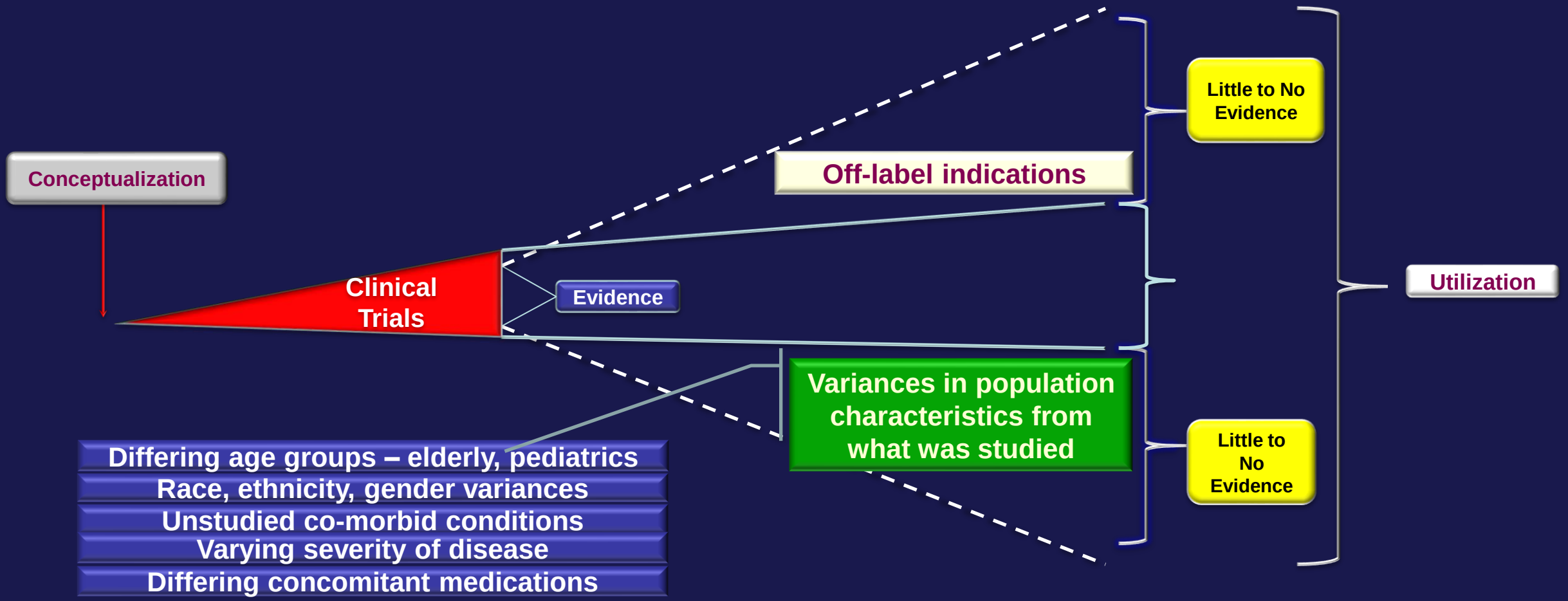
Pablo Picasso, *Femme aux mains jointes (étude pour "Les Demoiselles d'Avignon")*, 1907, Huile sur toile, 90,5 71,5 cm , Musée Picasso, Paris © Succession Picasso 2023 - Design : Fabrice Urviez - laika-design.fr

Better Treatments

Finding better treatments for the world's biggest health problems by:

- conducting high-quality clinical research on treatments for a broad range of common chronic and critical conditions;
- developing new, scalable medicines and technologies for preventing and treating common chronic and critical conditions in high- and low-income settings; and
- using more efficient approaches to generating reliable evidence about treatments for common chronic and critical conditions.

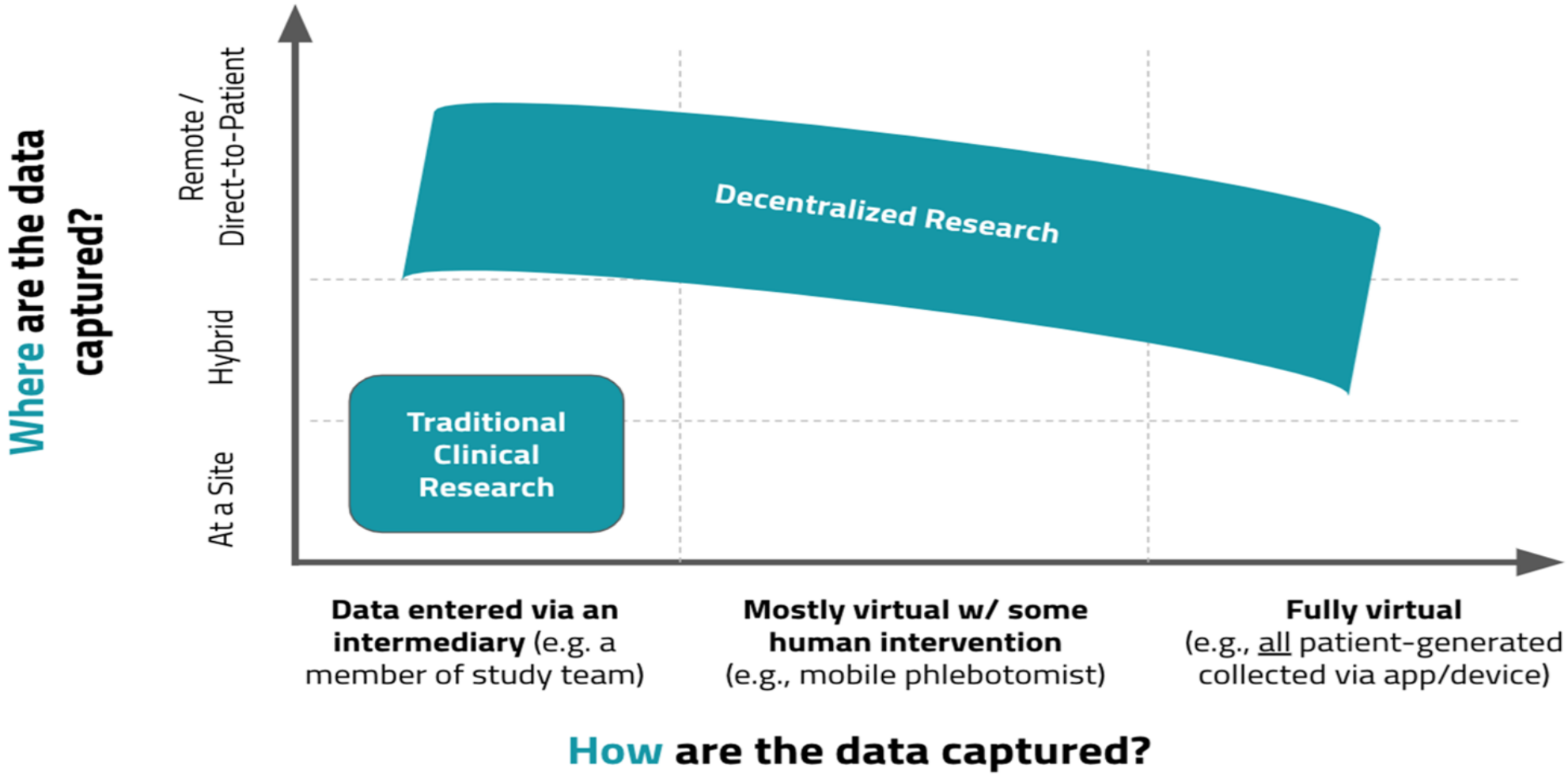
Just 5% of eligible patients participate in clinical research!

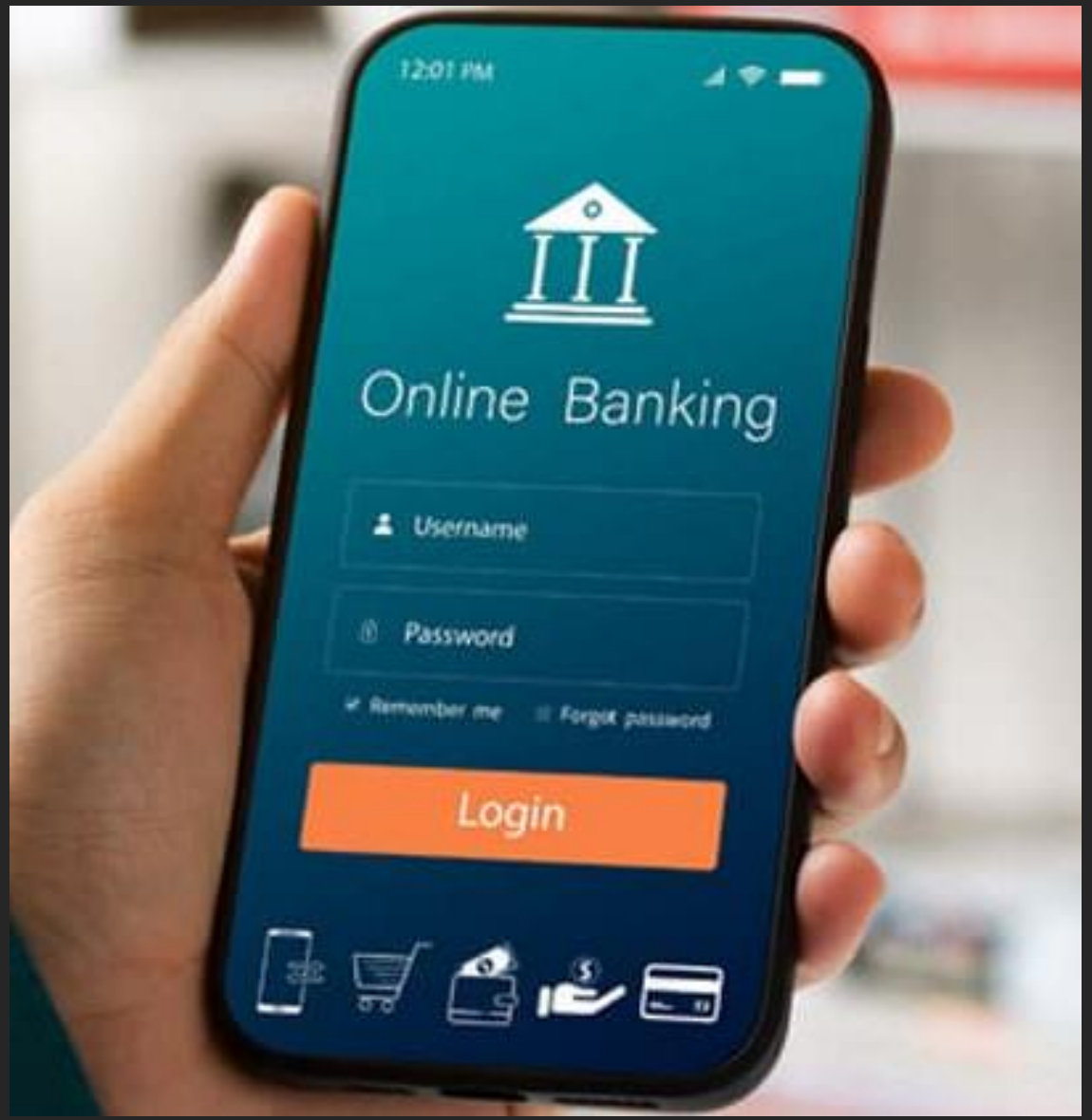


Clinical trial participants travel 67 miles to study sites on average

In 2021, ClinicalTrials.gov had about 350,000 national and international trials registered, which, using the average calculated by the Sustainable Clinical Trials Group, would give a carbon emission of an estimated 27·5 million tonnes of carbon dioxide equivalent (CO2e)

Decentralized studies have two components: decreased reliance (1) on an intermediary and (2) on a physical location

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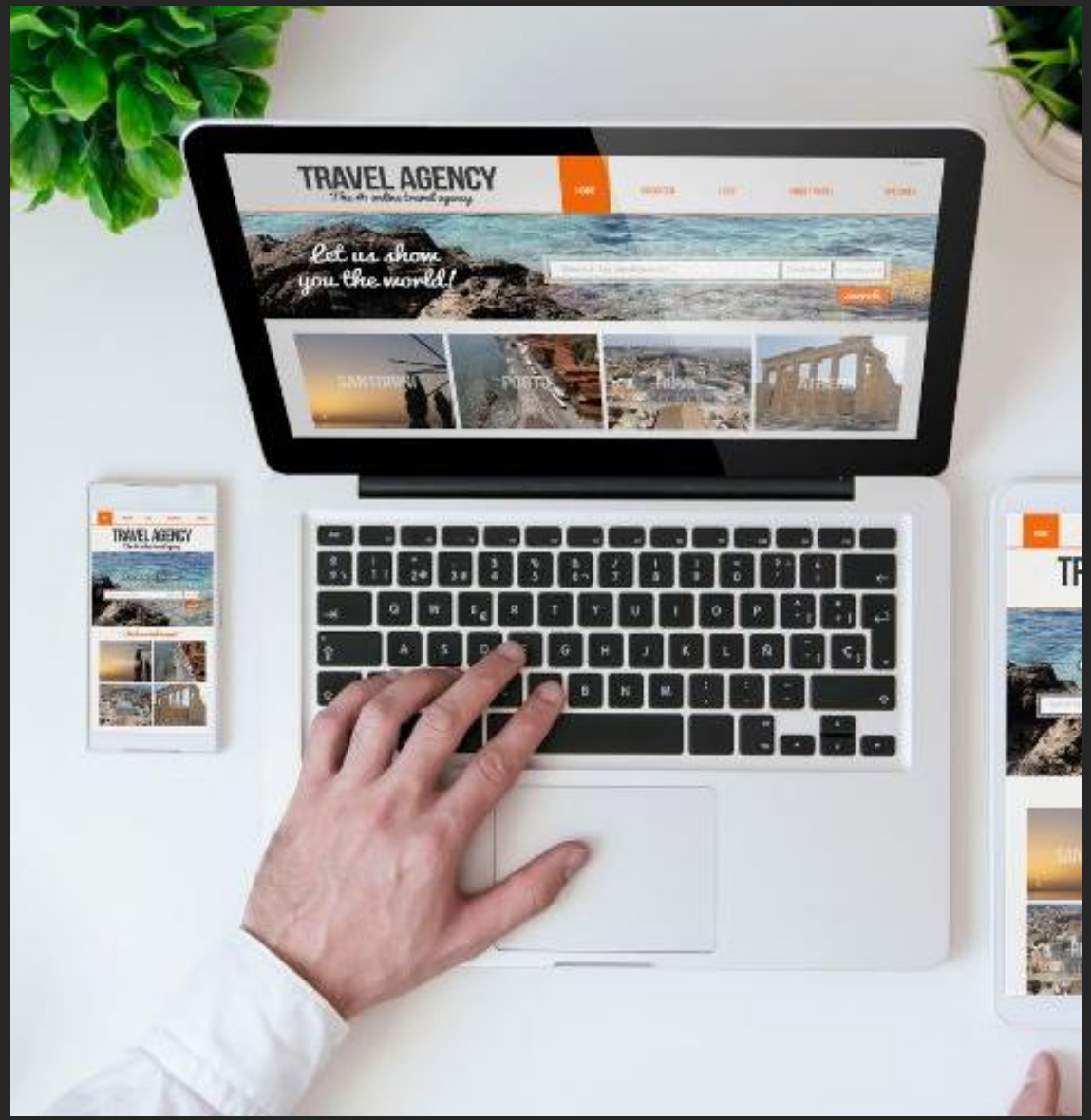
Online Banking
Username
Password
Remember me
Forgot password
Login


TRAVEL AGENCY
Let us show you the world!

Decentralized clinical trials meet patients where they are.

Clinical-trial designs

Fully decentralized ← → **Hybrid** ← → **Fully centralized**

All trial procedures are conducted virtually, enabled by digital technologies and supply delivery

Less complex trial procedures that don't require in-person visits (eg, vital signs, electrocardiograms) are conducted via telehealthcare, remote data collection, or direct-to-patient supply

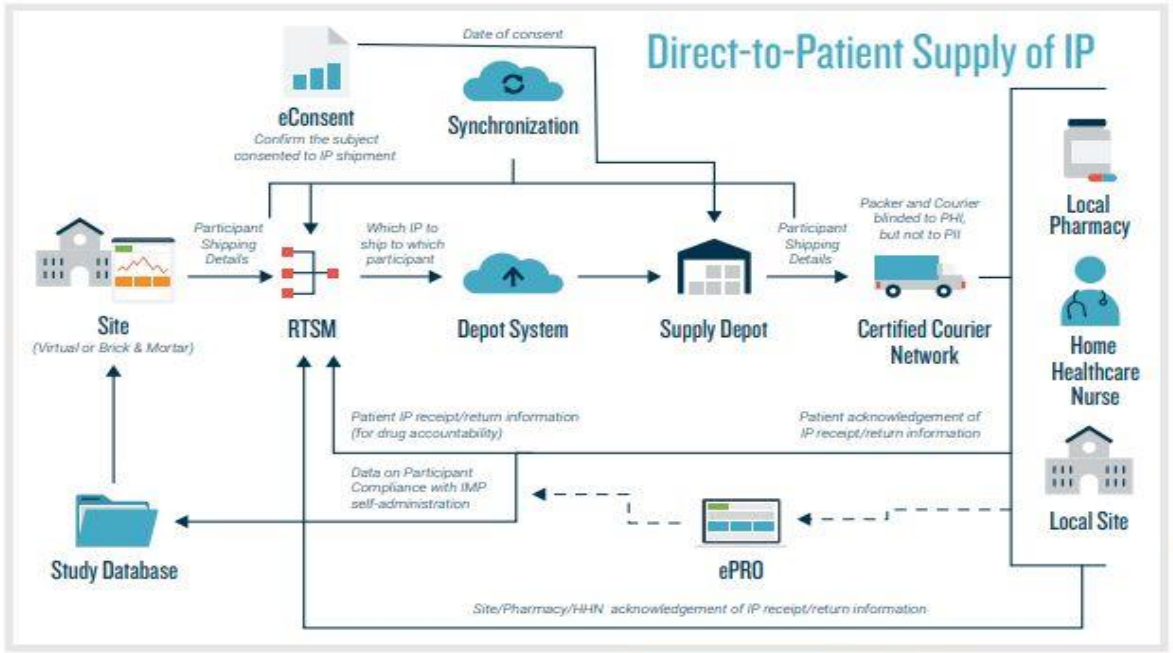
Less complex trial procedures that require in-person visits (eg, injections) are conducted via mobile clinicians or alternative sites (eg, mobile clinics, retail sites)

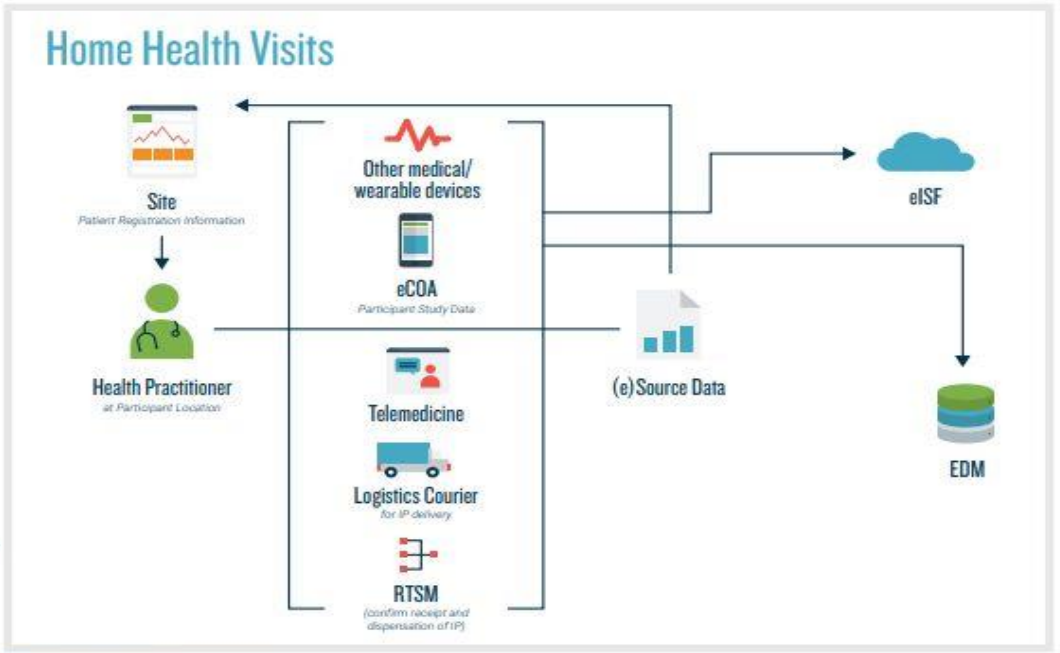
Complex trial procedures (eg, complex screening protocols, cell therapy, magnetic resonance imaging) are conducted via research sites (eg, academic medical centers) or local hospitals

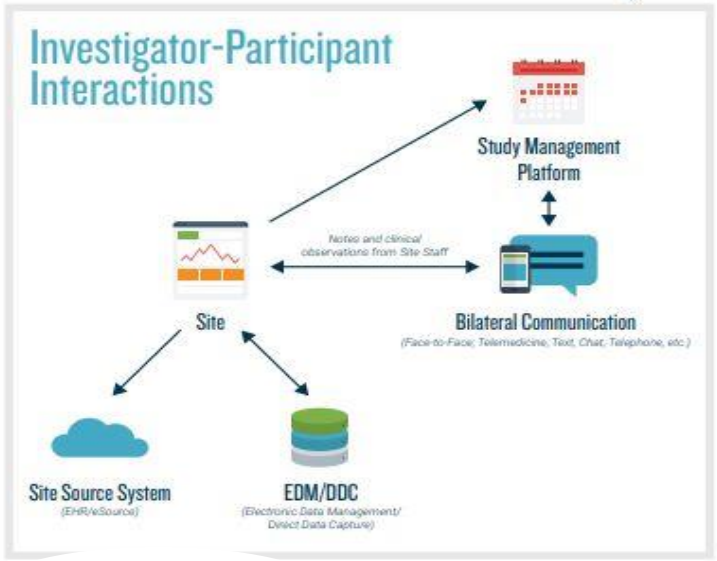
All trial procedures are conducted at a research site (eg, academic medical center)

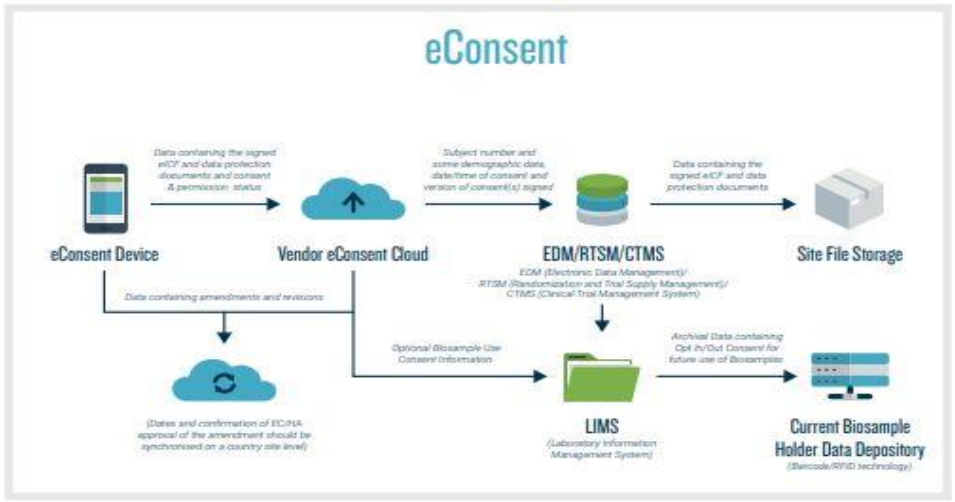
McKinsey & Company

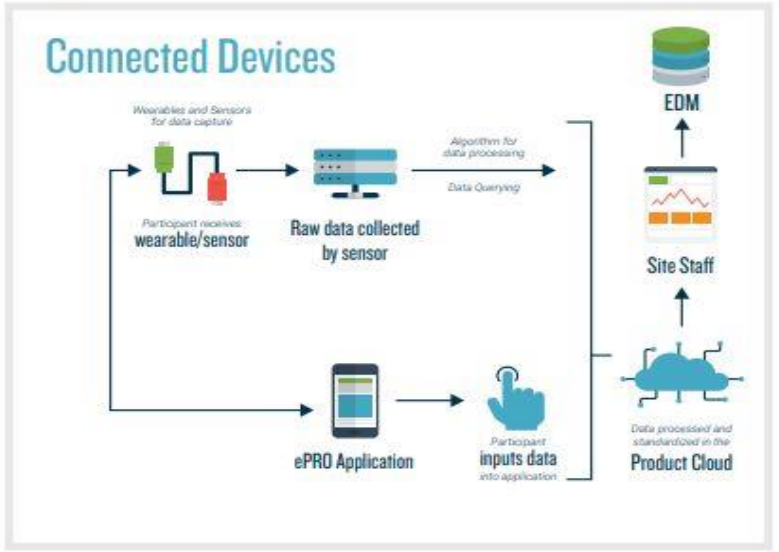
Overview of a Decentralized Clinical Trial

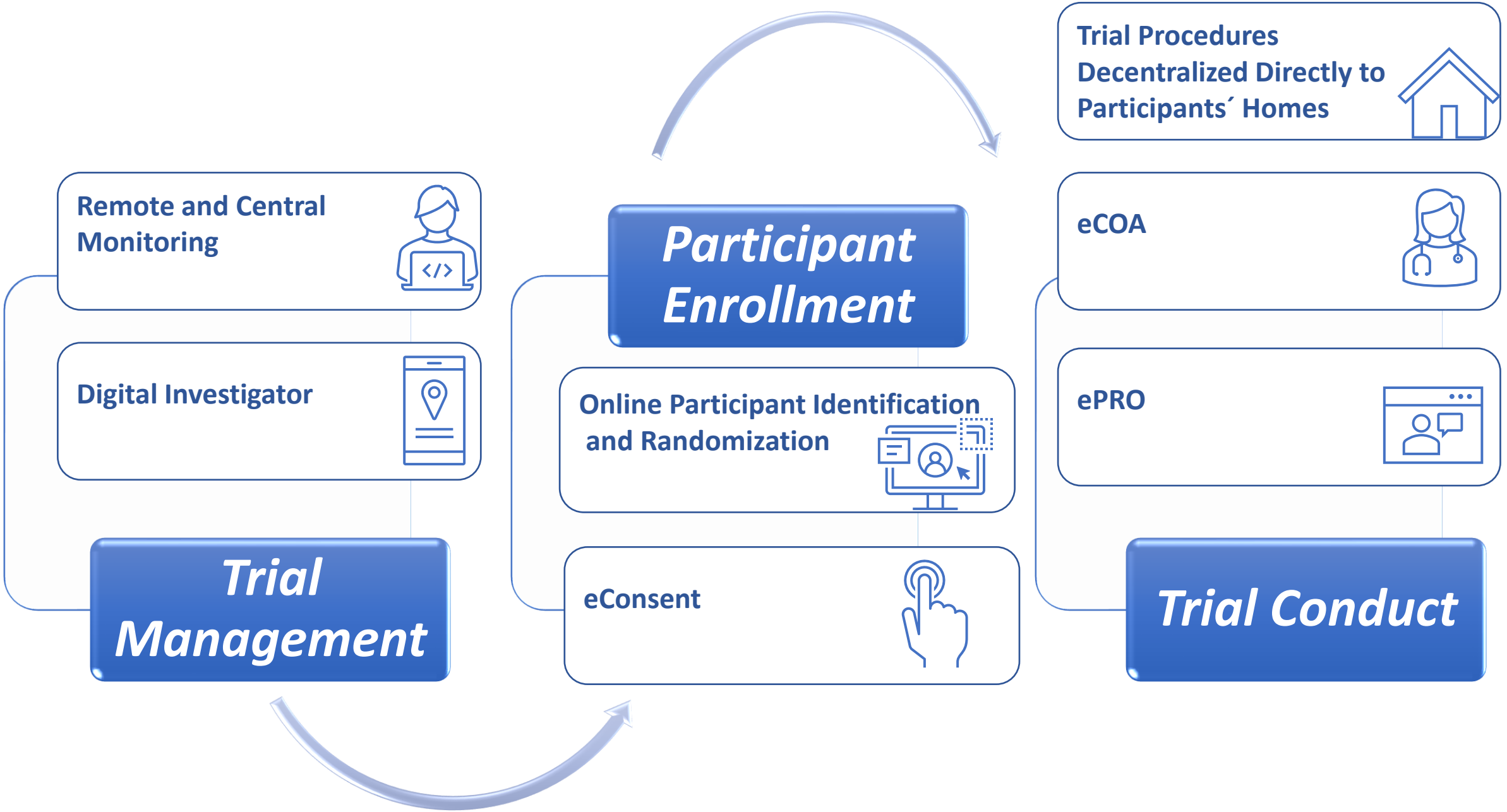












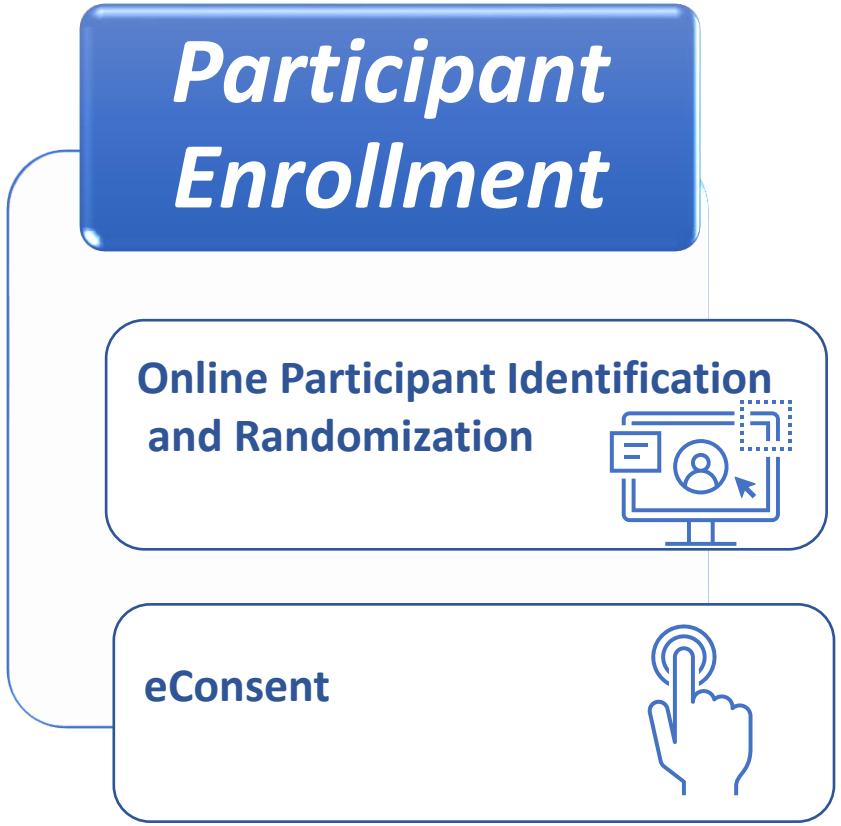
Berwanger O, Machline-Carrion MJ. Stroke. 2022;53:2967–2975

Involve diverse groups in recruitment strategy

Use routinely collected data, digital channels, social media and online communities

Digital recruitment can lead to multilingual pre-screening

Multiple approaches to ensure understanding through electronic consent process including video consenting, quizzes, etc



Faster Participant recruitment

Increased Diversity

Berwanger O, Machline-Carrion MJ. Stroke. 2022;53:2967–2975

Augment delivery with DCT medication adherence solutions, e.g., reminders, photos, videos, smart packaging

At-home self-collection kits increasingly familiar due to COVID-19, home healthcare visits, collect samples through local labs or pharmacies

Improved Participant Retention
Greater Convenience for Participants

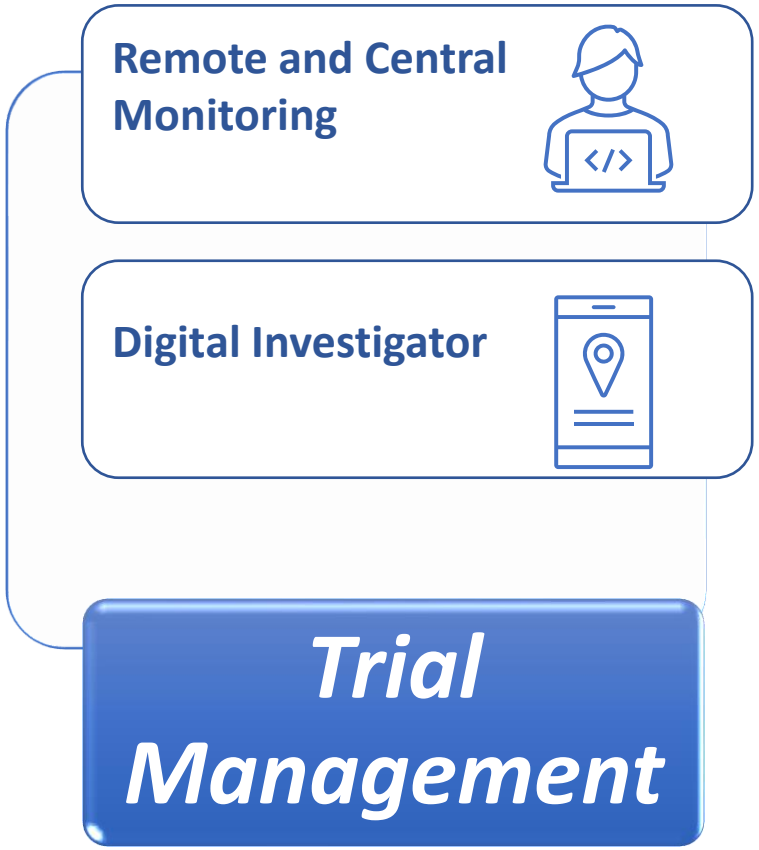
Trial Procedures Decentralized Directly to Participants´ Homes

eCOA

ePRO

Trial Conduct

Berwanger O, Machline-Carrion MJ. Stroke. 2022;53:2967–2975



Participant Protection

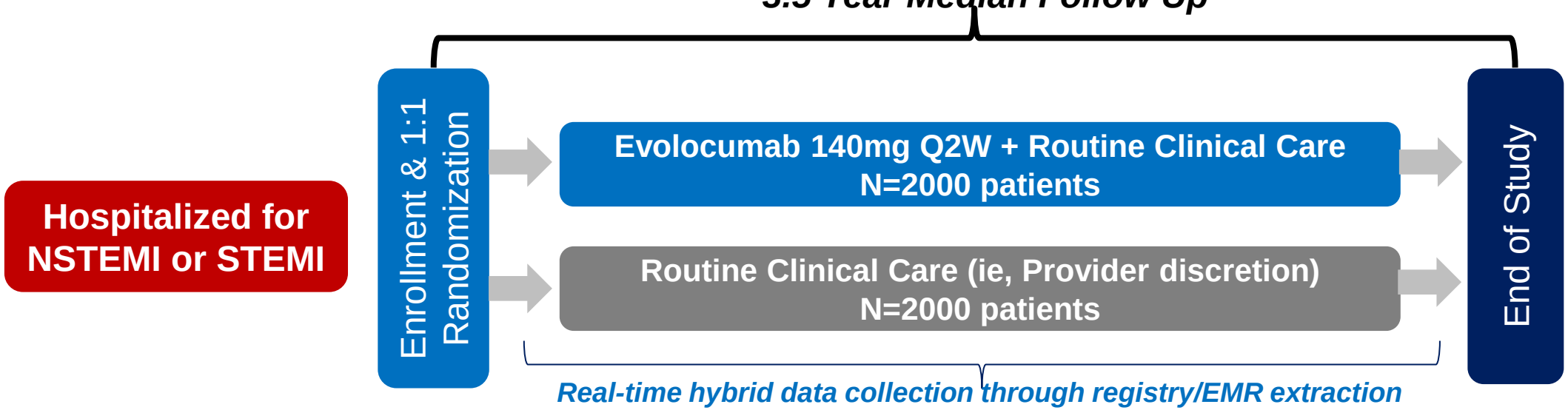
Data Quality

Reliability of Results

Berwanger O, Machline-Carrion MJ. Stroke. 2022;53:2967–2975

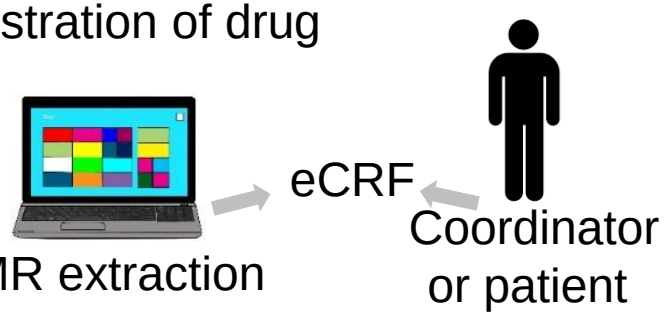
Mobile Clinical Trials Unit

EVOLVE-MI EVOLOCUMAB VERY EARLY AFTER MI – STUDY DESIGN



1° endpoint: total (first and subsequent) MI, ischemic stroke, any arterial revascularization, all-cause death

- Evolocumab dosed within 10 days of index MI. Home delivery and self-administration of drug
- ***Pragmatic data collection through EMR, patient- or coordinator-completed eCRF and national registries (in Sweden)***



eCRF electronic case report form, EMR electronic medical record, NSTEMI non-ST elevation myocardial infarction, STEMI ST elevation myocardial infarction

ALBERT EINSTEIN
SOCIEDADE BENEFICENTE ISRAELITA BRASILEIRA

CPC Clinical Research

NCT05284747

UCR

Innovations in Protocol Development

EVOLVE-MI

- **Minimal inclusion / exclusion**
- **Minimal procedures and ability to screen/randomize same day**
- **Simplified schedule of events**
- **Streamlined safety**

Innovations in Trial Operations

Traditional Trial	EVOLVE-MI
Manual entry into eCRF, many fields, complex navigation	Hybrid data collection
Drug dispensed at visits	Hybrid – optimized for each environment
Study labs	Minimal, local lab at baseline
Identification of events via study coordinator/PI	Hybrid endpoint collection
Central event adjudication	Hybrid adjudication
Separate IWRS/IXRS requiring multiple site logins	Randomization directly in EDC

Early Experience

EVOLVE-MI

- **First sites enrolled within a day of activation**
- *“Screening & enrollment were smooth, and it was nice to be able to randomize within the EDC.”*
- *“Patients are interested, almost everyone qualifies, and the data entry is not burdensome.”*

Research Goal: Better Treatments
Finding better treatments for the world's biggest health problems

PRAGMATIC COMPONENT
- Streamlined eligibility criteria
- Streamlined procedures
- Use of routinely collected data or hybrid data collection

HIGH QUALITY
- Low risk of bias (concealed randomization, blinding, ITT analysis)
- Innovative designs (platform trials, adaptative trials)

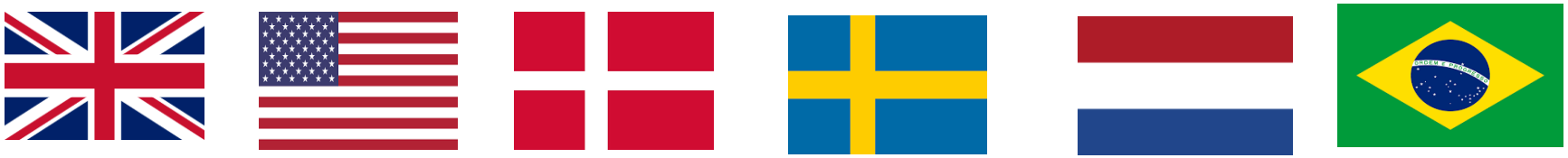
RELIABLE RESULTS
- High statistical power (large-scale, global)
- Statistical methods (win ratio, RMST, total events, Bayesian, etc.)

INNOVATIVE APPROACH
- Drug distribution directly to participants
- Follow-up surveys directly to participants
- AI applications (endpoint adjudication)
- Use of wearable technology and digital tools

DIVERSITY
- Capacity building in LMICs
- Sex-disaggregated and gender-disaggregated analysis

PARTICIPANT ENGAGEMENT
- Participants as members of the steering committee and trial team

Potential Networks for Large-Scale Pragmatic Decentralized Trials



- Design and Conduct of Large-Scale Pragmatic Decentralized Trials
- Use of Routinely Collected Data

COGNITUM
ARO Consortium

MESSAGE
Medical Science Sex and Gender Equity

wellcome

Oversight of Clinical Studies

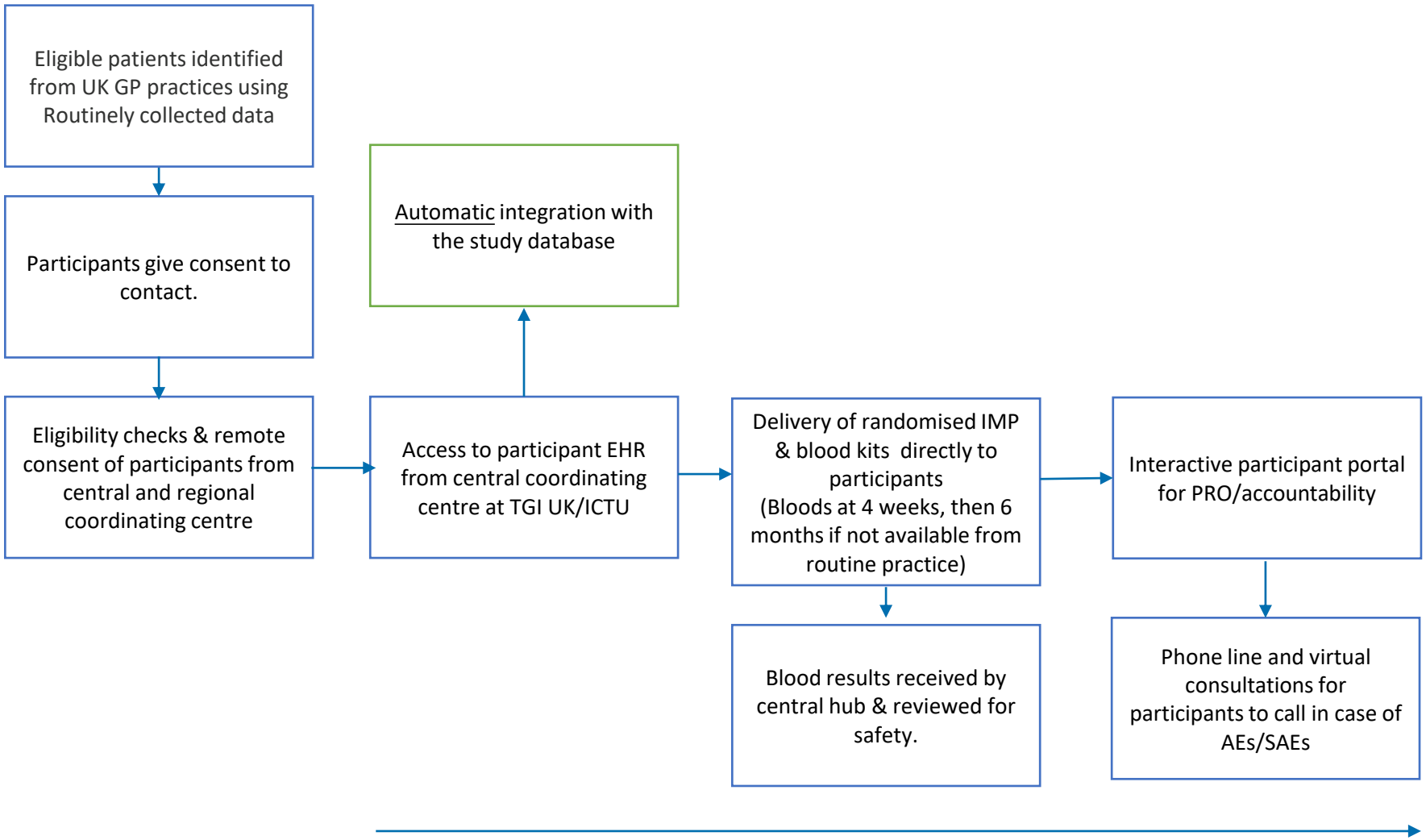
Global Project Team, based in the UK with conjoint appointments at TGI UK and ICTU and consisting of the following staff:

- Chief Investigator
- Senior Project Manager
- Safety Monitor
- Quality Assurance Manager
- Clinical Trial Assistant
- Data Management Team
- Statistical Team
- Adjudicators
- Participant Representative

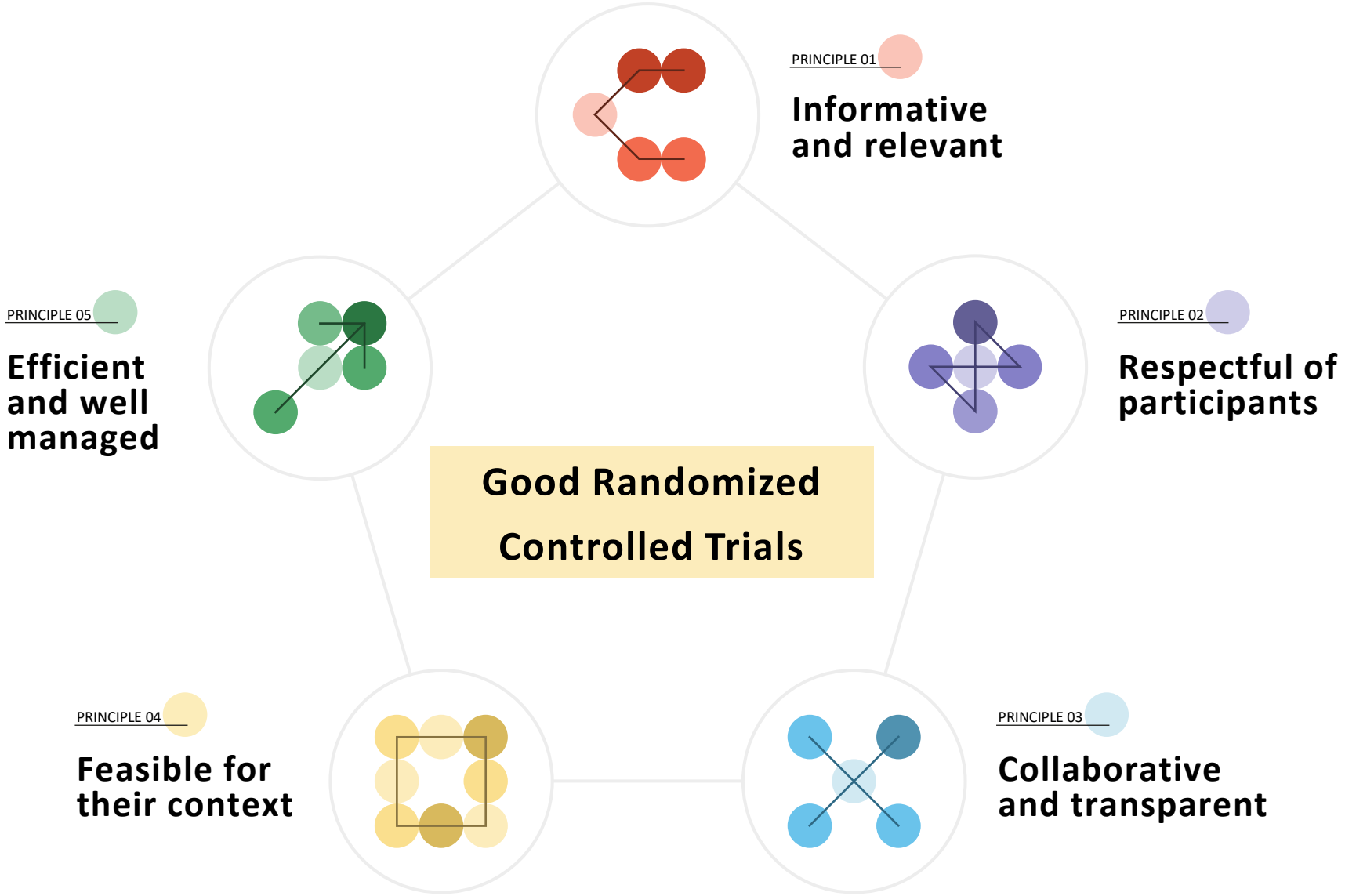
Regional coordinating centre (RCC) in each country consisting of the following staff:

- Country-Lead Investigator Project Manager
- Medical Monitors
- Research Nurses
- Clinical Research Associates
- Participant representative

Trial Procedures (example: UK)



Good Trials: Produce a scientifically sound answer to a relevant question



good clinical trials

Take Home Points

- Pragmatic trials are a reality, here to stay
- Greater “decentralization” of most trials in the future
- Greater use of digital technology over time
- Promise: rapid enrollment and study completion, lower cost, more convenient to patients, greater generalizability and diversity
- Not “one size fits all”. As always, approach should be tailored to the clinical question that is being addressed

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

Noelle Cocoros, DSc, MPH

Principal Research Scientist
Harvard Pilgram Health Care Institute

Principal Associate in Population Medicine
Harvard Medical School

Harvard Pilgrim Health Care Institute

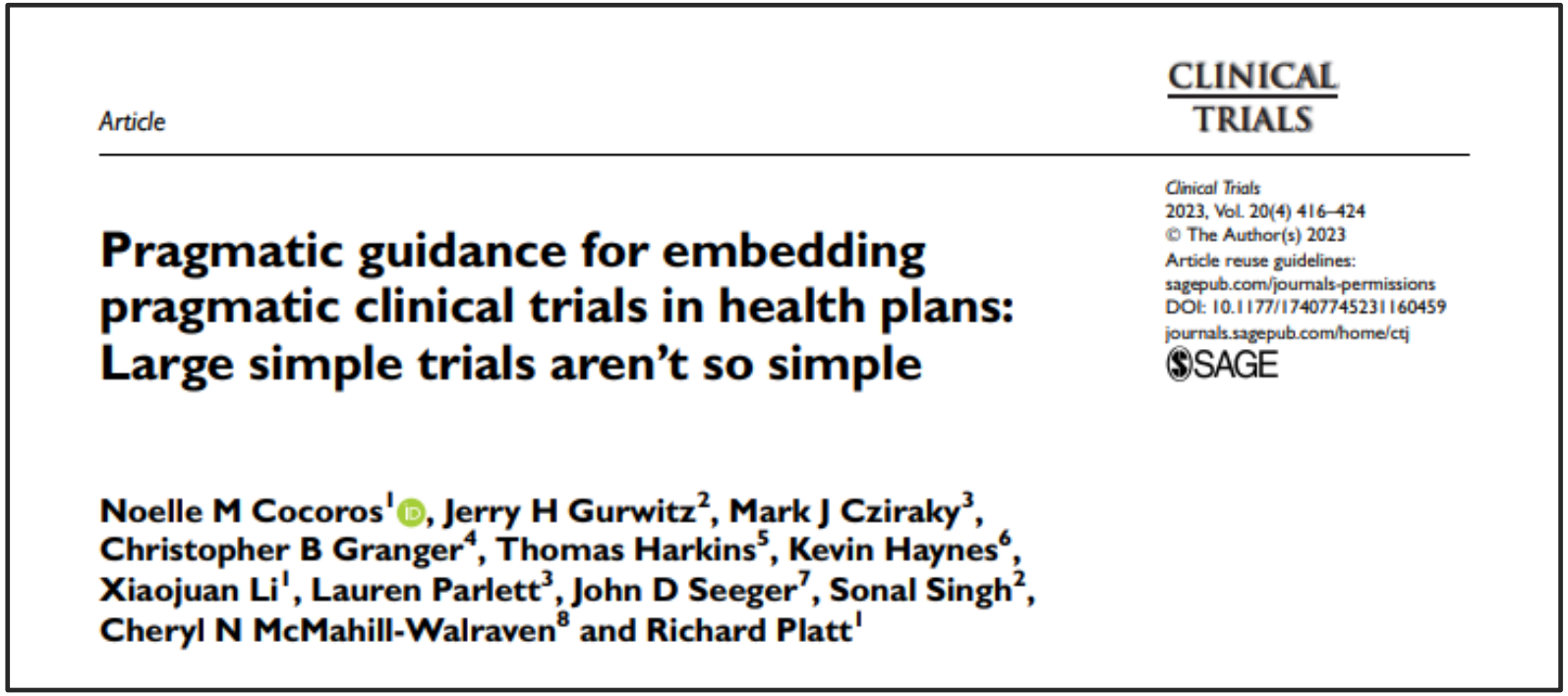
Pragmatic guidance for pragmatic trials

Noelle M. Cocoros, DSc, MPH

September 13, 2023

Topics

- Background & context
- Advantages, challenges
- Lessons learned



Article

CLINICAL TRIALS

Pragmatic guidance for embedding pragmatic clinical trials in health plans: Large simple trials aren't so simple

Noelle M Cocoros[1], Jerry H Gurwitz[2], Mark J Cziraky[3], Christopher B Granger[4], Thomas Harkins[5], Kevin Haynes[6], Xiaojuan Li[1], Lauren Parlett[3], John D Seeger[7], Sonal Singh[2], Cheryl N McMahill-Walraven[8] and Richard Platt[1]

Clinical Trials
2023, Vol. 20(4) 416–424

DOI: 10.1177/17407745231160459
journals.sagepub.com/home/ctj
SAGE

Lessons learned from trials embedded in US health plans

- Briefly: Health plans/insurers, claims data; US FDA Sentinel Initiative; NIH Collaboratory Distributed Research Network

Example trials:

- IMPACT-AFib – completed 
- D-PRESCRIBE-AD – ongoing 
- ACHIEVE – planning phase 

Design

CLINICAL TRIALS

Clinical Trials
1–8

DOI: 10.1177/1740774518812776
journals.sagepub.com/home/ctj
SAGE

FDA-Catalyst—Using FDA's Sentinel Initiative for large-scale pragmatic randomized trials: Approach and lessons learned during the planning phase of the first trial

Noelle M Cocoros[1], Sean D Pokorney[2], Kevin Haynes[3], Crystal Garcia[1], Hussein R Al-Khalidi[4], Sana M Al-Khatib[2], Patrick Archdeacon[5], Jennifer C Goldsack[6], Thomas Harkins[7], Nancy D Lin[8], David Martin[5], Debbe McCall[9], Vinit Nair[7], Lauren Parlett[3], Robert Temple[5], Cheryl McMahill-Walraven[10], Christopher B Granger[2] and Richard Platt[1]

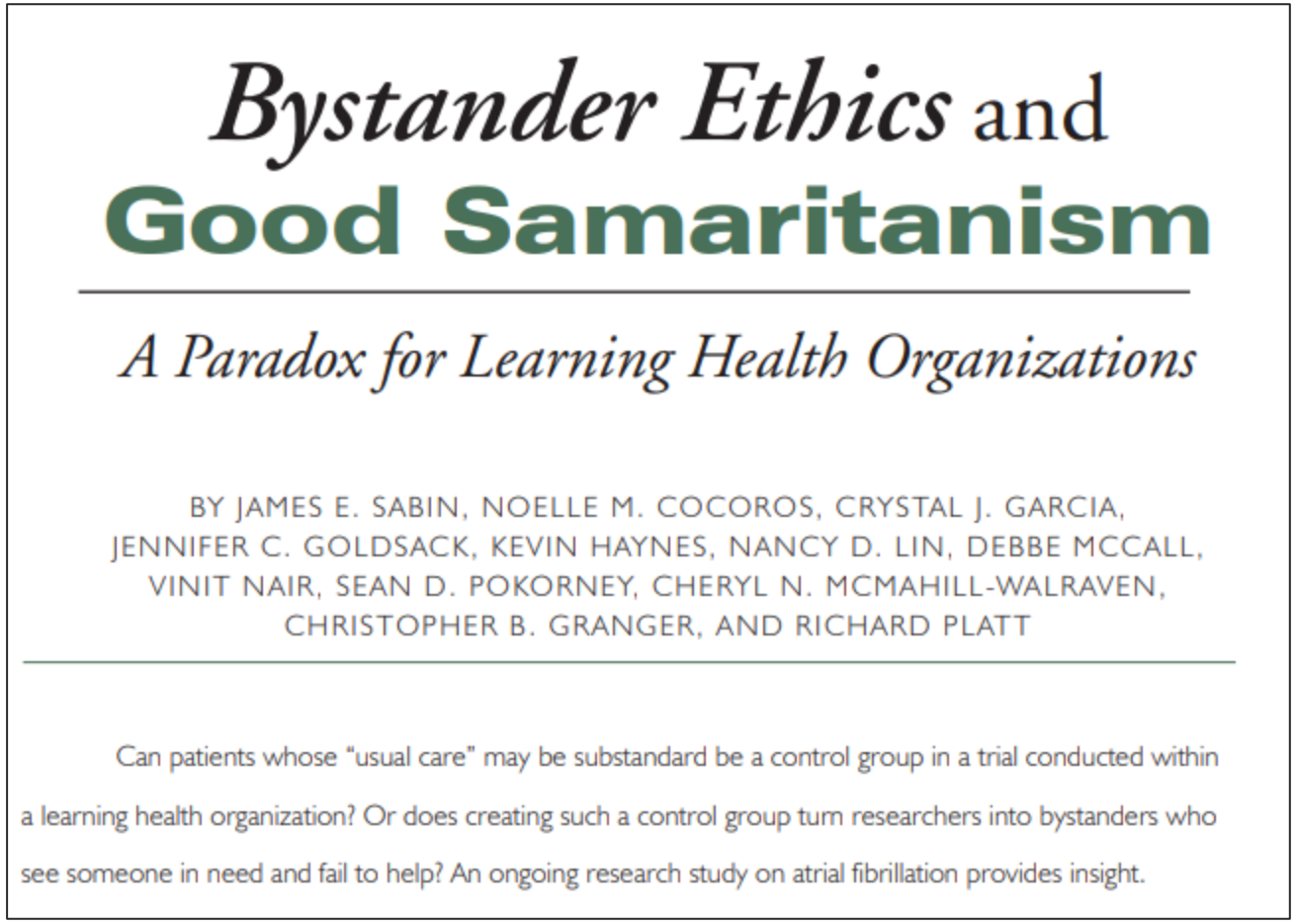
CLINICAL TRIALS

Clinical Trials
2020, Vol. 17(4) 360–367

DOI: 10.1177/1740774520928426
journals.sagepub.com/home/ctj
SAGE

Practical challenges in the conduct of pragmatic trials embedded in health plans: Lessons of IMPACT-AFib, an FDA-Catalyst trial

Crystal J Garcia[1], Kevin Haynes[2], Sean D Pokorney[3], Nancy D Lin[4], Cheryl McMahill-Walraven[5], Vinit Nair[6], Lauren Parlett[2], David Martin[7], Hussein R Al-Khalidi[8], Debbe McCall[9], Christopher B Granger[3], Richard Platt[1] and Noelle M Cocoros[1]



Bystander Ethics and Good Samaritanism

A Paradox for Learning Health Organizations

BY JAMES E. SABIN, NOELLE M. COCOROS, CRYSTAL J. GARCIA, JENNIFER C. GOLDSACK, KEVIN HAYNES, NANCY D. LIN, DEBBE MCCALL, VINIT NAIR, SEAN D. POKORNEY, CHERYL N. MCMAHILL-WALRAVEN, CHRISTOPHER B. GRANGER, AND RICHARD PLATT

Can patients whose "usual care" may be substandard be a control group in a trial conducted within a learning health organization? Or does creating such a control group turn researchers into bystanders who see someone in need and fail to help? An ongoing research study on atrial fibrillation provides insight.

Hasting Center Report, July-Aug 2019

Advantages

Large sample size

IMPACT-AFib randomized >190,000

Numerous efficiencies

Leverage existing infrastructure

Minimize cross-site variation

Generalizability

Easy adoption of intervention

Lessons learned: Planning phase

Experts at sites

- Early, sustained engagement
- Internal champion(s)
- Continuity of staff

IRB

- Centralized whenever possible

Study populations

- Restrictions can apply

Identifying clinical providers can be challenging in claims data

- Prepare for this in advance

Lessons learned: Planning phase

Include a patient representative

Anticipate loss to follow up, especially with health plans

Claims or EHR data

- Data quality
- Conduct feasibility analyses
- Use validated algorithms
- Make decisions about conduct
  - Distributed program, “common protocol”, or hybrid?
- Need for “Fresh” data
- Save data

Lessons learned: Implementation

Patient, provider engagement

- Intensely scrutinized by health plans
- Range of modes of contact available

Analysis

- Claims data lags
- Address time from randomization to study start
  - Modified intent-to-treat analyses

Advantages

- Large sample sizes
- Highly efficient when setting & data are fit-for-purpose
- Site-based expertise

Challenges

- Many logistical considerations – especially when multi-site
- Applicable for select set of study questions

Harvard Pilgrim Health Care Institute

Thank You

Please contact me with questions or if interested in learning more about the NIH Collaboratory Distributed Research Network

noelle_cocoros@harvardpilgrim.org

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

Adrian Hernandez, MD, MHS

Cardiologist, Vice Dean and Executive Director of Duke Clinical Research
Duke University School of Medicine

Bending the Curve: Having the Trial Meet the Patient!

Adrian Hernandez, MD, MHS
Vice Dean and Executive Director
Duke Clinical Research Institute
Duke University School of Medicine

@texhern

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Topics

- What's the problem?
- What's a practical approach?
- What are some case examples and lessons?
- What questions to ask to ensure success?

Untying the Gordian Knot of Clinical Trials

An Image Created by DALL-E/ OPEN-AI

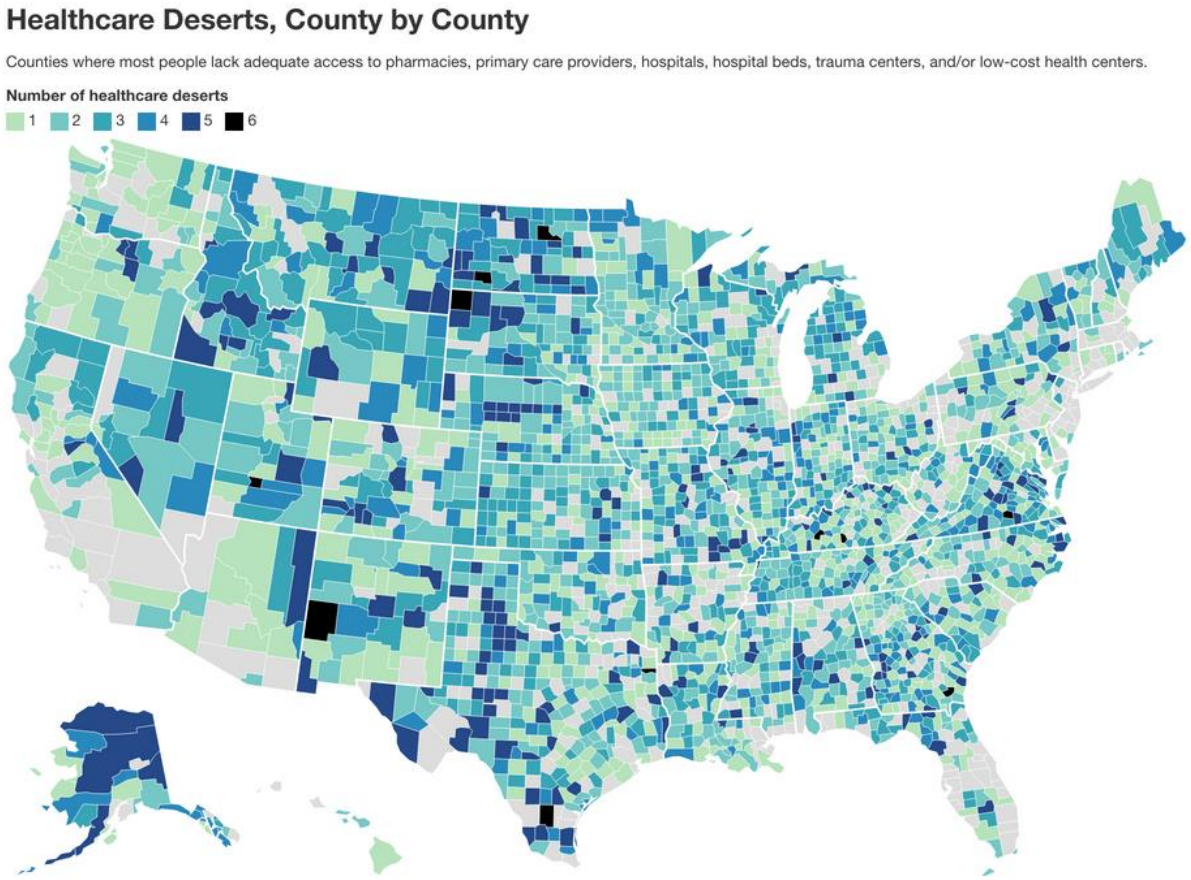
Have you or ____ participated in research?

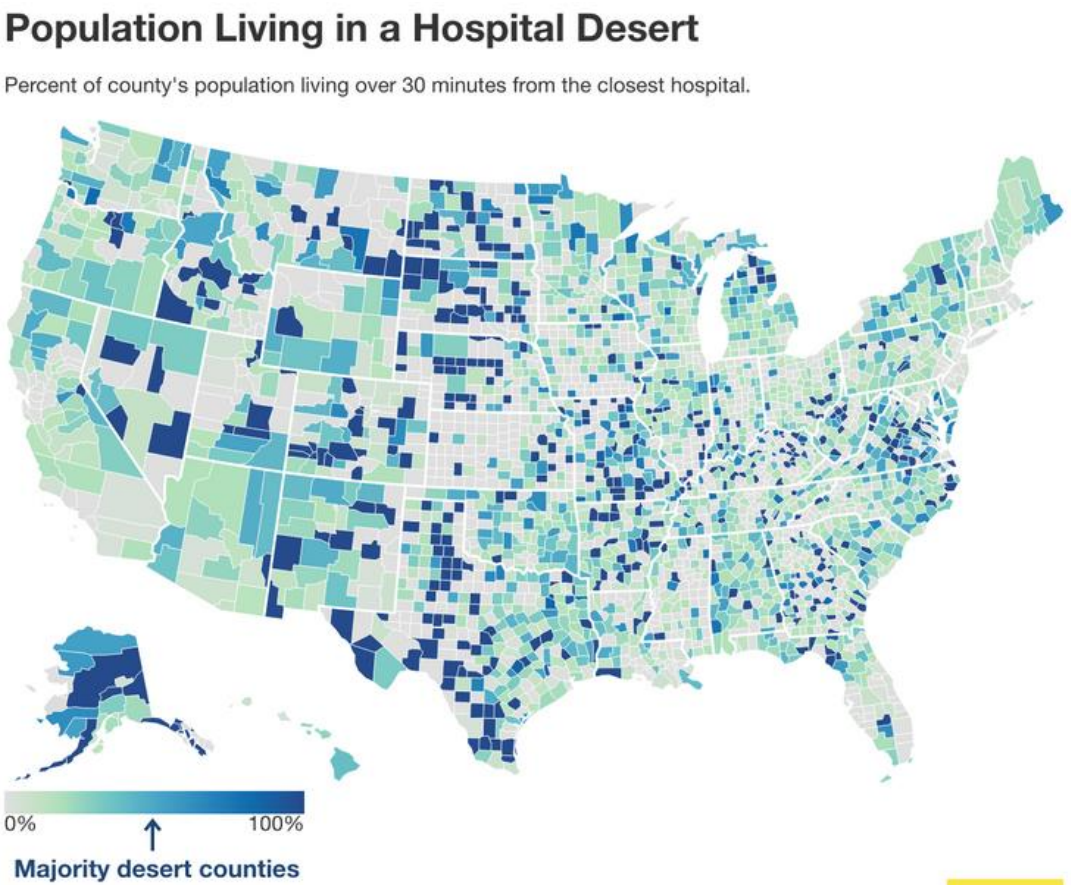
Did you enjoy it?

What does it really feel like to be in a trial?

And who can or would do it again?

Covering Clinical Trial Deserts





How do you cover the landscape?

What is something convenient and within a few miles of every person?

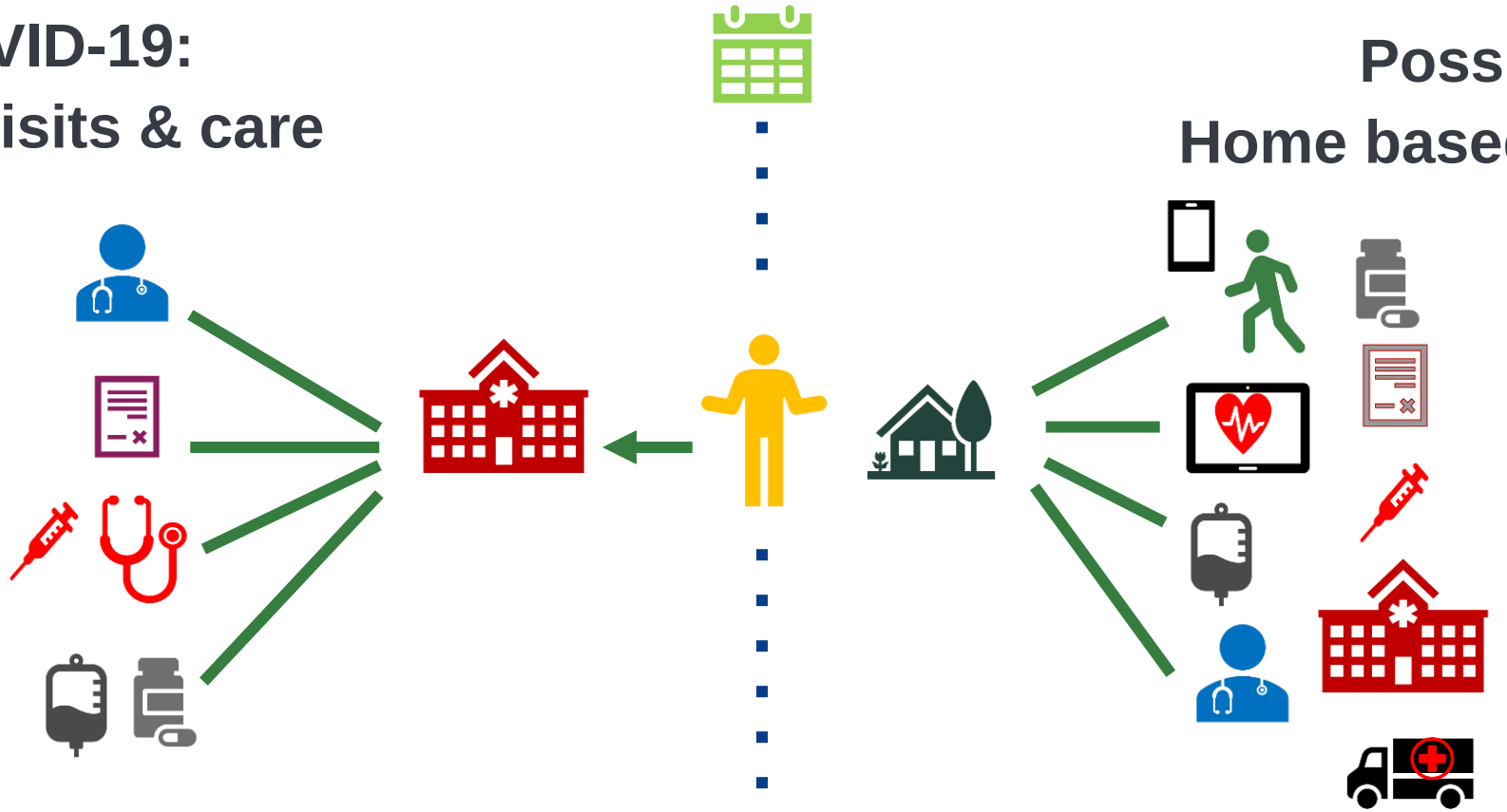
How do you cover the landscape?

What is something convenient and within a few miles of every person?

A Changed World of Possibilities: Pre-Covid to Post COVID

Pre-COVID-19:
Site based visits & care

Possibilities:
Home based visits & care



CTTI

https://ctti-clinicaltrials.org/our-work/digital-health-

A Changed World of Possibilities: Pre-Covid to Post COVID

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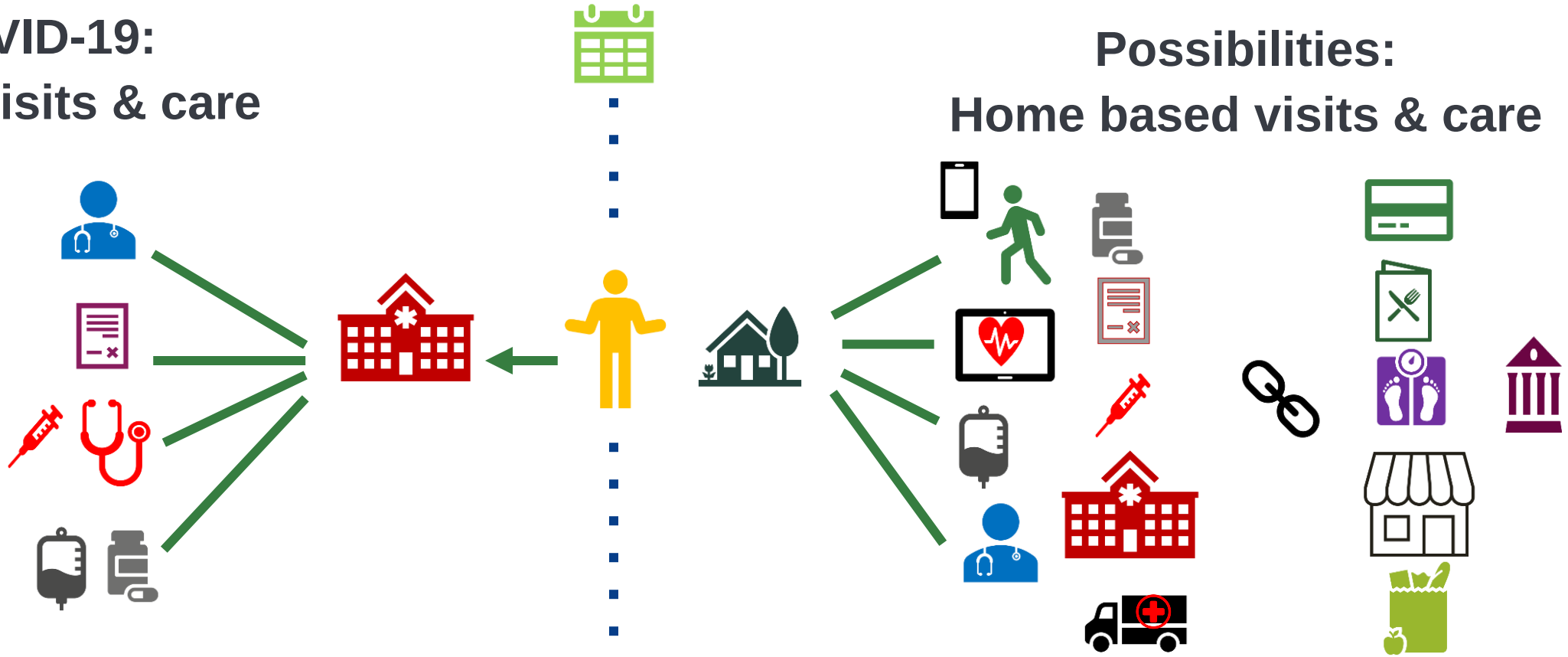


CTTI

https://ctti-clinicaltrials.org/our-work/digital-health-

ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications

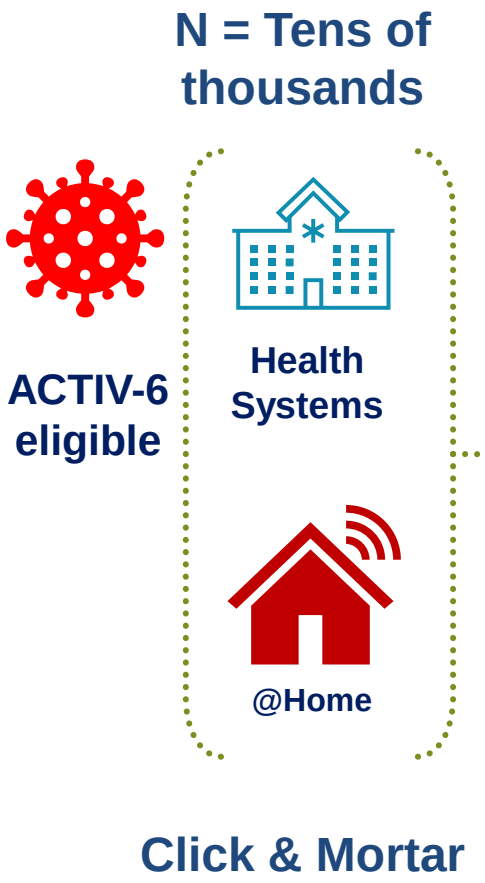
ACTIV-6

Key clinical questions

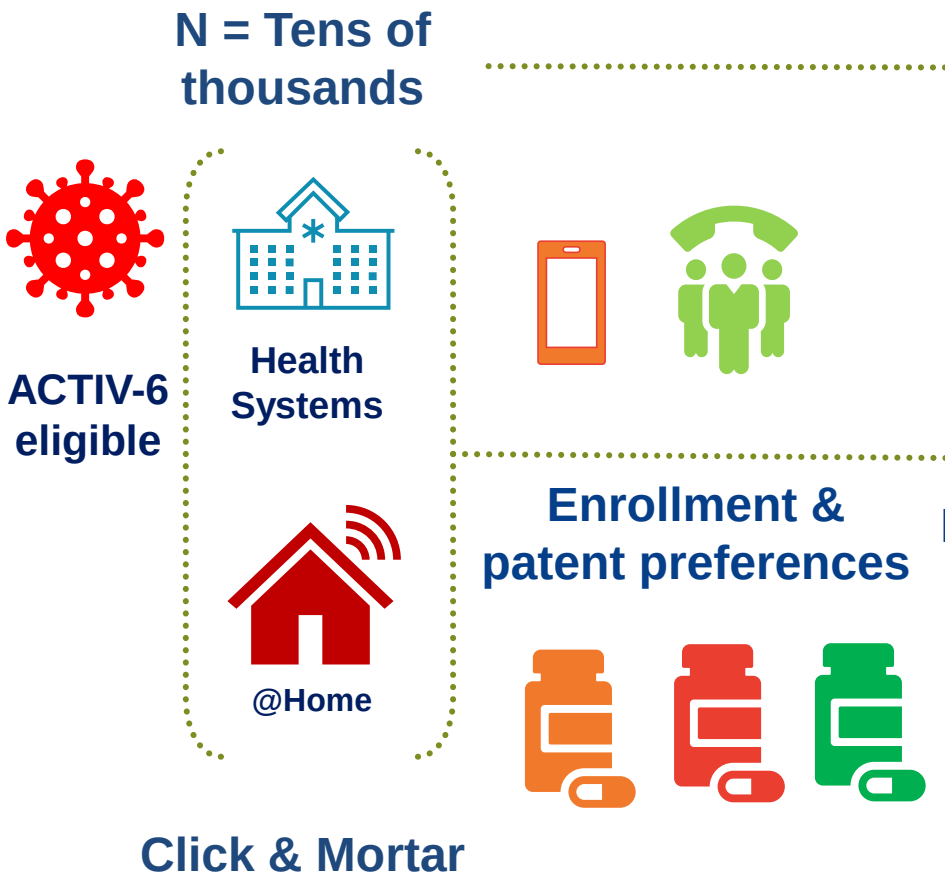
How to help someone *feel better faster* with newly diagnosed mild-moderate COVID-19?

How to *prevent hospitalizations or death* in someone with newly diagnosed mild-moderate COVID-19?

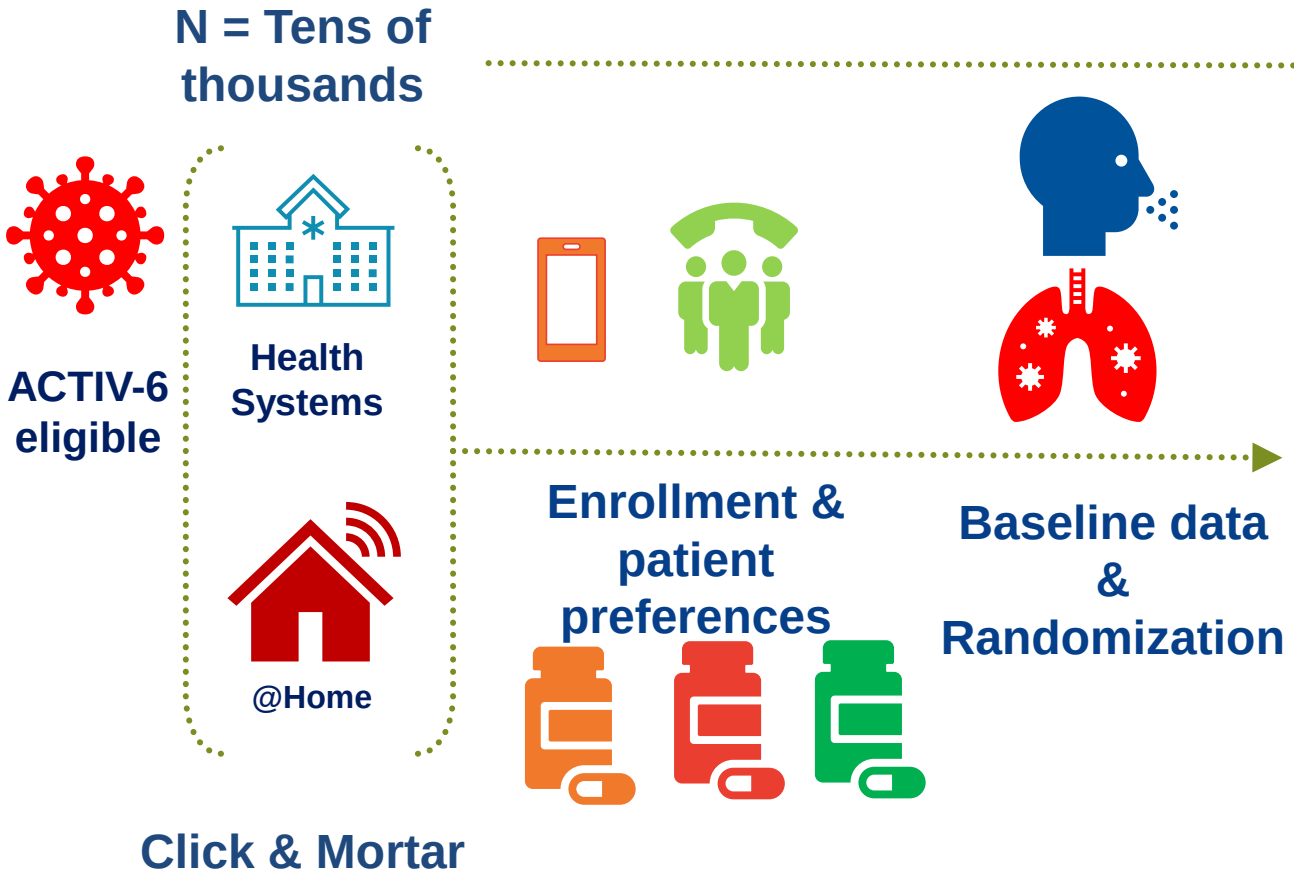
ACTIV-6 Hybrid Approach: Click & Mortar



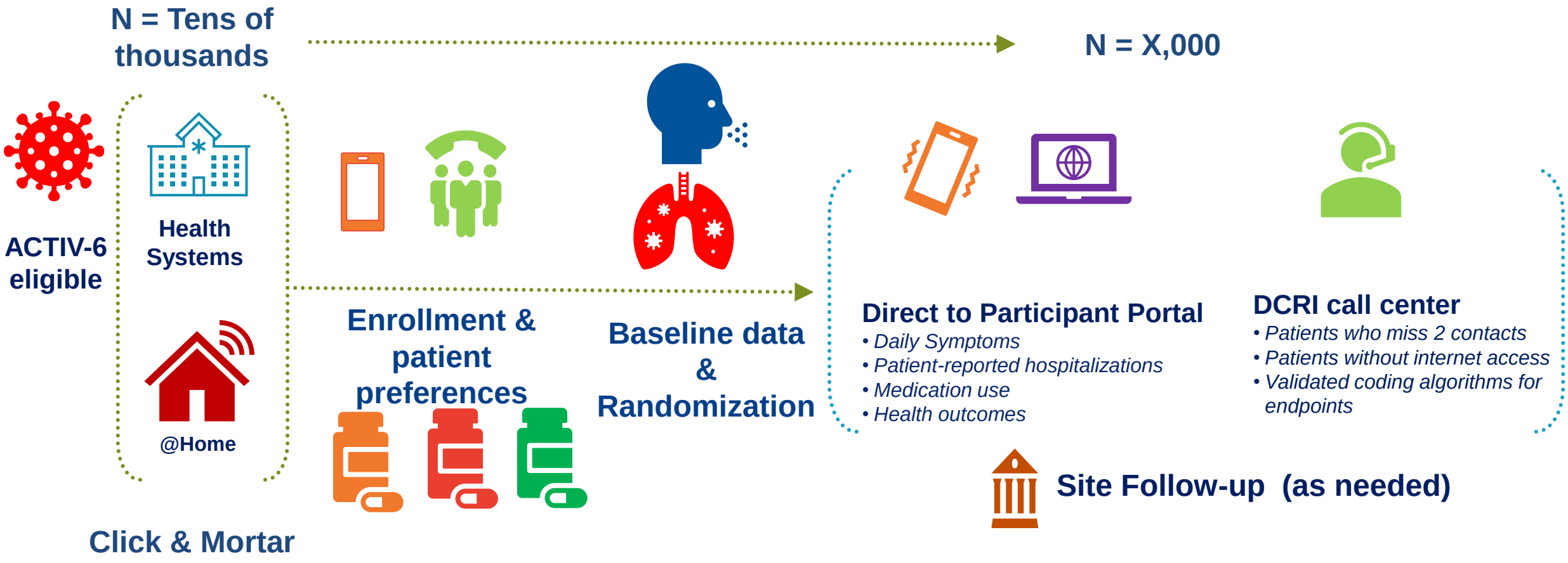
ACTIV-6 Hybrid Approach: Engagement



ACTIV-6 Hybrid Approach: Recruitment

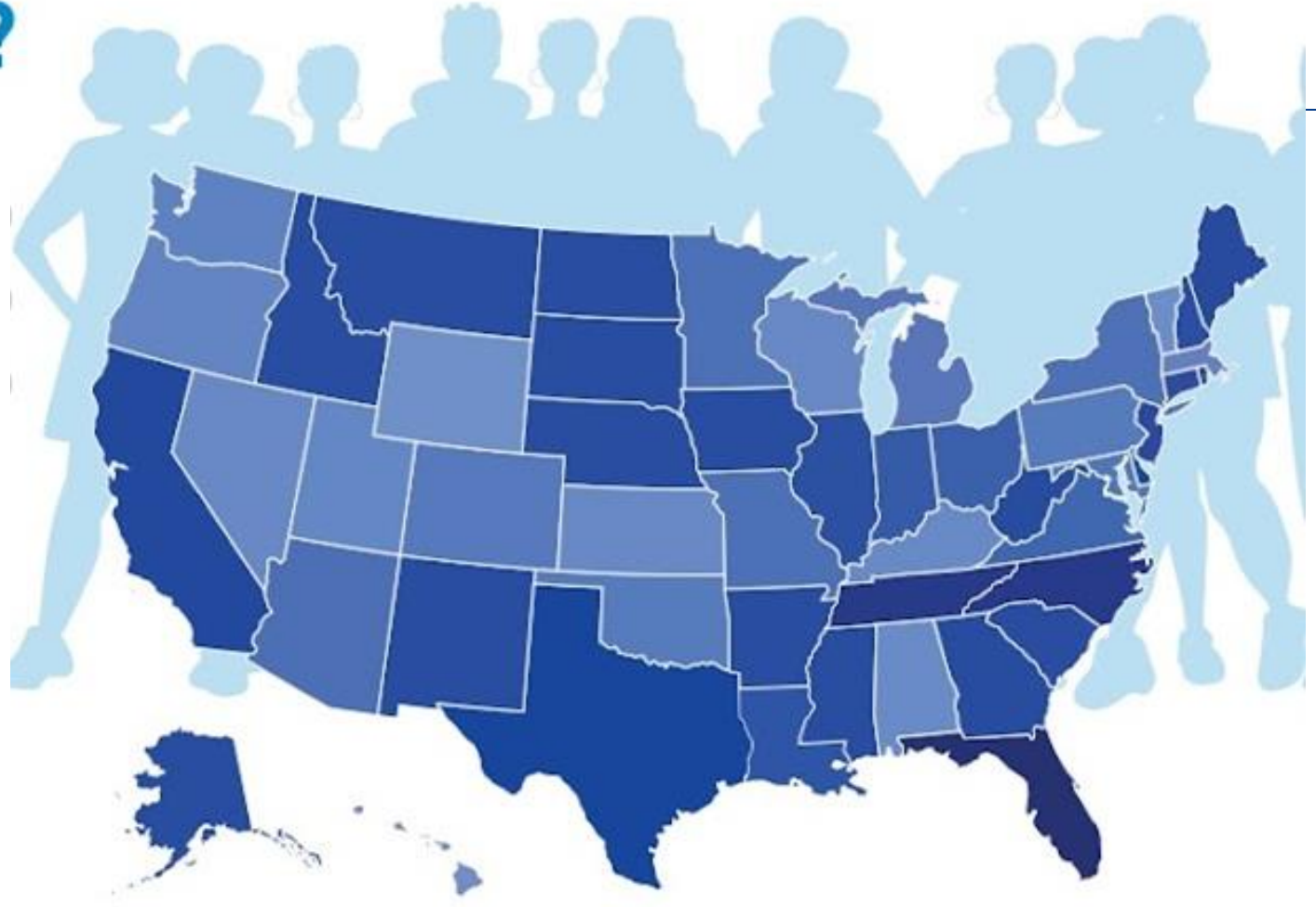


ACTIV-6 Hybrid Approach: Follow-up



Who is participating?

- All 50 US States
- 93 sites
- >26K engaged portal
  - 23K began consent process
  - >13K consented
  - >9800 consented to at least 1 arm
- >7700 randomized
- RANDOMIZATION 60->400 WEEK
- 5 Arms Completed and results reported
- 1 Arm enrolled and results pending
- 1 Arm launched (Metformin) Sept 2023



ACTIV-6

@ACTIV6study

Adaptable

The Aspirin Study

Study Snapshot

- **First large-scale pragmatic trial** conducted via PCORnet in learning health care systems
- **15,000 patients** at high risk for ischemic events randomly assigned in a 1:1 ratio to receive an aspirin dose of either 81 mg per day or 325 mg per day
- **40 PCORnet sites** enrolled for 3 years
- A **patient partner** first reported results at ACC 2021

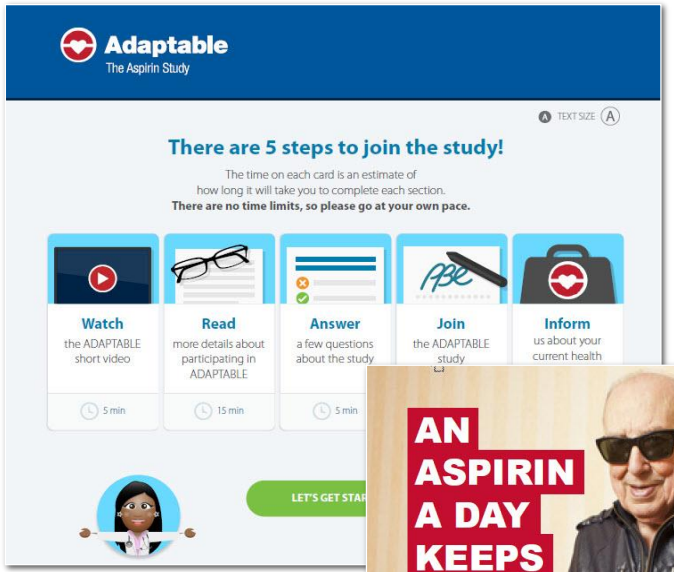
ADAPTABLE,
The Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness

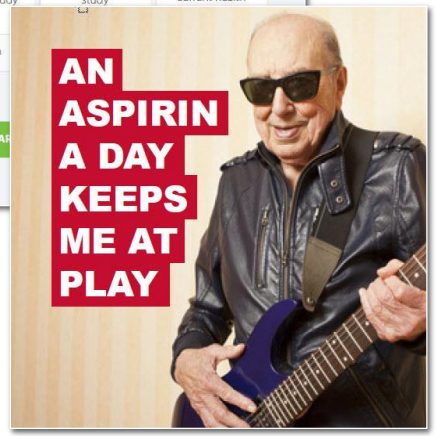
Is a low- or standard-dose aspirin better for preventing heart attacks and stroke in patients with coronary artery disease?

PRAGMATIC APPROACH

- Leveraged electronic health records (EHRs) to identify over 650,000 eligible patients across 40 sites
- Developed recruitment strategies leveraging high and low touch methods to **approach over 450,000 eligible patients** across 3 years of enrollment
- Utilized virtual patient portal where over 31,000 patients used unique access codes to enter the portal and over 15,000 enrolled using **e-Consent**
- Simplified baseline and follow-up data collection through patient-reported outcomes with **over 49,000 virtual visits** completed

An engaged community





Tweet

C. Michael Gibson MD
@CMichaelGibson

This is the FIRST TIME we have had a participant in a trial present the background for why the study was done and the primary results!

> C. Michael Gibson MD @CMichaelGibson · May 15
> .@schuyler_jones and @patientispard join me to discuss the patient-centered ADAPTABLE trial. Watch the full discussion: tv.clinicaltrialresults.org/play.php?submi...
>
> #ACC21

What wasn't as engaging?

Results of Health Plan Outreach

	Phase 1		Phase 2		Total	
	N	%	N	%	N	%
Outreached	133,373		51,777		185,150	
Portal Visit	890	0.7%	662	1.3%	1,552	0.8%
Enrollees	238	27%	119	18%	357	23%

- 8 per 1,000 outreaches resulted in portal visit interest in the study
- 2 per 1,000 outreaches resulted in an enrolled participant

Completing the Check List: Decentralization of Clinical Trials

Trial Characteristic	Hard	Easy
Engagement (Patient, Clinician)		
Eligibility criteria confirmation		
Representative cohort		
Consent Comprehension Format		
Data Collection		
Quality assurance (Source documents)		
Safety/Pharmacovigilance		
Endpoint adjudication/validation		

Conclusions:

Science & Health

Speed of Science

Questions >>> Answers

People Matter

Engagement

Experience

Equity

Meet the Real World

Be Convenient

Be Smart

Be Trusted

Clinicians

Families

Communities

TO BEND THE CURVE

Gain Lives

Lose Less

More Value

Discussion

REAGAN-UDALL FOUNDATION FOR THE FDA

Moderator

Khair ElZarrad, PhD, MPH

Panelists

Otavio Berwanger, MD, PhD

Noelle Cocoros, DSc, MPH

Adrian Hernandez, MD, MHS

Thank You!

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