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.
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:30 am</td>
<td>Welcome &amp; Overview</td>
<td></td>
</tr>
<tr>
<td>7:35 am</td>
<td>Recap of Previous Day</td>
<td></td>
</tr>
<tr>
<td>7:45 am</td>
<td>Otavio Berwanger, MD, PhD</td>
<td></td>
</tr>
<tr>
<td>8:05 am</td>
<td>Noelle Cocoros, DSc, MPH</td>
<td></td>
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<tr>
<td>8:25 am</td>
<td>Adrian Hernandez, MD, MHS</td>
<td></td>
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<tr>
<td>8:45 am</td>
<td>Moderated Discussion</td>
<td></td>
</tr>
<tr>
<td>9:25 am</td>
<td>Closing Remarks &amp; Adjournment</td>
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</table>
Why Are We Here Today?

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.
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
Otavio Berwanger, MD, PhD

Executive Director
The George Institute for Global Health

Chair in Clinical Trials
Imperial College London
Pragmatic & Decentralized Clinical Trials

Prof. Otavio Berwanger
Executive Director - The George Institute for Global Health UK
Chair in Clinical Trials, Imperial College London
London, United Kingdom
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.
Little to No Evidence

Clinical Trials

Differing age groups – elderly, pediatrics
Race, ethnicity, gender variances
Unstudied co-morbid conditions
Varying severity of disease
Differing concomitant medications

Evidence

Off-label indications

Variance in population characteristics from what was studied

Little to No Evidence

Utilization

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.
Decentralized clinical trials meet patients where they are.

Clinical-trial designs

- **Fully decentralized**
  - All trial procedures are conducted virtually, enabled by digital technologies and supply delivery.

- **Hybrid**
  - Less complex trial procedures that don't require in-person visits (e.g., vital signs, electrocardiograms) are conducted via telehealthcare, remote data collection, or direct-to-patient supply.
  - Less complex trial procedures that require in-person visits (e.g., injections) are conducted via mobile clinicians or alternative sites (e.g., mobile clinics, retail sites).

- **Fully centralized**
  - Complex trial procedures (e.g., complex screening protocols, cell therapy, magnetic resonance imaging) are conducted via research sites (e.g., academic medical centers) or local hospitals.
  - All trial procedures are conducted at a research site (e.g., academic medical center).

McKinsey & Company
Overview of a Decentralized Clinical Trial
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

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

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
EVOLOCUMAB VERY EARLY AFTER MI – STUDY DESIGN

~3.5 Year Median Follow Up

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)**

- Evolved & 1:1 Randomization
- Evolocumab 140mg Q2W + Routine Clinical Care N=2000 patients
- Routine Clinical Care (ie, Provider discretion) N=2000 patients

Real-time hybrid data collection through registry/EMR extraction

NCT05284747
Innovations in Protocol Development

- Minimal inclusion / exclusion
- Minimal procedures and ability to screen/randomize same day
- Simplified schedule of events
- Streamlined safety
## Innovations in Trial Operations

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

- 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
### Oversight of Clinical Studies

<table>
<thead>
<tr>
<th><strong>Global Project Team</strong>, based in the UK with conjoint appointments at TGI UK and ICTU and consisting of the following staff:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Chief Investigator</td>
</tr>
<tr>
<td>▪ Senior Project Manager</td>
</tr>
<tr>
<td>▪ Safety Monitor</td>
</tr>
<tr>
<td>▪ Quality Assurance Manager</td>
</tr>
<tr>
<td>▪ Clinical Trial Assistant</td>
</tr>
<tr>
<td>▪ Data Management Team</td>
</tr>
<tr>
<td>▪ Statistical Team</td>
</tr>
<tr>
<td>▪ Adjudicators</td>
</tr>
<tr>
<td>▪ Participant Representative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Regional coordinating centre (RCC) in each country consisting of the following staff:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Country-Lead Investigator Project Manager</td>
</tr>
<tr>
<td>▪ Medical Monitors</td>
</tr>
<tr>
<td>▪ Research Nurses</td>
</tr>
<tr>
<td>▪ Clinical Research Associates</td>
</tr>
<tr>
<td>▪ Participant representative</td>
</tr>
</tbody>
</table>
Trial Procedures (example: UK)

1. Eligible patients identified from UK GP practices using Routinely collected data
2. Participants give consent to contact.
3. Eligibility checks & remote consent of participants from central and regional coordinating centre
4. Access to participant EHR from central coordinating centre at TGI UK/ICTU
5. Delivery of randomised IMP & blood kits directly to participants (Bloods at 4 weeks, then 6 months if not available from routine practice)
6. Automatic integration with the study database
7. Interactive participant portal for PRO/accountability
8. Blood results received by central hub & reviewed for safety.
9. Phone line and virtual consultations for participants to call in case of AEs/SAEs
10. All participant visits remote
Good Trials: Produce a scientifically sound answer to a relevant question

**PRINCIPLE 01**
Informative and relevant

**PRINCIPLE 02**
Respectful of participants

**PRINCIPLE 03**
Collaborative and transparent

**PRINCIPLE 04**
Feasible for their context

**PRINCIPLE 05**
Efficient and well managed

Good Randomized Controlled 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
Noelle Cocoros, DSc, MPH

Principal Research Scientist
Harvard Pilgrim Health Care Institute

Principal Associate in Population Medicine
Harvard Medical School
Pragmatic guidance for pragmatic trials

Noelle M. Cocoros, DSc, MPH
September 13, 2023
Topics

- Background & context
- Advantages, challenges
- Lessons learned

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

Noelle M Cocoros, Jerry H Gurwitz, Mark J Cziraky, Christopher B Granger, Thomas Harkins, Kevin Haynes, Xiaojuan Li, Lauren Parlett, John D Seeger, Sonal Singh, Cheryl N McMahill-Walraven and Richard Platt
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

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 Cocoros¹, Sean D Pokorney², Kevin Haynes³, Crystal Garcia¹, Hussein R Al-Khalidi⁴, Sana M Al-Khatib², Patrick Archdeacon⁵, Jennifer C Goldsack⁶, Thomas Harkins⁷, Nancy D Lin⁸, David Martin⁵, Debbe McCall⁹, Vinit Nair⁷, Lauren Parlett⁵, Robert Temple⁵, Cheryl McMahill-Walraven¹⁰, Christopher B Granger² and Richard Platt¹

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

Crystal J Garcia¹, Kevin Haynes², Sean D Pokorney³, Nancy D Lin⁴, Cheryl McMahill-Walraven⁵, Vinit Nair⁶, Lauren Parlett⁵, David Martin⁷, Hussein R Al-Khalidi⁸, Debbe McCall⁹, Christopher B Granger³, Richard Platt¹ and Noelle M Cocoros¹
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.
## Advantages

<table>
<thead>
<tr>
<th>Large sample size</th>
<th>IMPACT-AFib randomized &gt;190,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numerous efficiencies</td>
<td>Leverage existing infrastructure</td>
</tr>
<tr>
<td>Generalizability</td>
<td>Minimize cross-site variation</td>
</tr>
<tr>
<td></td>
<td>Easy adoption of intervention</td>
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</tbody>
</table>
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
Thank You

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

noelle_cocoros@harvardpilgrim.org
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
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
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

Healthcare Deserts, County by County
Counties where most people lack adequate access to pharmacies, primary care providers, hospitals, hospital beds, trauma centers, and/or low-cost health centers.

Population Living in a Hospital Desert
Percent of county’s population living over 30 minutes from the closest hospital.
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

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

Pre-COVID-19:
Site based visits & care

Possibilities:
Home based visits & care

CTTI

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

N = Tens of thousands

ACTIV-6 eligible

Health Systems

@Home

Click & Mortar
ACTIV-6 Hybrid Approach: Engagement

N = Tens of thousands

ACTIV-6 eligible

Health Systems

Enrollment & patent preferences

Click & Mortar

@Home

Direct to Participant Portal
• Daily Symptoms
• Patient-reported hospitalizations
• Medication use
• Health outcomes

DCRI call center
• Patients who miss 2 contacts
• Patients without internet access
• Validated coding algorithms for endpoints

Baseline data
ACTIV-6 Hybrid Approach: Recruitment

- ACTIV-6 eligible
- Health Systems
- @Home
- Enroll & Patient Preferences
- Baseline Data & Randomization

N = Tens of thousands

Click & Mortar

DCRI call center

Daily Symptoms
Patient-reported hospitalizations
Medication use
Health outcomes

Patients who miss 2 contacts
Patients without internet access
Validated coding algorithms for endpoints

Baseline data & Randomization

Tens of thousands

Site Follow-up (as needed)
ACTIV-6 Hybrid Approach: Follow-up

N = Tens of thousands

ACTIV-6 eligible

Health Systems

Enrollment & patient preferences

@Home

Click & Mortar

Baseline data & Randomization

Direct to Participant Portal
- Daily Symptoms
- Patient-reported hospitalizations
- Medication use
- Health outcomes

DCRI call center
- Patients who miss 2 contacts
- Patients without internet access
- Validated coding algorithms for endpoints

Site Follow-up (as needed)

N = X,000

Site Follow-up (as needed)
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
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
What wasn’t as engaging?

**Results of Health Plan Outreach**

<table>
<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th></th>
<th>Phase 2</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Outreached</td>
<td>133,373</td>
<td></td>
<td>51,777</td>
<td></td>
<td>185,150</td>
<td></td>
</tr>
<tr>
<td>Portal Visit</td>
<td>890</td>
<td>0.7%</td>
<td>662</td>
<td>1.3%</td>
<td>1,552</td>
<td>0.8%</td>
</tr>
<tr>
<td>Enrollees</td>
<td>238</td>
<td>27%</td>
<td>119</td>
<td>18%</td>
<td>357</td>
<td>23%</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th>Trial Characteristic</th>
<th>Hard</th>
<th>Easy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engagement (Patient, Clinician)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria confirmation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representative cohort</td>
<td></td>
<td></td>
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<tr>
<td>Consent</td>
<td></td>
<td></td>
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<tr>
<td>Comprehension Format</td>
<td></td>
<td></td>
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<tr>
<td>Data Collection</td>
<td></td>
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<tr>
<td>Quality assurance (Source documents)</td>
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<td></td>
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<tr>
<td>Safety/Pharmacovigilance</td>
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<tr>
<td>Endpoint adjudication/validation</td>
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</tbody>
</table>

*Source: Duke Clinical Research Institute*
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
Moderator
Khair ElZarrad, PhD, MPH

Panelists
Otavio Berwanger, MD, PhD
Noelle Cocoros, DSc, MPH
Adrian Hernandez, MD, MHS
Thank You!

www.ReaganUdall.org