Public Workshop to Enhance Clinical Study Diversity

November 29 – 30, 2023 / 10 a.m. – 2:00 p.m. EST
Meeting will begin at 10:00 a.m. EST
Day 1 Opening Remarks

Karen Hicks
M.D., FACC, Deputy Director, Office of Medical Policy (OMP)
Center for Drug Evaluation and Research (CDER)
US Food and Drug Administration (FDA)
Day 1 - Agenda

• Overview of clinical study diversity
  – Where we are now?

• Establishment of clinical study enrollment goals
  – Use of disease prevalence or incidence data

• Approaches to support the inclusion of historically underrepresented populations
  – Age, Sex, Race, Ethnicity, Pregnancy, Lactation, Disability
  – Overcoming barriers to participation
A docket is open for the public to submit electronic or written comments related to the topics addressed during this workshop.

**Link to provide comments to the docket**

**Docket Number:** FDA-2023-N-2462

**Comment Period Closes:** January 29, 2024
Keynote Address

Patrizia Cavazzoni
Director, Center for Drug Evaluation and Research
US Food and Drug Administration
Importance of Diversity and Inclusion in Clinical Trials

• Clinical trials provide critical evidence regarding whether a medical product is safe and effective.

• Clinical trials should, to the extent possible, enroll a population that is representative of the diversity of the population that will use the medical product, if approved.

• FDA is committed to increasing the participation of underrepresented populations in clinical trials through:
  – Issuing guidance(s)
  – Encouraging the use of innovative trial designs
  – Leveraging “fit-for-purpose” technology
FDA’s Longstanding Commitment to Promote Diversity & Inclusion: Topics of Published Guidances for Industry

- Specific populations e.g.
  - Underrepresented racial and ethnic populations
  - Older adults
  - Pregnant individuals
  - Lactating individuals
  - Sex

- Innovative trial designs and technologies e.g.
  - Decentralized clinical trials
  - Digital health technologies

- And many others
A Balanced Approach is Needed
Timeline of Key Events

April 2022
• Draft Diversity Plans Guidance

June 2022
• Diversity Plans Implementation Committee (DPIC)

December 2022
• Food and Drug Omnibus Reform Act (FDORA)
Food and Drug Omnibus Reform Act

• December 2022 – the Food and Drug Omnibus Reform Act (FDORA) was passed.

• Sponsors will be required to submit Diversity Action Plans for Phase 3 or other pivotal trials.

• FDA to convene a public workshop to enhance clinical study diversity.
  – This two-day virtual public workshop is one of the deliverables to fulfill these FDORA requirements.

• FDA is required to update existing guidance or release new guidance on Diversity Action Plans.
Common Goal

- Ensuring that the clinical study of a drug or device reflects the diversity of the population for which it is being developed is not only important for the patients who will ultimately use the drug or device after approval, but also of interest to:
  - industry
  - clinicians
  - study participants
  - health care systems
  - other interested parties
Moving Forward

• To achieve meaningful representation in clinical trials, it will take our combined effort.
  – FDA is only one piece of this puzzle.

• To obtain the data we need for the diverse population that will use the medical product, if approved, will take **ALL** of us working together:
  – sharing ideas
  – sharing experiences
  – sharing best practices
Key Takeaways

• FDA has a longstanding commitment to promote diversity and inclusion of underrepresented populations in clinical trials.

• Enrollment in clinical trials should, to the extent possible, reflect the diversity of the population that will use the medical product, if approved.

• A pragmatic approach that balances FDA’s intent to increase diversity in clinical trials with bringing urgent medical treatments to patients as soon as possible is needed.

• To achieve meaningful representation in clinical studies, it takes the combined effort of all interested parties in the clinical trials enterprise.
Clinical Study Diversity – A Brief Overview: Where are We Now?

ELDRIN F. LEWIS, MD, MPH, FAHA
SIMON H. STERTZER, MD PROFESSOR OF MEDICINE
CHIEF, CARDIOVASCULAR DIVISION
STANFORD UNIVERSITY

Public Workshop to Enhance Clinical Study Diversity
November 29 - 30, 2023 / 10 a.m. – 200 p.m. EST

November 29, 2023
Disclosures

Novartis (Consulting, Institutional research support)
Akebia (Consulting, Institutional research support)
Merck (Consulting, Institutional research support)
Dal-Cor (Consulting)
Astra Zeneca (Consulting)
Barriers to Enrollment and Strategies

Levers: Trust and Publication Requirements

Legacy of Tuskegee Experiment and “HeLa cells”

October 1972

FINAL REPORT
of the
Tuskegee Syphilis Study
Ad Hoc Advisory Panel

Panel members: 5 blacks and 4 whites

In Tuskegee, Painful History Sheds Light on Efforts to Vaccinate African Americans – Houston Public Media
Legacy of Tuskegee Experiment and “HeLa cells”

“Researchers have found that the disclosure of the infamous Tuskegee syphilis study in 1972 is correlated with increases in medical mistrust and mortality among African-American men. Their subsequent Oakland project seeks to better understand African-American wariness of medicine and health care providers.”

JANUARY 6, 2017
Stanford researchers explore legacy of Tuskegee syphilis study today

“Researchers have found that the disclosure of the infamous Tuskegee syphilis study in 1972 is correlated with increases in medical mistrust and mortality among African-American men. Their subsequent Oakland project seeks to better understand African-American wariness of medicine and health care providers.”

https://news.stanford.edu/2017/01/06/stanford-researchers-explore-legacy-tuskegee-syphilis-study-today/#:~:text=Researchers%20have%20found%20that%20the,medicine%20and%20health%20care%20providers.
Strategies to Build Trust

- Embed into the Community
- Diversify the Workforce
- Simplify Consent Forms
Structural Racism and Need for Race/Ethnicity Data

Are you even trying to stop racism if you don’t collect data on race?

In the UK, US, and Canada, it is commonplace for public institutions—like the healthcare system, and the national census—to ask for your race or ethnicity. Because of this, they have robust statistics on the identities of their citizens. These nations, however, are the outliers.

Most of the world’s wealthiest countries don’t collect any data on the racial or ethnic identity of their people. In many cases, it’s illegal. France doesn’t keep official statistics of how many Black residents it
• Survey of OECD Countries
• Imputed for France/Estonia (non-response)

No collection of ethnicity and race
CDER and CBER Requirements

- Beginning in May 2017
- Presentation of demographic data (section 2.7.4.1.3 and table 2.7.4.2)
- Suggests a tabular display of demographic characteristics by treatment group
Race and ethnicity enrollment reporting in United States-based clinical trials registered on ClinicalTrials.gov
Distribution of trials and the representation of each racial/ethnic group organized by racial/ethnic category

- 2010 Census
- Only trials reporting all 5 categories
Distribution of trials and the representation of each racial/ethnic group organized by racial/ethnic category

White Participants

Latino Participants

Black Participants

Asian Participants
Institutional and Regulatory Strategies

Publication Strategies
- N/A for non-reporting countries
- Diversity of teams
- Standard reporting of demographics
- SDoH elements
Standardization for Health Equity Research

ELEVATING the focus on:
- Disparities
- Anti-racism
- Health equity
- Community-engaged/community-based participatory research
- Implementation science

COLLECTIONS include:
- Disparities and health equity
- Race, ethnicity, and health
- Social determinants of health
- Women’s health, sex, and gender
Eldrin F. Lewis, MD, MPH, FAHA, FACC
Simon H. Stertzer, MD Professor of Medicine
Chief, Division of Cardiovascular Medicine
Stanford University School of Medicine
E-mail: eflewis@Stanford.edu

@EldrinL
Website: med.stanford.edu/cvmedicine
Laura Mauri

Senior VP and COO
Medical and Regulatory Officer
Medtronic
The medical device industry is on a journey to increase diverse representation in clinical trials.

Clinical evidence supports a wide range of medical devices:

- Therapeutic
- Diagnostic
- Decision Support
Unique realities and opportunities in medical device trials

Study design

• Can be focused on well understood mechanisms, use surrogate endpoints, and/or single arm study designs

• Devices may directly collect physiologic data

• Regulatory balance toward post market for additional data on subgroups and indication expansion

Site selection

• High volume procedural centers are not evenly distributed across communities

Patient recruitment

• Investigators and recruitment through traditional referral pathways may not reach the eligible population
New approaches to patient recruiting, including direct-to-patient communication and social media

Potential levers to increase diversity in medical device trials

Patient engagement during study design process

Partnerships with community groups in locations with underrepresented populations
What got us here won’t get us there

The entire healthcare system has a shared role in driving forward progress
FDA Public Workshop to Enhance to Clinical Study Diversity

Clinical Study Diversity: A Brief Overview: Where are we now?

Allison Cuff Shimooka, COO, TransCelerate BioPharma Inc.

November 29th, 2023
TransCelerate was conceived to improve the health of people around the world by **accelerating and simplifying** the research and development of innovative new therapies.

In 2012, R&D Leaders formed a non-profit to collaborate to tackle common operational challenges. Combining the words “Transform” and “Accelerate”, TransCelerate was launched.

**Member driven mission** to collaborate across the global biopharmaceutical research and development community to **identify, prioritize, design, and facilitate** the implementation of solutions designed to drive the **efficient, effective and high-quality delivery of new medicines**.

TransCelerate has grown from **10 pioneering companies** to **22 Member Companies**, fostering **interactions** across ecosystem stakeholders, towards improvement in key value drivers in clinical research.
Diversity of Participants in Clinical Trials

**Vision**

Focused on providing **tools & information** to organizations working to improve the **representation of patient populations in clinical trials** for which the studied drugs are intended to be prescribed/used.

- **2014**
  - **KICKED OFF INITIAL EFFORT**
  - Kicked off initial effort to bring awareness to need for diversity in clinical trials

- **2016**
  - **DELIVERED BETTER PRACTICE MATERIALS**
  - Delivered targeted better practice materials for sites and sponsors

- **2021**
  - **KICKED OFF RENEWED EFFORT**
  - Focused on actionable tools and resources needed to improve outcomes for diversification of participants in clinical trials

- **Today**
  - **DESIGN & LAUNCH OF SOLUTIONS**
  - Currently developing solutions in key areas of scope, including diversity roundtable events, assessment, and toolkits.

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Diversity of Participants in Clinical Trials

Initiative Solutions

Reference Table and Landscape of Available Resources

Provides descriptions and links to publicly available resources for Patients, Sponsors, and Sites/HCPs. It also includes a visual landscape of the resources described and linked in the reference tables. Additionally, the landscape indicates resources that serve overlapping stakeholder communities.

Sponsor Toolkit Portfolio and Program-Level Considerations for Diversity, Equity and Inclusion of Participants in Clinical Trials (DEICT)

Consists of a set of considerations designed to support sponsors with improving diversity in clinical trials related to protocol design and development.

Diversity Community-Based Site Engagement and Capacity Building

Provides an aggregated collection of insights and perspectives from the attending organizations of a June 9 Roundtable Event, regarding considerations that sponsors, sites, and others have taken to enhance engagement and capacity building for community-based sites.

Sponsor Toolkit Site Engagement and Capacity Building Considerations for Diversity, Equity and Inclusion of Participants in Clinical Trials (DEICT)

This toolkit is comprised of a set of mitigation considerations designed to support efforts to sustainably partner with sites to enable the enrollment and retention of underrepresented patient populations in clinical trials. These mitigation considerations consist of perspectives from a series of stakeholder discussions and a Diversity Roundtable event and suggest considerations across different maturity levels.

Additional Solutions with US Focus: U.S. Regulatory Landscape, FDA Diversity Plan Early Insights and Considerations
GET IN TOUCH!
MY STORY...
Breast cancer is the most fatal health issue for Black women. Our disease is different, unique and warrants special and focused attention. Black women diagnosed with breast cancer face:

- **41%** Higher mortality rate compared to white women.
- **39%** Higher risk of breast cancer recurrence.
- **71%** Higher relative risk of death compared to white women.
Black women under 35 get breast cancer at twice the rate and die at three times the rate.

Black women under 50 are twice as likely to die from breast cancer.

Black women are nearly twice as likely as White women to receive a breast cancer diagnosis at an advanced stage of the disease.

Black women are 3 times more likely to have triple negative breast cancer. 40% of TNBC patients are under 40.
Black women are more likely than White women to die of breast cancer at any age across any sub-type.

Black women have the lowest 5-year relative breast cancer survival rate compared to all other racial/ethnic groups for every stage of diagnosis and every breast cancer subtype.
The physiology of Black women has not been a consideration in clinical trial research.

- The clinical trials for the current standard of care drugs have had little to no inclusion of Black women.
- The average Black women participation rate for current breast cancer clinical trials is less than 3%.

Clinical trial education, recruiting, and participation are not commensurate with the state of disease.
HOW IS THE ECOSYSTEM FAILING BLACK WOMEN?

Doctors don’t invite Black women to clinical trials. When the patient brings up the conversation, they still walk away not sufficiently informed.
What Can the Ecosystem Do Better?

Educate with Cultural Agility!

Fear of the unknown!

Can’t continue to blame the fear on the earned medical mistrust and the social determinants of health.
“Don’t do a clinical trial! You will get the sugar pill and die.”
Metastatic Patient
Words like *underserved* and *unrepresented* should not be used in patient-facing language.

Pronouns like ‘you’ and ‘they’ are disturbing and undermine trust.

Talking at them and about them
VERSUS
Talking to them and with them

What Can the Ecosystem Do Better?
What Can the Ecosystem Do Better?

What’s Black about it?

- Must show that you really care about the audience and are willing to invest in it.
- Must be intentional in every word and visual
- Patient voice is the voice of TRUST
How Is the Ecosystem Failing Black Women?

How Is The FDA Guidance Changing the Game?

The diversity evaluation process does not yet have proven metrics.
OUR

When We Tri(al) MOVEMENT

1. Acknowledges earned mistrust in medical research and re-establish trust.

2. Dispels myths about clinical trial research and educate around the basics and benefits of research.

3. Empowers Black breast cancer patients to advocate for themselves.
We Support Trials With:

Recruiting Consulting
Site Guidance And Training
Nurse Navigators To Support Patients
WEBSITE VISITS
126,999
39,118 unique visits

CLINICAL TRIALS SEARCH
14,572
The Golden Rule

Treat others the way YOU want to be treated.
THANK YOU!
Session 2: Establishment of Clinical Study Enrollment Goals & Use of Disease Prevalence or Incidence Data
Matching measures to goals in efforts to promote clinical trial diversity

Scott D. Halpern, MD, PhD

John M. Eisenberg Professor of Medicine, Epidemiology, and Medical Ethics & Health Policy
Director, Palliative and Advanced Illness Research (PAIR) Center
Director, Behavioral Economics to Transform Trial Enrollment Representativeness (BETTER) Center
University of Pennsylvania Perelman School of Medicine
Trial participation barriers and facilitators

<table>
<thead>
<tr>
<th>Approach</th>
<th>Recruitment</th>
<th>Retention</th>
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<tbody>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Image" /> Diverse population with / at risk for disease</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /> Potential barriers: (current state) • Sites/mechanisms of approach • Research team composition</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /> Potential barriers: (current state) • Mistrust, discomfort • Travel- and time-related barriers</td>
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<td><img src="https://via.placeholder.com/150" alt="Image" /> BE facilitation strategies: • Default enrollment • Use of mobile technologies</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /> Approached sample with somewhat less representation</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /> BE facilitation strategies: • Opt-out consent • Enhanced active choice • Financial incentives</td>
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<td><img src="https://via.placeholder.com/150" alt="Image" /> BE facilitation strategies: • Financial incentives • Reducing or supporting in-person commitments</td>
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<td><img src="https://via.placeholder.com/150" alt="Image" /> Final RCT sample with further decreased representation</td>
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Participation-to-Prevalence Ratio (PPR)

- Approach Recruitment Retention
- ![Image](https://via.placeholder.com/150) is ![Image](https://via.placeholder.com/150)
Virtues of Participation-to-Prevalence Ratio (PPR)

• Single metric that can be used across RCTs of different diseases

• Aligned with goal of equitably distributing potential benefits of trial participation
Problems with sole reliance on Participation-to-Prevalence Ratio (PPR)

- Accurate prevalence data across groups are often unavailable
- Geographic heterogeneity – population prevalence where?
- PPR can be “gamed”
  - Selectively recruiting from sites with high %s of underrepresented groups
  - Oversampling underrepresented patients
- Improving equity of opportunity may or may not improve PPR
- Poorly aligned with goal of augmenting biomedical knowledge
# Why Diverse Clinical Trial Participation Matters

Aaron L. Schwartz, M.D., Ph.D., Marcella Alsan, M.D., Ph.D., Alanna A. Morris, M.D., and Scott D. Halpern, M.D., Ph.D.

## Goals of Increasing Diversity in Clinical Trials.

<table>
<thead>
<tr>
<th>Goal</th>
<th>Key Challenges</th>
<th>Implications</th>
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<tbody>
<tr>
<td>Building trust in medical research and institutions</td>
<td>Distrust of medical and scientific professions can be an important obstacle to receiving effective medical care.</td>
<td>The effect on public trust of the design and conduct of clinical trials can be as important to public health as trials’ results. Investments should be made in elucidating how clinical trial practices affect public trust.</td>
</tr>
<tr>
<td>Promoting fairness for potential participants and their communities</td>
<td>Opportunities to participate in trials are limited. Preferences, resources, and trust all affect willingness to participate in trials. Health systems’ capacities to conduct trials vary among communities.</td>
<td>Overcoming unjust barriers to participation for disenfranchised groups will require affirmative outreach and recruitment actions. Grading trials on inclusive outreach and recruitment practices, rather than solely enrollment demographics, may better reflect recruitment equity. Investing in trial capacity in marginalized communities may benefit such communities broadly by improving adoption of innovations.</td>
</tr>
<tr>
<td>Generating biomedical knowledge</td>
<td>Sample sizes are often too small to permit assessment of treatment efficacy within particular subgroups. Clinically significant differences in treatment efficacy between groups that are underrepresented and those that are overrepresented in trials may not be common. Efforts to diversify trials address only some of the barriers to efficient patient recruitment.</td>
<td>Investigators should acknowledge that more inclusive trials may not show whether a treatment is effective for certain patient subgroups or meaningfully shift estimates of the treatment’s efficacy. Shifting the focus of trials to diseases that disproportionately affect marginalized groups may more effectively generate knowledge benefiting these groups. Future meta-research could clarify the importance and detectability of heterogeneous treatment effects.</td>
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Effectiveness and Ethics of Incentives for Research Participation in 2 Randomized Clinical Trials

Parent RCT 1: 4-arm trial of smoking cessation interventions among outpatients with depression

Parent RCT 2: gamification intervention vs. usual care to promote ambulation among inpatients

Main effectiveness outcome: signed consent to participate in parent trial

Ethical safety outcomes: undue* & unjust inducement
Equalized racial enrollment in a real smoking cessation trial with incentives without adverse ethical safety outcomes in any group

<table>
<thead>
<tr>
<th>Incentive</th>
<th>Black patients</th>
<th>White patients</th>
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<tbody>
<tr>
<td>$0</td>
<td>17%</td>
<td>30%</td>
</tr>
<tr>
<td>$200</td>
<td>36%</td>
<td>36%</td>
</tr>
<tr>
<td>$500</td>
<td>46%</td>
<td>49%</td>
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</table>
Recommendations

- Academic-Industry partnerships to test representativeness-promoting interventions in real RCTs
  - Outcomes fit for purpose: e.g., group-specific enrollment fractions
- Real-world and survey experiments exploring how interventions impact ethical safety outcomes (undue inducement) and trust
- All trials should fully capture the characteristics of all approached patients, not just those who consent
- Get over concerns about paying people to participate – or at least be open to further tests
Diversity in Clinical Trials
On the path to create health equity

Dooti Roy, PhD.
FDA Public Workshop to Enhance Clinical Study Diversity
November 29, 2023
Boehringer Ingelheim is committed to impact 50 million people in underserved communities by 2030 by empowering our employees, partners and social entrepreneurs to help co-create healthy, inclusive and sustainable communities.
“Health equity is achieved when everyone can attain their full potential for health and well-being” (WHO)

Boehringer focuses on clinical trial diversity as a part of eliminating healthcare disparities for people and animals in vulnerable communities.
The regulatory context

In response to publication of FDA guidance, Boehringer Ingelheim developed a “Diversity Plan Working Group”

- Cross-functional

- Established Business Practice and Diversity Plan Template documents to ensure teams were working similarly across therapeutic areas and development programs

- Created mechanisms for sharing completed plans and lessons learned

- Provided educational sessions

**Future focused: New Clinical Trial Diversity Lead and Team of Diversity Strategists**
Diversity Plan in Action

- Disease prevalence
- Recruitment and Retention plans
- Patient engagement
- Site and Investigator diversity

1. Prepare Diversity Plan
2. Submit Diversity Plan to FDA for Review
3. Receive and Incorporate FDA Feedback
4. Share Diversity Plan Learnings for Future Plans

Diversity Plans

Boehringer Ingelheim

FDA Public Workshop: Diversity in Clinical Trials | November 2023
Ensuring diversity in clinical trial is a multi-faceted, nuanced endeavor

Focused commitment, strategy and execution at a broad spectrum of correlated topics are critical components for success

Learn ↔ adapt
Monitoring diversity during trial conduct

• A R-Shiny based interactive data visualization dashboard has been implemented

• Site and trial level monitoring

• Enables during conduct real time tracking of diversity metrics

• Keeps teams on target and focused

• Insights for future use
## Patients at the center

### Diversity and Inclusion Patient Council
- Standing committee of diverse patients
- Direct input into a variety of topics e.g., clinical trial materials, design considerations
- EMPA-ASi trial

### Yale Diversity Study
- Oncology
- Cross-industry
- Understand facilitators and barriers to participation in early phase clinical trial
- Focus on underrepresented patients

### Hear Your Heart
- Empower Black and Latina women with heart failure who experience a higher mortality rate
- Encourage patients to prioritize their heart health

---

**Co-creating solutions together with the under-served patient community:** goal of turning those solutions back to the communities to create **impact for generations.**

---

1. Heart Failure: Health Disparities & Inequities for Women | BI US (boehringer-ingelheim.com)
2. Confronting health disparities in clinical trials | Boehringer Ingelheim US (boehringer-ingelheim.com)
3. Achieving Health Equity: The Importance of Patient Input at Every Phase of Care | Boehringer Ingelheim US (boehringer-ingelheim.com)
It really takes a village.

Acknowledgement:

Elizabeth Meissner
Dr. Yabing Mai
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Dr. Hilary Wilson
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Kathleen Collins
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Sharon Attick
Paul Petraro
Christian Niyonkuru
Establishment of Clinical Study Enrollment
Goals & Use of Disease Prevalence or Incidence Data

FDA Workshop
November 29, 2023
Bobbi Bogaev Chapman, MD
Vice President, Heart Failure
Disclosures

Bobbi Bogaev Chapman, MD
Vice President, Heart Failure

Full time employee for Abiomed
Prevalence of Disease and Enrollment Targets

Published clinical trial data
Observational registries
Real world evidence
Human Factors Consideration in Device Design

1980s
- Large, heavy durable pulsatile pumps
- Invasive sternotomy

Heartmate XVE

1990s
- Lighter durable axial blood pumps
- Invasive sternotomy pumps

Heartmate II

2000s
- Smaller durable magnetically levitated centrifugal pumps
- Thoracotomy option

HVAD

2010s
- Thoracotomy option

Heartmate III

2022
- The world’s first minimally invasive, intravascular durable LVAD

Impella BTR

J&J MedTech
Enrollment Targets

Age

Race

Ethnicity

Gender
Strategies to Diversify Enrollment

- Clinical Trial Leadership
- Site Selection
- Site Principal Investigators
- Education to Patients and Primary Providers
- Community Engagement
- Remote Monitoring
Community Engagement: Patient Advisory Group

Patients
Caregivers
Research Coordinators
Physician Principal Investigators
Reimbursement Challenges to Equitable Enrollment

- Caregiver and Travel Reimbursement
- Category B CMS Reimbursement
- Variable IRB Policies
Multi-stakeholder Alignment is Needed to Enhance Diversity, Equity, and Inclusion in Clinical Trials

Community Health Systems → Industry and Trial Sponsors → Academic Institutions → Physicians and Providers

Community Health Systems → Research Coordinators → Institutional Review Boards → CMS

Community Health Systems → Biostatisticians → Bioethicists → FDA

Community Health Systems → Commercial Payors
Thank you

If you have more questions, please contact:
Bobbi Bogaev Chapman, MD
Vice President, Heart Failure

rchapm11@its.jnj.com
FDA Public Workshop

Enhancing Clinical Study Diversity:
Introductory Comments

November 29, 2023

Thomas R. Fleming, Ph.D.
Professor, Dept. of Biostatistics
University of Washington

The FDA has made “critically important contributions” to the “pursuit and implementation of evidence-based approaches for the prevention & treatment of diseases” *

FDA Public Workshop

Enhancing Clinical Study Diversity

Objectives of this Session:

Discuss the establishment of goals for enrollment in clinical trials, including the relevance of the estimated U.S. prevalence or incidence of the disease or condition for which the drug or device is being developed.

Discuss how and when to collect and present the prevalence or incidence data on a disease or condition by demographic subgroup, possible sources for such data and methodologies for assessing such data.
Enhancing Clinical Study Diversity

Enhancing evidence-based medicine is of central importance.

Clinical Trials should be properly designed and conducted.

Among key design and conduct considerations are:

- **Having proper primary & secondary endpoints:** ‘Feels, functions, survives’ measures or validated biomarkers
- **Being randomized, when possible, to enhance reliability**
- **Use of Controls receiving a proper version of Standard-of-Care**
- **Ensuring evidence-based generalizability of results**
  - Enabling properly informative descriptive presentations by important baseline characteristics
Ensuring proper generalizability of clinical trial results:

Quality Research: *Active* rather than *Passive* Approaches are Needed

- Establishing of enrollment targets in clinical trials, including proper engagement of often underrepresented populations
  - Targets enlightened by the prevalence or incidence data for a disease or condition by demographic subgroup

- Creative proactive approaches to increase ability to achieve targets
  - Selection of sites that increase diversity of enrollees
  - Ensure adequate engagement of North American sites

- Monitoring enrollment diversity throughout trial conduct
  - Shared responsibilities of the study sponsor and the DMC
Enhancing Clinical Study Diversity
—An important role of Data Monitoring Committees

Data Monitoring Committee (DMC) Mission:
“Safeguard the interests of study participants as well as
to preserve the integrity and credibility of clinical trials,
enabling them to achieve both timely and reliable evaluations of
experimental interventions for the benefit of the broader clinical community.”

✓ DMCs: Enhancing engagement of often underrepresented populations

“There is need for proper diversity in clinical trial leadership, in DMC membership,
and in patients enrolled in the clinical trial.
Not only should DMCs have inclusion of diverse members,
but DMCs also should monitor the composition of the trial cohort...
DMC’s have an opportunity throughout trial conduct to examine
the representation of the enrolled cohort, and to make recommendations
to enhance enrollment of specific groups that may be under-represented in the trial.
This may include considerations around geography, race, sex, age, and other
populations of interest.” (HFC Article: To be submitted)
Conclusions: Enhancing Clinical Study Diversity

Ensuring proper generalizability of clinical trial results:

Quality Research: *Active* rather than *Passive* Approaches are Needed

- **Establishing of enrollment targets in clinical trials, including proper engagement of often underrepresented populations**
  - Targets enlightened by the prevalence or incidence data for a disease or condition by demographic subgroup

- **Creative proactive approaches to increase ability to achieve targets**
  - Selection of sites that increase diversity of enrollees
  - Ensure adequate engagement of North American sites

- **Monitoring enrollment diversity throughout trial conduct**
  - Shared responsibilities of the study sponsor and the DMC
The FDA has made “critically important contributions” to the “pursuit and implementation of evidence-based approaches for the prevention & treatment of diseases” *

Session 3A: Approaches to Support the Inclusion of Underrepresented Populations and to Encourage Clinical Study Participation – Age, Race, Ethnicity, Sex, Pregnancy, and Lactation

Moderator: Larissa Aviles-Santa
Director, Division of Clinical and Health Services Research, NIMHD, NIH

Rose Blackburne
VP, Global Therapeutic Area Head, General Medicine & Women’s Health, Medical Science & Strategy (MSS) PPD, Thermo Fisher Scientific Company

Anne Lyerly
Professor of Social Medicine, The University of North Carolina at Chapel Hill

Michelle Kipke
Professor of Pediatrics, Associate VP of Strategic Health Initiatives, Keck School of Medicine, University of Southern California

Jennifer Jones-McMeans
Divisional VP of Global Clinical Affairs, Abbott

Dawn Corbett
Inclusion Policy Officer, Office of Extramural Research, NIH

Public Workshop to Enhance Clinical Study Diversity
FDORA Virtual Public Workshop to Enhance Clinical Study Diversity convened by CTTI and FDA
November 2023

Session 3A: Approaches to Support the Inclusion of Underrepresented Populations and to Encourage Clinical Study Participation – Age, Race, Ethnicity, Sex, Pregnancy and Lactation

Rose Blackburne, MD, MBA
Vice President, Global Head, General Medicine and Women’s Health, Medical Science and Strategy
PPD, part of Thermo Fisher Scientific

The world leader in serving science
Key Innovative Solutions to Address Diversity in Clinical Trials

- Targeted minority patient engagement plans
- Enhanced site and patient educational materials and decentralized trial tools
- Digital tools, SiteCoach, data-driven feasibility and site placement
- Protocol optimization, broadened and inclusive study design recommendations
- Patient concierge, travel and transportation reimbursement

Identified Barriers to Achieving Proper Diversity in Clinical Trials

- Historic lack of trust and cultural competency
  - Unconscious biased towards patients and their willingness to participate in clinical trials
- Limited health literacy and clinical trial awareness
  - Historic unethical clinical research practices
  - Varying levels of understanding, ICF reading level too high
- Limited access to clinical trials
  - Traditional sites lack proper training and experience recruiting minority patients
- Overly restrictive eligibility criteria and complicated protocol design
  - Eligibility criteria inadvertently excluding minorities due to comorbidities and lab values ranges
- Financial toxicity and burden in personal life
  - Distance to site, child/senior care, impact on work schedules, logistical cost
<table>
<thead>
<tr>
<th>Pre-Trial</th>
<th>Clinical Development</th>
<th>Filing, Approval &amp; Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

**Engaging communities and patients as partners**

- Inclusive and broadened study design
- Acknowledge and alleviate barriers to recruitment and retention
- Metrics & tracking with data-driven decision-making

*Sponsors should submit the Plan to the relevant IND application as soon as practicable during drug development but no later than when a sponsor is seeking feedback regarding the applicable pivotal trial(s) for the drug (often at the EOP2 meeting). The Plan can be submitted to the IND as part of a milestone meeting package, or on its own. ([FDA Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry](https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ConsiderationsforClinicalTrials/UnderrepresentedRacialAndEthnicPopulations/))
Engaging Communities and Patients as Partners

**Establish Rapport**
- Get to know community well ahead of a trial
- Attend/sponsor community events
- Host open house events for community members to tour research sites

**Build Shared Values**
- Host focus groups for patients and community members to share perspectives
- Establish patient advisory boards and steering committees
- Elicit feedback to understand the factors that impact recruitment and retention
- Invite community members and patient champions as consultants throughout the study lifecycle
- Use patient and community input to develop culturally appropriate health and research materials

**Support and Train**
- Thank-you letters for trial participation; disseminate study results to participants and community
- Collect feedback from patients and caregivers after participation has ended
- Maintain authentic relationships and stay involved in community

**Stay Involved**
Many populations are inadvertently excluded, including and not limited to:

- People with cognitive and physical disabilities
- People living with HIV, hepatitis
- People with co-morbidities
- People with substance use disorders
- Individuals with laboratory values that can vary by race and ethnicity (e.g., serum creatinine)

It is important to assess and broaden eligibility criteria where possible, to ensure certain populations are not unintentionally excluded.
Strategies must consider the languages and varying levels of health/digital literacy, broadband access for digital tools, and accessibility among potential participants to enable inclusive and equitable participation.
Collect and track relevant demographic data in real time (e.g., race and ethnicity, sex, socioeconomic measures) and conduct ongoing data-driven assessment.

For relevant studies, collection of sexual orientation and gender identity (SOGI) data should be considered:

- **Current gender identity** (Person’s current internal sense of gender.) “How do you describe yourself?”
- **Sex assigned at birth** (Sex perceived at birth based typically on genitalia and listed on their birth certificate.)
- **Sexual orientation** (Person’s romantic, relational and sexual orientation toward one or multiple genders.) “Do you think of yourself as …”

Clearly define and track KPIs to monitor program performance and refine strategies to effectively reach target patient populations.

### Sample KPIs: Monitoring and Measuring Program Performance

<table>
<thead>
<tr>
<th>KPI</th>
<th>Metric Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site has staff with language capabilities matching patients</td>
<td>Site has staff/translators to include diverse populations of the community (Spanish, Creole, Tagalog, Mandarin, etc.)</td>
</tr>
<tr>
<td>Site assessed for accessibility standards (mobility, sensory, vision, audio, etc.)</td>
<td>Site is inclusive of and accessible to patients with disabilities</td>
</tr>
<tr>
<td>Site staff trainings (e.g., unconscious bias, cultural competence, psychological safety)</td>
<td>Site (investigators, CRCs, etc.) participates in diversity training</td>
</tr>
<tr>
<td>Site staff demographics reflect community diversity demographics</td>
<td>Site staff demographics reflects the community they serve</td>
</tr>
<tr>
<td>Specific plan per site/study to enroll and retain diverse participants</td>
<td>Numerical, percentage or ratio recruitment goal set for ethnicity, gender unique to each site and the surrounding community that matches overall study recruitment goal</td>
</tr>
</tbody>
</table>

Everyone should be able to see themselves represented in clinical trial data collection, with no penalty for those who opt out of sharing their personal information.
Thank you

Ethical Considerations for Inclusion of Pregnant Persons in Biomedical Research

Anne Drapkin Lyerly, MD, MA
Professor, Departments of Social Medicine and Ob-Gyn
Center for Bioethics

Public Workshop to Enhance Clinical Study Diversity
Toward a Paradigm of Inclusion

**Second Wave Initiative**
- Toward the Responsible Inclusion of Pregnant Women in Medical Research

**PHASES**
- Pregnancy + HIV/AIDS: Seeking Equitable Study
  - Guidance launched July 2020

**PREVENT**
- Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies

**PREPARE**
- Promoting Equity for Pregnant Adolescents in REsearch

Highlighted harms of exclusion, research as ethical imperative

*FD_CUDA* Draft Guidance

Harms of Exclusion from Research

- Ineffective treatment
  - Undertreatment/toxicity, exposure to disease

- Inappropriate risk
  - Treatment unsafe for fetus or pregnant person

- Reticence
  - Avoidance of beneficial drugs

- Exclusion from beneficial trials
  - “Protected to death”
Barriers

- Drug development and approval pathway
- Risk reasoning
- Protectionism
- Legal and logistical challenges
- Lack of training and experience
- Justificatory asymmetry
- Myths and misconceptions
In a few words, what do you think is the greatest barrier to including pregnant women in clinical trials?
Conceptual Shifts Toward Inclusion

**Exclusion**

- *Vulnerable population*
- *Protection from research*
- *Presumptive exclusion*

**Inclusion**
Conceptual Shifts Toward Inclusion

**Exclusion**
- Vulnerable population
- Protection *from* research
- Presumptive exclusion

**Inclusion**
- Complex population
- Protection *through* research
- Fair inclusion
Ethical Foundations of Research in Pregnancy

Protection
from intervention-related risks

Access
to the benefits of new technologies

Respect
for pregnant people’s own health
Strategies to advance ethical inclusion

Affirm the need for research with pregnant populations.

Enhance training of those involved in conduct and evaluation of research.

Design for inclusion, integrating pregnant people and gathering pregnancy-specific data.

Evaluate for inclusion, and require justification for exclusion.

Center pregnant persons throughout the design, evaluation and conduct and reporting of trials.
Work from the PHASES and PREPARE Projects supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award number R01AI108368. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

hivpregnancyethics.org  
@pregnancyethics
Session 3B: Approaches to Support the Inclusion and Clinical Study Participation of Individuals with Disabilities Including Intellectual or Developmental Disabilities

Moderator: David Resnik
Bioethicist, National Institute of Environmental Health Sciences, NIH

Willyanne Decormier Plosky
Program Director, Multi-Regional Clinical Trials Center Harvard University

Kellie Malloy Foerter
VP, Global Trial Management, Immunology, Cardiovascular and Neuroscience, BMS

Ari Ne’eman
PhD Candidate, Harvard University

Alison Barkoff
Performing the Duties of the ACL Administrator and Assistant Secretary for Aging

Public Workshop to Enhance Clinical Study Diversity
Session 3B:
Approaches to Support the Inclusion and Clinical Study Participation of Individuals with Disabilities Including Intellectual or Developmental Disabilities

Public Workshop to Enhance Clinical Study Diversity
November 29, 2023
Disclaimer

• This material and opinions expressed here are not intended to represent the position of Brigham and Women's Hospital, Mass General Brigham, Harvard University, HHS, FDA, or any organization, institution, or entity.

• The MRCT Center is supported by voluntary contributions from foundations, corporations, international organizations, academic institutions, and government entities (see https://mrctcenter.org/), as well as by grants. We are committed to autonomy in our work and to transparency in our relationships.

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The MRCT Center is a research and policy center focused on addressing the conduct, oversight, ethics, and regulatory environment of clinical trials.

**Our Vision**

Improve the integrity, safety, and rigor of global clinical trials.

**Our Mission**

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.
“We are regular people. We should have the same health care as others.”

- 1 billion people and 240 million children globally have a disability.
- There are many different kinds disabilities. People can identify as having more than one.
- Federal laws like Section 504 of the Rehabilitation Act and Section 1557 of the Affordable Care Act (ACA) prohibit discrimination against people with disabilities and require equal access to healthcare.
- Diversity Action Plans are now required for Phase 3 and later trials. Guidance from the Food and Drug Administration (FDA) focuses on race and ethnicity but does mention disability. People with disabilities are the largest minority group in the US (1 in 4 adults; 1 in 3 Black and Hispanic adults).
Excluding People With Disabilities From Clinical Research: Eligibility Criteria Lack Clarity And Justification

- 99% of studies required informed consent.
- 85% allowed for investigator discretion to exclude people.
- Only 24% of the exclusions had a listed justification. The listed justifications were often very broad.
- People with cognitive and intellectual/developmental disabilities were excluded in 42% of overall studies (dementia, depression, diabetes, lung cancer), and in approximately 90% of dementia studies.

“We have the right to information in a way we can understand. Buildings must have a way for us to get in. We have the right to get the help we need.”

| 1. Be respectful | • Don’t assume: Ask, and practice active listening. Provide the opportunity for participants to take time to think and to ask for something to be repeated, rephrased, or expressed visually.  
• Respect autonomy, treat people with disabilities as capable adults, and speak directly to the individual (e.g., not to a family caregiver or supporter). When possible, keep your face and mouth visible. Treat physical aids as an individual’s personal space. Do not pet or walk beside service animals.  
• Ask the participant how they would prefer to be addressed (e.g., person-first language, identity-first language)(see Tool B1.1). Use plain [“every day” or easy-read] language. Use clear sentences, break down ideas, ask questions one at a time, and avoid medical jargon and acronyms.  
• Provide a quiet and relaxing environment. Avoid cell phones, computers, and ambient office noise and smells while communicating with the participant. |
|------------------|-------------------------------------------------------------------------------------------------|
| 3. Design for clarity and consistency | • Provide consistent labeling, terminology, and headers. Define terminology and any unusual words.  
• Supply instructions, reminders, and opportunity for easy error correction.  
• Use breadcrumbs (e.g. Home > Tools > Accessibility by Design Toolkit), mega menus (i.e. a dropdown menu or expandable navigation area that shows in |

“Society must break down the walls that keep us from having the same rights as everyone else. Discrimination is one wall.”

- Revise eligibility criteria in study protocols. Provide justification for exclusions.
- Expect to provide reasonable accommodations, and clearly state they will be available.

<table>
<thead>
<tr>
<th>Problematic</th>
<th>Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject is judged by (or is in the opinion of) the Investigator inappropriate for the study.</td>
<td>Subject is documented by the Investigator to be inappropriate for the study due to the following specific scientific, safety, or ethical reasons: [Specify] (e.g., subject has a cochlear implant and can’t complete the necessary MRI for safety reasons).</td>
</tr>
<tr>
<td>Subject has any condition that confounds the ability to interpret data from the study.</td>
<td>Subject has a physical or mental condition, as predetermined by the study team, that is expected to significantly impact study data interpretation: [Specify] Predetermination of significant impact is due to the following specific scientific reasons: [Specify] (e.g., subject has a condition documented to be associated with atypical enzyme [X] function).</td>
</tr>
<tr>
<td>Participant lacks capacity to consent for themselves.</td>
<td>Participant lacks the cognitive capacity to consent for themselves, as determined [when capacity is questionable] by a capacity assessment conducted with a supporter and any other accommodations desired by the participant.</td>
</tr>
</tbody>
</table>
**Supported Decision-Making**

**A Guide for Supporting Clinical Trial Participants With Cognitive or Communication Challenges**

People who take part in research are called **participants**. Supported decision-making is a strategy that lets participants choose **supporters** to assist them.

Supporters can be family members or friends. Others may be allowed, but it depends on the state law.

Supporters assist participants to learn more about the study and explain to researchers what they need and want.

**Q: What Can I Do?**

A supporter who is assisting with supported decision-making can:

- Discuss what actions might help the participant make decisions.
- Explain new things in easier ways for the participant, such as with stories or pictures.
- Work with the participant to think through the good and bad things about each option.
- Talk with the participant about their questions and concerns.
- Help access the participant’s health, financial, school, and other information. You can do this without a special “ok” (permission) if that is the rule in your state.
- If the participant needs or wants you to, help the participant tell the research team about their questions and decisions. Check that the research team understands.

---

- Supported decision-making.
- Participation as researchers: RE4ALL: Accessible Research Ethics Education for Community Research Partners. Available from: [https://re4all.org/](https://re4all.org/)
Thank you

Please note: All quotes in the slide headings were drawn from “We Have Human Rights” A Handbook for People with Developmental Disabilities. From the Harvard Law School Project on Disability. Available at: https://hpod.law.harvard.edu/pdf/we-have-human-rights.pdf
Closing remarks

Sally Okun
Executive Director,
Clinical Trials Transformation Initiative (CTTI)

Public Workshop to Enhance Clinical Study Diversity
Public Workshop to Enhance Clinical Study Diversity

November 29 – 30, 2023 / 10 a.m. – 2:00 p.m. EST
Meeting will begin at 10:00 a.m. EST
Day 2 Opening remarks

CDR Mathilda Fienkeng
Director, Division of Medical Policy Development
Office of Medical Policy
Center for Drug Evaluation and Research
FDA

Public Workshop to Enhance Clinical Study Diversity
Day 2 - Agenda

• Approaches to support the inclusion of individuals with mental illness
  – Approaches to enhance inclusion in clinical studies
  – Overcoming informed consent barriers

• Study elements that may enhance trial diversity
  o Decentralized studies
  o Digital health tools
  o Clinical endpoints
  o Biomarker selection
  o Study analyses

• Public dissemination of demographic enrollment data

• Community engagement

• Moving forward
A docket is open for the public to submit electronic or written comments related to the topics addressed during this workshop.

Link to provide comments to the docket
Docket Number: FDA-2023-N-2462
Comment Period Closes: January 29, 2024
Session 3C: Approaches to Support the Inclusion and Clinical Study Participation of Individuals with Mental Illness

Moderator: Paul Appelbaum
Professor of Psychiatry, Medicine & Law
Columbia University

Patricia Areán
Director, Division of Services and Intervention Research, NIMH

Allissa Torres
Director of Mental Health Equity, Mental Health America

Scott Kim
Senior Investigator, Department of Bioethics, NIH Clinical Center

Eric Lenze
Professor and Head, Department of Psychiatry, Washington University
School of Medicine

Public Workshop to Enhance Clinical Study Diversity
Including people with mental illnesses in clinical trials.

Patricia A. Areán, PhD.
Director, NIMH Division of Services and Interventions Research
Importance of inclusion

- Rates of mental illness in US adults is ~20%, with 7% suffering from severe mental illness. ¹
- People with diabetes are 2-3 times more likely to suffer from depression than those without diabetes; nearly half of people with bipolar disorder suffer from diabetes. ²⁻³
- 8-15% of people with cancer suffer from depression. ³
- 23% of people with epilepsy suffer from depression and anxiety. ⁴
- People with Autism also tend to suffer from many chronic health conditions.
Impact of mental illness on health.

• People with severe mental illness die 25 years earlier, with leading health cause being heart disease. ⁵

• Mild depression increases healthcare cost two-fold, and major depression three-fold, compared to those without depression. ⁶

• Mental illness can attenuate the effectiveness of physical health conditions (diabetes, heart disease). ⁶
People with mental health conditions often experience health care disparities and are very often excluded from clinical trials.  

• Lack of guidelines for clinicians.
• Limits to generalizability.
• Safety of drugs or devices ignores the risk to those with mental health risks.
• Is an example of discriminatory practice against a large group of people in the US.
Why do we exclude?

• Assumptions about capacity to consent to research.
• Concerns about retention rates or interrupted participation owing to hospitalization.
• Lack of guidance as to how to measure, monitor and manage psychiatric symptoms in the context of physical health.
• Institutional Review Board variation in whether people with mental illnesses are vulnerable populations.


Patricia Areán, PhD
Division Director NIMH Services and Interventions
patricia.arean@nih.gov
nimh.nih.gov
Follow NIMH on Social Media @NIMHgov
Session 4: Appropriate Use of Decentralized Studies, Digital Health Tools, and Other Trial Elements to Support the Inclusion of Underrepresented Populations in Clinical Studies

Moderator:
Craig Tendler
Vice President, Oncology Clinical Development, Diagnostics, & Global Medical Affairs Janssen

Craig Lipset
Co-Founder and Co-Chair, Decentralized Trials and Research Alliance

Laura Esserman
Professor of Surgery & Radiology, School of Medicine, University of California, San Francisco

Luther T. Clark
Deputy Chief Patient Officer, Merck

Alanna Morris
Associate Professor, Department of Medicine, Emory University School of Medicine

Ivor Horn
Director of Health Equity and Product Inclusion, Google

Public Workshop to Enhance Clinical Study Diversity
Appropriate Use of Decentralized Studies to Support the Inclusion of Underrepresented Populations

Craig H Lipset
@craigslist
30 November 2023

Views expressed do not necessarily represent my current affiliations
Decentralized Clinical Trials [DCT]: Defined

Clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites

- Inclusive of hybrid and fully-remote
- Create optionality and choice
- May be at home
- Or may be pharmacy, community centers, local health providers, pop-up sites, mobile units, etc.

FDA Draft Guidance: “Decentralized Clinical Trials for Drugs, Biological Products, and 2 Devices” May 2023
Decentralized Clinical Trials [DCT]: Defined

<table>
<thead>
<tr>
<th>Source</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Draft Guidance</td>
<td>...some or all of the trial-related activities occur at locations other than traditional clinical trial sites.</td>
</tr>
<tr>
<td>May 2023</td>
<td></td>
</tr>
<tr>
<td>EMA Recommendations</td>
<td>...using procedures conducted outside the traditional ‘clinical trial site’.</td>
</tr>
<tr>
<td>December 2022</td>
<td></td>
</tr>
<tr>
<td>CTTI</td>
<td>... those in which some or all study assessments or visits are conducted at locations other than the investigator site via any or all ...DCT elements.</td>
</tr>
<tr>
<td>DTRA</td>
<td>...utilizing technology, processes, and/or services that create the opportunity to reduce or eliminate the need for participants to physically visit a traditional research site.</td>
</tr>
<tr>
<td>IMI Trials@Home</td>
<td>...make use of digital innovations and other related methods to make them more accessible to participants; by moving clinical trial activities to the participant’s home or to other local settings this minimises or eliminates physical visits to a clinical trial centre.</td>
</tr>
</tbody>
</table>

**Different words / Same themes:**
- Umbrella term inclusive of hybrid and fully-remote approaches
- Represents a collection of decentralized methods and tools (both processes and technologies)
- Focus on providing options for participation outside of a traditional “site”
Reasons to Decentralize Trials

**Patient Factors**
- Experience & Access
- Representation & Equity

**Business Continuity**
- Maintaining trials in an unpredictable environment

**Sustainability**
- Support Green Trials and ESG commitments
Decentralized as a Tool for Diversity Plans

Rural / Frontier
Leverage DCT to manage distance

Underserved
Leverage DCT to address barriers with time & travel

Ability Issues
Leverage DCT to support those physically unable to reach a site
Decentralized Contributes to Access [but may also Unlocks the “HCP”]

Investigator Delegation of Activities

- When permitted by the trial protocol, investigators may delegate trial-related activities to local HCPs to perform trial-related procedures that require in-person interactions with trial participants.
- A critical consideration when delegating trial-related activities to local HCPs is the potential for variability in the approach across different practices.
- Videoconferencing and other technologies may be useful to allow investigators to oversee trial personnel performing activities described in the trial protocol at participants’ locations.

Documentation: Investigators, Subinvestigators, Local HCPs

- Drug trials (Form 1572)
  - When trial personnel contribute directly and significantly to the trial data, they should be included on Form FDA 1572 as subinvestigators.
  - Local HCPs (as defined in the draft guidance) should not be listed on Form FDA 1572 as subinvestigators. However, local HCPs should be included in a task log.
- For device trials, local HCPs are generally not considered investigators and should not be included in the IDE list of investigators. However, these local HCPs should be included in a task log.
More Investigators Can Bring More Diversity, But Does Not Address Equitable Access

Without addressing the barriers to stimulating referrals into research studies,

“More investigators” (diverse investigators in diverse communities) may help research sponsors enroll more diverse patients

But will not address equitable research access for all.

Access will still be based on serendipity.

For equitable access, we need all providers to have pathways to stimulate referrals

And the draft DCT guidance language on a role for HCPs in research is the right start.
Special Considerations for DCT to Support Diversity

**Not a silver bullet**
DCT supports access, but still require DAP to ensure representative patients are being invited to participate

**Digital divide**
Must ensure participation is feasible for those without technology or bandwidth and help support digital literacy

**General considerations**
- Representative patient insights
- Proper investigator oversight
- Appropriate role for HCPs
- Aspire to optionality and choice
- Patients should feel more connected to care and support
Research Community Resources for DCT at DTRA.org
The Wisdom Study

Laura Esserman, MD MBA
on behalf of the WISDOM consortium
Revolutionizing Breast Cancer Screening
to Ensure that tomorrow will be better than today
A Few Important Things to Know About Screening

• Screening every year vs every other year has gotten politicized

• Finding cancers under 2cm, equally treatable with identical outcomes
  • Stage 1 cancers HR+, molecularly low risk get endocrine therapy
  • Stage 1 cancers that are Her2+, TNBC- less aggressive

• Mortality is not impacted up to 2cm because of improvement in treatments and outcomes
Where Has Screening Fallen Short?

• 42,370 women still die every year despite screening
• We are not finding the fast growing tumors at earlier stages
  • In the I-SPY TRIAL (stage 2/3 cancers)- the vast majority are NOT screen detected
• We treat stage 0 cancers (DCIS) like stage 1 cancer (likely overtreatment)
• Call back rates are high (especially for women in the 40’s)
• We are not using the tools we have to PREVENT breast cancer
  • 276,480 diagnosed in 2021
Breast cancer is not a single disease
Rate of tumor progression explains benefit (lack of) from screening

More for the people who need it, less for those who do not
What is the solution? Improve our screening algorithm

✓ Integrate risk assessment, screening, and prevention

✓ Allow women to join regardless of where they get their care

✓ Test a strategy where everyone is not screened the same

✓ Improve identification of women at risk for fast growing and “interval” cancers (WISDOM 2.0)
Wisdom

(Women Informed to Screen Depending on Measures of risk)

A study of women aged 40-75 without a history of breast cancer that compares:

- Personalized breast screening
- Standard (annual) screening

Study Questions

1. Safety – Is it just as good at avoiding high risk cancers?
2. Morbidity – Will it reduce biopsies & false positives?
3. Prevention – Will it encourage prevention in high-risk women?
4. Acceptance – Is it accepted by women?
5. Value – Is it better?

Accrual ended February 2023; Read out of Trial Feb 2025; WISDOM 2.0 started July 2023
Personalized Screening Group

**RISK FACTORS**
- Mammogram
  - Breast density
- Health Questionnaire
  - Family history, comorbidities, previous biopsies, age, race/ethnicity
- Genomic profiling
  - 9 Gene Panel, SNPs
  - Saliva collection

**SCREENING RECOMMENDATIONS (based on risk)**
- **Guidelines-based Frequencies**
  - No screening until age 50
  - Every other year (biennial) mammograms
  - Annual mammograms
  - Annual mammograms + MRI

**ADDITIONAL SERVICES**
- (for highest risk cohorts)
  - 1:1 Breast Health Specialist
  - Breast Health Decisions Tool
WISDOM: Genetic testing

Family history is not the best way to find women who inherit a mutation-

We have a simple test to find these errors- rare but critical and we should look starting at age 30
How do patients participate?

Women enroll and participate online
- No requirement to travel to a recruitment center
- Study website wisdomstudy.org
- Mobile, tablets, computers

All study services are rendered virtually
- Breast Health Specialist available telehealth
- No additional visits

Provide information back to participants
- Deliver screening assignments and reports to personal participant account

Personal and Confidential
• Over 55k women across the US have joined
• Women from every state in the US
• Over 20,000 learned their genetic risk for breast cancer
• Over 2,000 learned they are at elevated risk and received counseling from us
• We’ve identified over 500 active cancers in women who didn’t know they had it
  • Self report highly accurate (based on registry, EMR)
Current risk models perform poorly in non-White groups

Decline in performance with increasing genetic divergence from the training population

In WISDOM- we have ancestry specific SNPs

Prediction accuracy relative to European ancestry for 17 quantitative traits
(Martin et al, 2019 Nat Genet.)
Low representation of non-White groups

Persons of European ancestry are ~16% of global population but make up 70% of risk studies

- Availability
- Accessibility
- Participation
Improvements in Racial and Ethnic Diversity

• Significant improvement in representation since 2020

• 1.7% Black/African American participants through 2019; in Q4 2022, WISDOM included over 16% Black/AA participants

• Overall study numbers show gradual improvement each quarter and year

<table>
<thead>
<tr>
<th>Year/Timeframe</th>
<th>White alone, non-Hispanic or Latino</th>
<th>Black or African American alone</th>
<th>American Indian and Alaskan Native alone</th>
<th>Asian alone, non-Hispanic or Latino</th>
<th>Native Hawaiian and Other Pacific Islander alone, non-Hispanic or Latino</th>
<th>Two or More Race, non-Hispanic or Latino</th>
<th>Hispanic or Latino</th>
<th>Unknown, Prefer not to answer, some other race not listed</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start-2019</td>
<td>81.4%</td>
<td>1.7%</td>
<td>0.2%</td>
<td>4.5%</td>
<td>0.2%</td>
<td>2.9%</td>
<td>7.9%</td>
<td>1.3%</td>
<td>21,399</td>
</tr>
<tr>
<td>2020</td>
<td>74.2%</td>
<td>4.2%</td>
<td>0.3%</td>
<td>6.0%</td>
<td>0.1%</td>
<td>3.4%</td>
<td>10.5%</td>
<td>1.3%</td>
<td>7,725</td>
</tr>
<tr>
<td>2021</td>
<td>73.4%</td>
<td>8.1%</td>
<td>0.3%</td>
<td>4.0%</td>
<td>0.1%</td>
<td>0.3%</td>
<td>10.1%</td>
<td>0.8%</td>
<td>10,053</td>
</tr>
<tr>
<td>2022</td>
<td>67.1%</td>
<td>11.9%</td>
<td>0.5%</td>
<td>4.6%</td>
<td>0.1%</td>
<td>3.7%</td>
<td>11.5%</td>
<td>0.8%</td>
<td>10,108</td>
</tr>
<tr>
<td>Q1 2023</td>
<td>57.9%</td>
<td>18.1%</td>
<td>0.1%</td>
<td>5.6%</td>
<td>0.7%</td>
<td>3.8%</td>
<td>12.2%</td>
<td>1.6%</td>
<td>1,076</td>
</tr>
<tr>
<td>All Time</td>
<td>75.3%</td>
<td>5.7%</td>
<td>0.3%</td>
<td>4.7%</td>
<td>0.2%</td>
<td>3.2%</td>
<td>9.5%</td>
<td>1.1%</td>
<td>50,300</td>
</tr>
<tr>
<td>US Population</td>
<td>60.1%</td>
<td>13.4%</td>
<td>1.3%</td>
<td>5.9%</td>
<td>0.2%</td>
<td>2.8%</td>
<td>18.5%</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>
Available in English and Spanish

• **Spanish**
  - Printed Materials
  - All study communications, questionnaires, education for high-risk participants, letters

• **Plain-language**
  - Materials tailored to make sure they are understandable to everyone
Supporting the Inclusion of Underrepresented Populations in Clinical Studies:
Clinical Endpoints & Study Analysis

FDA/CTTI Workshop to Enhance Clinical Study Diversity;
Session Number: 4
Appropriate Use of Decentralized Studies, Digital Health Tools, and Other Trial Elements
to Support the Inclusion of Underrepresented Populations in Clinical Studies

Thursday, November 30, 2023; 10:35-11:35 AM EST
Barriers to Inclusion in Clinical Trials

**Critical Barriers**
- Lack of Awareness
- Access
- Mistrust
- Logistical and Resource Constraints
- Shortage of Sites, Networks, and Investigators in Underrepresented Communities

**Key Stakeholders**
- Patients & Community Members
- Healthcare Providers
- Investigators
- Coordinators, Clinical Sites
- Sponsors


Clinical Trial Endpoints

Endpoints

- Measures designed to test the efficacy and safety of study medications (mortality, disease progression, other clinical events, measures of function, etc.)

Patient-Centered Endpoints

- Outcomes or measures relevant and meaningful to patients, aligned with patient preferences, needs, and priorities (quality of life, knowledge and satisfaction, caregiver burden, etc.)

“The Patient Matters in the End(point)”*

Patient engagement early in trial design, including identification of endpoints that matter to them, can help overcome critical barriers, including mistrust and SDOH, leading to more patient-centered trials, better participant recruitment, retention and outcomes

Patient Engagement, Community Partnerships, and Collaborations

Patient-Centered Research and Outcomes

- Patients, caregivers, and patient advocates advising on all aspects of the research, including patient-relevant, patient-centered endpoints and outcomes

Successful Patient/Community Engagement

- Establishing meaningful partnerships
- Demonstrating mutual benefits
- Collaborating early and often

Patient insights and feedback impacting study design and conduct
Enhancing Clinical Trial Relevance, Value, and Equity for Underrepresented Populations

Studying Relevance and Value

- Results relevant to and understood by participants and communities
- Consistency of treatment benefits and/or risk differences
- Participant experience and feedback to improve design of future trials

“Underrepresented groups acutely feel the disconnect between trial efficacy and real-world effectiveness both because they do not see themselves in trials and because under-representation can affect trial results”

Studying Attrition: Indicator of Social Vulnerability

- Representative clinical trials includes recruitment, enrollment, and equity in trial completion
- Differential attrition of participants can lead to bias and limit generalizability of results
- Participant attrition may be associated with financial resource strain and/or other vulnerability indicators, independent of race or gender
- Understanding differential attrition may help advance patient care, outcomes and equity

“...enrolling a diverse population provides the best opportunity for an informed analysis of important subgroups, illuminating potential signals of disproportionate benefit or risk...”

Shah SJ, Essien UR. Equitable Representation in Clinical Trials: Looking Beyond Table 1. Circ Cardiovasc Qual Outcomes. 2022 May;15(5).


Relationship Between Social Vulnerability Indicators and Trial Participant Attrition: Findings From the HVAVLE Trial


Equitable Clinical Trial Representation Beyond Recruiting and Enrollment: Gateway to Innovative Therapies

Advancing science, health care solutions, health outcomes, confidence in trial results and equity
Achieving Increased Clinical Trial Inclusion and Participation

Patient-Centered
• Patient and community awareness, education, training, partnerships and collaborations
• Achieving optimal outcomes with minimal added burden to patients
• Meaningful, ongoing patient engagement
• Earning and building trust and trustworthiness

Inclusive Study Design and Conduct
• Meaningful, relevant, measurable & equitable endpoints and outcomes for patients and communities

Sustainability
• Demonstration of benefits, implications and relevance of study findings for impacted individuals and communities
• Equitable representation beyond recruiting and enrollment
• Recognition and addressing social determinants of health (SDOH) and vulnerability indicators
Thank you
Session 5A: Post-Approval Dissemination of Clinical Study Enrollment Demographic Data to Public

Moderator: James Hildreth
President and CEO, Meharry Medical College

Paula Boyles
External Clinical Trial Data Sharing Program Lead, Pfizer

Cynthia Chauhan
Patient Representative/Advocate, Independent

Tarek Hammad
VP, Head of Medical Safety, Marketed Products, GPSE, Takeda Pharmaceutical Company

Barbara Bierer
Professor of Medicine, Center for Bioethics, Harvard Medical School

Public Workshop to Enhance Clinical Study Diversity
FDA / CTTI Workshop to Enhance Clinical Study Diversity

Post-Approval Dissemination of Clinical Study Enrollment Demographic Data to the Public

Presented by Paula Boyles
Health information equity helps improve patient outcomes

Health information equity is the sharing of information in a way that is accessible and understandable to all people, allowing everyone to reach their full potential for health.\(^1\)

Studies show that low health literacy (the degree to which individuals can understand and use information to inform health-related decisions)\(^2\) can increase mortality rates.\(^3-5\)

People with the knowledge needed to become actively engaged in their health care have better outcomes, according to research.\(^6\)

To achieve better health outcomes, we must produce patient-facing content that is easy to read, understand and act on.\(^7\)

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1Berkman https://doi.org/10.1002/aris.1442370112
Information Equity – Introduction to design Equity (umn.edu)
Health equity Leadership & Exchange Network, 2020

2What Is Health Literacy? | Health Literacy | CDC


6CDC: Patient Engagement | Health Literacy | CDC

The Pfizer Clinical Trials Ecosystem delivers a World Class consumer experience for Participants

**Information Seekers**

- PfizerClinicalTrials.com
- PfizerLink.com
- PfizerClinicalTrialAlumni.com

**Awareness → Education → Action**

**Former Participants → Get back**

- Pfizer will provide your study documents with information about your clinical trial's results when all participants have completed their trial. We also provide study results on PfizerClinics.com and summaries of the results in our Clinical Study Report

Additionally, for certain Pfizer-sponsored clinical trials, "Patient-Reported Outcomes" can be found by visiting your Pfizer clinical trial and using the search function. These are numerical descriptions of the changes and results that you have observed in response to taking a medication. Additionally, the study results are provided in understandable language and accessible to the general public.

- Share your story about being a Pfizer clinical trial participant.
Pfizer is committed to Health Equity via Participant Data Return

- **Fulfill our social contract** with participants by enabling response to any data requests and allowing patients to opt-in to data return.
- **Empower** participants with data based upon accepted health literacy principles to make more informed healthcare decisions by providing necessary context to their clinical trial data, and facilitate continued care beyond trial.
- **Maintain engagement** with participants to improve trial experience, and in turn optimize trial adherence and retention.

Clinical Trial Participants have demanded the ability to Access, Visualize, and Share their data, and Clinical Researchers have a responsibility to provide more Transparency and Engagement with participants.
Pfizer Clinical Trial Alumni Site (PCTA)

PfizerClinicalTrialAlumni.com is an opt-in portal that helps Pfizer clinical trial participants find information, resources, and data related to their current or prior study.

PCTA allows participants to feel connected to Pfizer and their trial, well after their study has completed.
TransCelerate's Individual Participant Data Return (iPDR) initiative is developing solutions to support flexible processes for the planned, intentional, and meaningful return of pre-defined individual data to participants who choose to receive it.

**Participant Data Return Resource Pack [PUBLICLY AVAILABLE]**
A document that provides access to a consolidated set of resources from across the clinical research ecosystem that can assist with returning individual data globally.

**Individual Participant Data Return Package [COMING SOON]**

**Considerations Guide**
Provides considerations for implementing the return of individual data.

**Template**
Provides a customizable template example of how a study team might capture important operational details for enabling individual data return at a study or program level.

**Socialization Presentation**
A presentation to educate key internal stakeholders of the potential value of returning participant data in clinical studies and to obtain support to operationalize within sponsor organization.
Conclusion

Common efforts across industry

Solutions are NOT “one size fits all”

Ensure we reach ALL populations globally
Session 5B: Community Engagement

Moderator: Tesheia Johnson  
Deputy Director and COO, Yale Center for Clinical Investigation

Ileana Pina  
Professor of Medicine, Thomas Jefferson University

B. Angeloe Burch, Sr.  
African American Community Collaborative, Inc.

Reed Tuckson  
Managing Director, Tuckson Health Connections, LLC

Perla Nunes  
Perla Nunes, Consulting

Billy Caceres  
Assistant Professor, Columbia University School of Medicine

Kali Zhou  
Assistant Professor of Clinical Medicine, Keck School of Medicine, University of Southern California

Public Workshop to Enhance Clinical Study Diversity
Enhance Clinical Study Diversity

The Role of Community

• The Definition of Community
  • Geographical
  • Racial
  • Ethnicity
  • Sex
  • Age

Whose responsibility to enroll or support diversity in clinical trials.

Need to bring the patients into the clinic environment prior to enrollment in clinical trials.

Pts in clinic make the best participants in RCT’s

Who to train?
Session 6: Moving Forward

Moderator: Nakela Cook
Executive Director, Patient-Centered Outcomes Research Institute

Peter Marks
Director, Center for Biologics Evaluation and Research, FDA

Jeff Shuren
Director, Center for Devices and Radiological Health, FDA

Peter Stein
Director, Office of New Drugs, Center for Drug Evaluation and Research, FDA

Marc Theoret
Deputy Director, Oncology Center for Excellence, FDA

Meghan McKenzie
Patient Inclusion and Health Equity, Chief Diversity Office, Genentech

Public Workshop to Enhance Clinical Study Diversity
Day 2 Closing Remarks

Karen Hicks
Deputy Director, Office of Medical Policy
Center for Drug Evaluation and Research
FDA
Public Workshop to Enhance Clinical Study Diversity

CLOSING REMARKS
Day 2

Karen A. Hicks, M.D., FACC
Deputy Director, Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration

November 30, 2023
FDA has a longstanding commitment to promote diversity in clinical trials

• Let’s not wait for Congress to pass additional legislation to move the needle
• Responsive guidelines that are informed by the community
• Engagement and communication
  – Sharing ideas
  – Sharing experiences
  – Sharing best practices
• Implementation of innovative approaches
  – “What got us here won’t get us there”
Patients First

• Acknowledge earned mistrust and establish trust
• Address the fear
• Invite patients to participate
• Simplify informed consent
• “Treat others the way YOU want to be treated”
• Create clinical trial environments that reflect love and care  
  – Warm blankets
  – Patient concierges (travel and transportation reimbursement, coordinate appointments, more)
• Eliminate the enrollment gaps  
  – Remuneration
  – Other strategies
• Meet patients where they are
• Shift paradigm from protecting patients from research to protecting patients through research
• Include patients and trial participants as trusted partners in research
Understand the Demographics and the Reasons

• All approached patients
  – Those not enrolled in the trial
    • Screen Failures
      – “Physician Discretion”
      – Scientific basis for exclusion/safety concern
    • Eligible patients that do not sign the informed consent
  – Those enrolled in the trial
    • Patients that discontinue from the trial or withdraw consent for participation
Monitor Enrollment Diversity throughout Trial Conduct

• Sponsors
  – Diversity Dashboards

• Data Monitoring Committees
Diversity is needed every step of the way

• FDA
• Industry
• Academic Institutions
• Institutional Review Boards
• Clinical Investigators
• Trial personnel
• Clinicians
• Participants
• Patient Advocacy Groups
• Health care systems
• Other members of the diversity community

Training and Education are Critical
FDA is committed to enhancing diversity in clinical trials

Our policies:

• Focus on the diversity of the population that will use the medical product, if approved
• Support a pragmatic approach
• Encourage the use of clinical trial designs that minimize complexity and reduce burden
• Leverage innovative “fit for purpose” technology
• Incorporate learnings from innovative trial designs and lessons learned from public health emergencies
• Promote fit-for-purpose approaches as well as innovations in design and technologies
• Encourage better informed consent process
• Facilitate the utilization of available healthcare infrastructure, processes, and workforce
To Achieve Meaningful Representation in Clinical Trials

It Takes a Village!
Post Comments to FDA Public Docket
FDORA Public Workshop to Enhance Clinical Study Diversity

A docket is open for the public to submit electronic or written comments related to the topics addressed during this workshop.

Link to provide comments to the docket
Docket Number: FDA-2023-N-2462
Comment Period Closes: January 29, 2024