MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

A USA perspective on diversity and inclusion

Barbara E. Bierer, MD
Professor of Medicine, Harvard Medical School
Faculty Director, MRCT Center
Director, Regulatory Foundations, Law and Ethics Program, Harvard Catalyst
bbierer@bwh.harvard.edu

3 October 2019 Australian Clinical Trials Conference

Australian Clinical Trials Alliance

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The MRCT Center

- Academic credibility
- Trusted collaborator
- Independent convener

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

Vision

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

How we work

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.

MRCT Center is affiliated with BWH and Harvard University

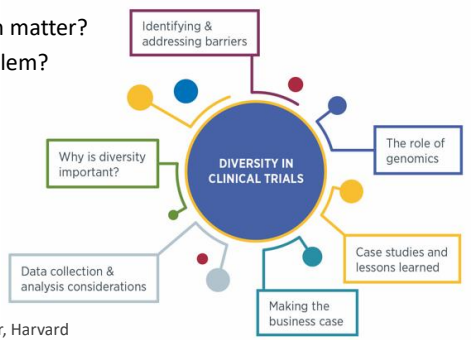
BRIGHAM AND WOMEN'S HOSPITAL

HARVARD UNIVERSITY

Agenda

- Introduction to MRCT Center
- Does diversity and inclusion matter?
- Do we (the US) have a problem?

  (By the way, the answer is yes)
- Approaches
- Solving for inclusion



Leadership:
- CAPT Richardae Araojo, FDA
- Barbara E. Bierer, MD, MRCT Center, Harvard
- Luther T. Clark, MD, Merck
- Milena Lolic, FDA
- David H. Strauss, MD, Columbia University

Diversity: a broad interpretation of the term

- Diversity
  - Demographic
    - Race, ethnicity, ancestry
    - Sex, gender
    - Age
    - Genetics
  - Non-demographic
    - Co-morbidities
    - Concurrent medications
    - Sexual and gender minorities
    - Differing axes of social determinants of disease
      - Economic status, Environmental factors, Education, Family size, etc.
    - Region (e.g. urban v rural, region and country)
    - Other extrinsic factors

Demographics impact responses to treatment: examples

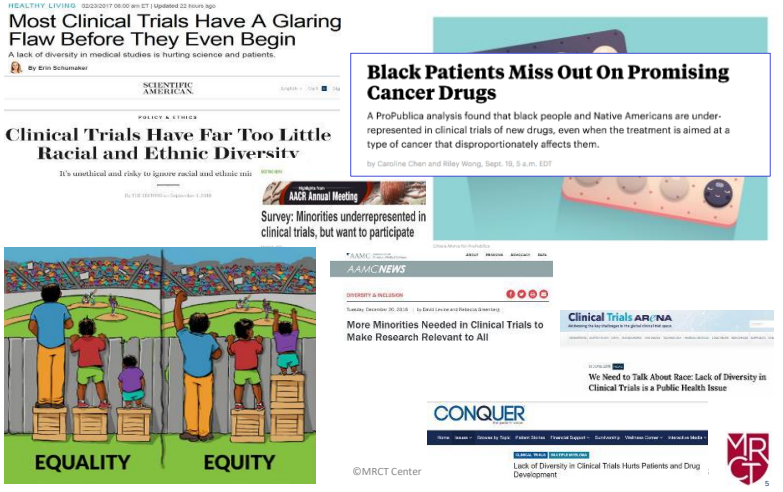
Demographics (age, sex, race), disease severity, disease duration, PK, comorbidities, concomitant drug use, etc. may affect responses to treatment.

Treatment	Response
BiDil (ISDN/Hydralazine)	VHeFT 1 and VHeFT 2 suggested; AHeFT demonstrated strong benefit in self-identified Blacks with heart failure; Explanation unknown
ACE Inhibitors	Hypertension in Blacks less responsive; Angioedema more common, greater risk
Clopidogrel	Less efficacious in persons with CYP2C19*2 or CYP2C19*3 allele; higher frequencies in East Asians, Native Hawaiians, other Pacific Islanders
Tamoxifen	Subgroup analysis may also be misleading; Original RCT suggested less efficacy in AA women; However, effective equally in AA and White women with ER-positive breast cancer

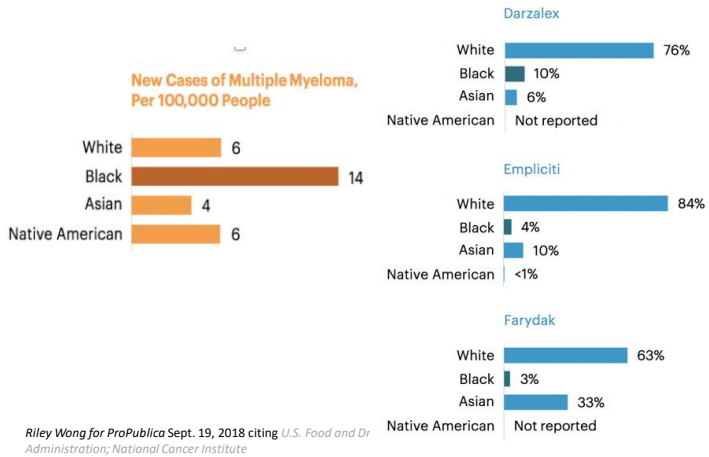
Not an academic question.
A question of heterogeneity of treatment effect.
A question of social justice and health equity.

Recent public attention, and not good news

Equity, not equality



Example
Multiple myeloma: Demographics and clinical trial drug development

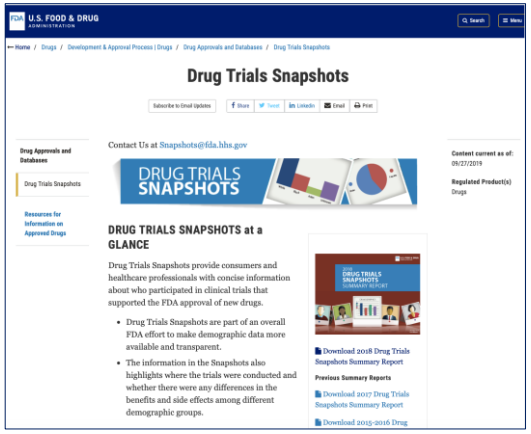


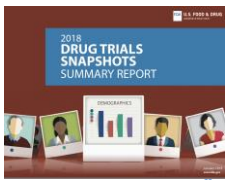
Riley Wong for ProPublica Sept. 19, 2018 citing *U.S. Food and Dr Administration; National Cancer Institute*

FDA: Clinically Relevant Enrollment

- FDA expectations are that sponsors enroll participants who reflect the **demographics for clinically relevant population**s with regard to age, gender, race, and ethnicity
- A **plan** to address inclusion of clinically relevant subpopulations should be submitted for discussion to the Agency at the earliest phase of development and, for drugs and biologics, no later than the end of the phase 2 meeting
- Inadequate participation and/or data analyses from clinically relevant subpopulations can lead to insufficient information pertaining to medical product safety and effectiveness for product labeling

How pervasive is the problem?





https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots

Drug Trials Snapshots: Summaries (2015)

	WOMEN	BLACK OR AFRICAN AMERICAN	ASIAN	WHITE	OTHER	AGE 65 AND OLDER	AGE 75 AND OLDER**	AGE 80 AND OLDER**
2015	40%	5%	12%	79%	4%	37%	15%	6%

Including AI/AN, NH/OPI, Unknown/Unreported

Between 2008 and 2013, 21% of new molecular entities approved by FDA, had racial or ethnic (or both) differences in safety, efficacy, pharmacokinetics or pharmacogenomics*

*Ramamoorthy A, Pacanowski MA, Bull J, et al: Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clin Pharmacol Ther 97:263-273, 2015; Frey WH. https://www.brookings.edu/blog/the-avenue/2018/03/14/the-us-will-become-minority-white-in-2045-census-projects/

* The percentages of the categories "American Indian or Alaska Native (AIAN)," "Native Hawaiian or Other Pacific Islander (NH/OPI)," and "Unknown/Unreported" were small enough that we combined them into the "Other" category for the purposes of this review.
**These particular subgroups were calculated as part of a Geriatrics Report and are not a regular feature of the Drug Trial Snapshots

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2016	48%	7%	11%	76%	7%	21%

	WOMEN	BLACK OR AFRICAN AMERICAN	ASIAN	WHITE	OTHER	AGE 65 AND OLDER
2017	55%	7%	11%	77%	14%	32%

	WOMEN	BLACK OR AFRICAN AMERICAN	ASIAN	WHITE	HISPANIC	AGE 65 AND OLDER
2018	56%	11%	10%	69%	14%	15%

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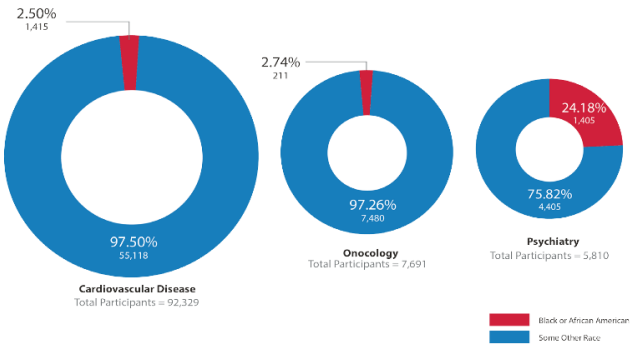
Participation of Black/AAs in Clinical Trials for Oncology, Cardiology, and Psychiatry



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2015-2016 FDA Global Participation in Clinical Trials Report; https://www.fda.gov/downloads/Drugs/InformationOnDrugs/UCM570195.pdf

Individual studies vary widely (2018)

BRAND NAME	INDICATION	WOMEN	WHITE	BLACK or AFRICAN AMERICAN	ASIAN	HISPANIC	AGE 65 and OLDER	UNITED STATES
KRINTAFEL	Prevention of malaria relapse caused by the parasite *Plasmodium vivax*	25%	2%	11%	19%	70%	2%	0%
XERAVA	Treatment of complicated intra-abdominal infections caused by bacteria	43%	98%	< 1	< 1	2%	30%	5%
LUCEMYRA	Treatment of symptoms associated with opioid withdrawal during abrupt opioid discontinuation.	28%	67%	22%	<1	17%	<1	100%

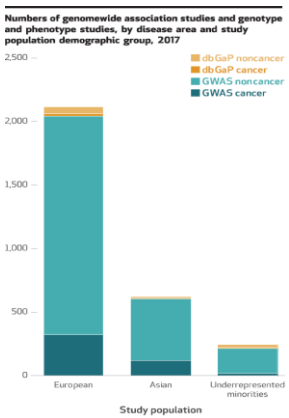
Questions arising

- What are the implications of underrepresentation for science and healthcare?
- How does underrepresentation challenge our notions of fairness/justice?
- What institutional, cultural, logistical, cultural factors are at play?
- Are remedies available and are remedies achievable?
  - Despite the *intention* to recruit diverse and representative study populations in order to detect such differences in drug metabolism, safety profile, or treatment outcome, this does not routinely occur.
  - Challenges including those related to recruitment, enrollment, and obtaining requisite statistical power limit most clinical trials from examining differences by *subgroup*.

Diversity Lacking In Genomic Databases

- Ethnic minorities underrepresented in genomic databases
- Lack of diversity affect understanding of the relationships of genes and disease in un- and under-studied populations
- Significant gaps in knowledge regarding potential health care disparities in genomic medicine and precision health remain
- Genomic databases need greater inclusion of diverse ancestral populations and ancestral information

Genomics and precision medicine may change our understanding of race and its utility in clinical practice and research. However, significant challenges exist that must be overcome for the promise of precision medicine to be realized.



Landry LG, Ali N, Williams DR, Rehm HL, Bonham VL. 37:5 Health Affairs 2018;37:5

A short list of challenges: real and perceived

Regulators/ Institutions/ Sponsors

Investigators/ Referring Physicians

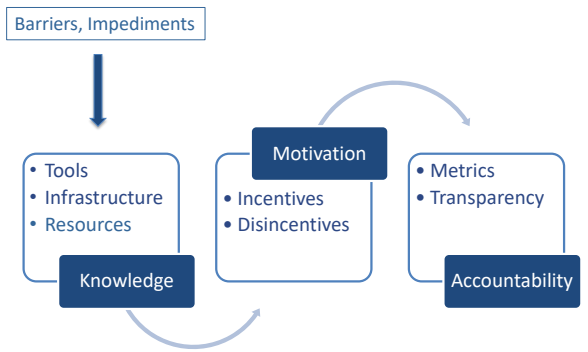
Research Staff

Data & Data Analysis

Patients// Communities

- Trial time and cost, inertial forces
- Uncertain scientific utility
- Inaccuracy of feasibility assessments
- Inadequate staffing and time constraints of PIs, staff
- Lack of continuous community engagement
- Recruitment and retention challenges
- Limited health literate communications
- Inclusion/exclusion criteria limiting enrollment
- Trial outcome measures of uncertain participant value
- Logistical issues of trial conduct
- Data collection variable
- Data analysis methodologies inconsistent
- Payment and other concerns
- Mistrust and distrust of research and clinical trials

Barriers, Impediments, Challenges ➡ Opportunities



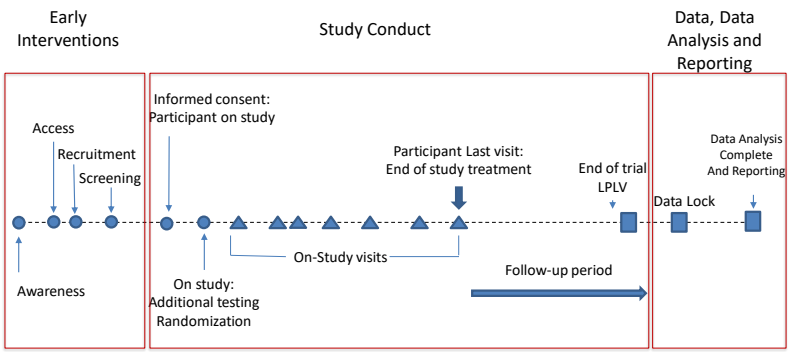
Work Group Members

Hayat Ahmed, MRCT Center
Richardae Araojo, FDA (Co-Chai
Salvatore (Salvo) Alesci, Takeda Pharmaceuticals International, Inc.
Maria Apostolaros, PhRMA
Barbara E. Bierer, MRCT Center, Brigham and Women's Hospital, Harvard Medical School (Co-Chair)
Racquel Bruton, Biogen
Elizabeth Cahn, Cancer Connection
Li Chen, Amgen
Luther Clark, Merck (Co-Chair)
Patrick Cullinan, Takeda Pharmaceuticals International, Inc.
Liza Dawson, NIAID/NIH
Theresa R. Devins, Boehringer Ingelheim Pharmaceuticals, Inc.
Anthony Edmonds, Takeda Pharmaceuticals International, Inc.
Rhonda Facile, CDISC
Rachael Fones, IQVIA
Anya Harry, GlaxoSmithKline
Melissa Heidelberg, Genentech/Roche
Quita Highsmith, Genentech/Roche
Aarthi B. Iyer, Kinetiq
Regina James, NIH/NIMHD
Jonathan Jackson, CARE Research Center, Massachusetts General Hospital
Tesheia Johnson, Yale Center for Clinical Investigation
Maria de Leon, DefeatParkinsons
Miiena Lolic, FDA (Co-chair)
Marcia Levenstein, Vivli
Roberto Lewis- Fernández, Columbia University
Eldrin Lewis, Brigham and Women's Hospital
Erin Muhlbradt, NCI-EVS & CDISC
Isabela Niculae, Biogen
Latha Palaniappan, Stanford University
Claude Petit, Boehringer Ingelheim Pharmaceuticals, Inc.
Claire Pigula, Biogen
Melissa Poindexter, Advances in Health
Nicole Richie, Genentech/Roche
Suzanne M. Rivera, Case Western Reserve University
Frank Rockhold, Duke Clinical Research Institute
Ricardo Rojo, Pfizer
Rosanne Rotondo, Novartis
Fabian Sandoval, Emerson Clinical Research Institute
Rick Sax, IQVIA
Hollie Schmidt, Accelerated Cure Project for Multiple Sclerosis
Karlin Schroeder, Parkinson's Foundation
Mary (Dicey) Scroggins, Pinkie Hugs, LLC
Lana Skirboll, Sanofi
Steve Snappin, formerly Amgen
Bhagyashree Sonwane, formerly MRCT Center
Stacy Springs, Bioethics Fellow at Harvard Medical School
David H. Strauss, MRCT Center, Columbia University (Co-Chair)
Sara Tadesse, Genentech/Roche
Anne Taylor, Columbia University Medical Center
Robert A. Winn , University of Illinois Cancer Center
Paul Underwood, Boston Scientific
Sarah White, MRCT Center (Co-Chair)
John Whyte, WebMD (Co-Chair)
Crispin Woolston, Sanofi
Honghui Zhou, Johnson & Johnson

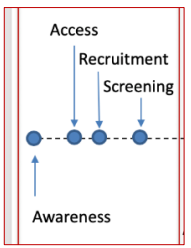
Product Development

- When in development phase should diversity be addressed?
- Concerns differ early in development, when little is known, versus Phase 3, versus post-marketing phase
- Real world data and observational studies should be considered in the continuum of understanding of the product
- Development and analysis of heterogeneity of treatment effect should be intentional and planned

Participant's Clinical Trial Journey



Early(ish) Interventions

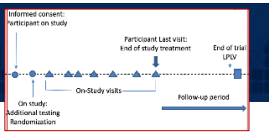


Deliverables:

- Statements of commitment
- Education and community engagement resources
- Clear communications
- Feasibility assessment measures
- Patient/participant engagement in trial design and planning
- Eligibility (inclusion/exclusion) criteria
- IRB tool for protocol evaluation

- Case Studies: investigational products, Successful interventions
- Business case(s) for inclusion
  Financial, incentives, disincentives
  Corporate responsibility, public good

Study conduct: Interventions



- Health literate communications and informed consent
- Study design and objectives that are relevant and meaningful to the population
- Logistical changes in study conduct
  - Bringing the trial to the participant (insofar as possible) & site location
  - Minimizing research procedures to absolutely necessary
  - Clinic hours outside of work hours and work days
  - Transportation arrangements
  - Childcare arrangements
  - Payment for reimbursable expenses and for time and burden of study
  - Disability access
  - Mobile technologies
- Post-trial access to medicines as necessary and referral for care
- Return of aggregate study results and, as possible, individual results
- Communication with referring physicians

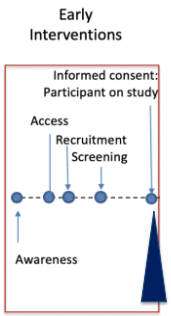
Transportation

Approach and Potential Solutions

- Problem recognition
- Review of existing transportation options for target populations.
- Ask participants directly about their transportation needs
- If necessary, ensuring access to or provision of reliable transport, including cost
  - Cost (pre-payment or reimbursement)
  - Parking
  - Public transportation (metro-card, vouchers)
  - Taxi (reimbursement)
  - Ride-sharing services
  - Site providing shuttle

  - May extend to family member or friend who will accompany participant

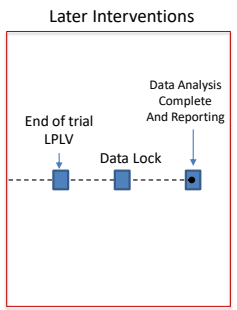
Preparing for Success in the Trial (PST): An onboarding tool



A protocol script for participant needs assessment after enrollment, envisioned as interaction with study coordinator

- How will you get to the clinic for your appointments? Can I help with that?
- Can we look at the calendar together?
- Who lives at home with you?
- Do you have someone that can help you at home?
- Is there someone we can contact if you are not available?
  - LINK to permissions form

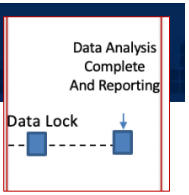
End of Study



Logistical considerations for End of Study:

- End of Study communication
- Post-trial access to medicines, as appropriate
- Referral for further care, as necessary
- Return of aggregate study results and, if/as possible, individual results
- Communication with referring physicians

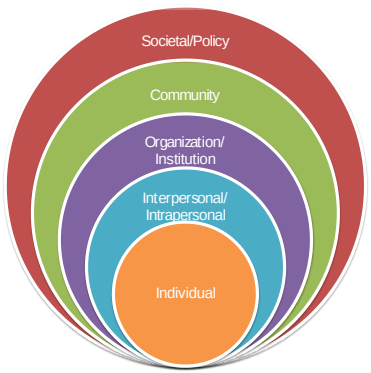
Data and Data Analysis: Interventions



- International agreement on definition of data elements
- Model methodologies of collection and data entry
  - Templates for data collection
- Genomic data (or samples) collected from diverse populations
- Robust PK/PD studies as indicated
- Development of novel approaches to and methods of data analysis
- Agreement on results reporting
- Commitment to data sharing (aggregate, individual participant data) to allow secondary analyses of pooled datasets
- Post-trial monitoring of real world data
- Research agenda
- Iterative progress

Patient Engagement

- Education
- Engaging patients in trial design and development
- Understanding patient experiences, perceptions, and preferences
- Culturally and linguistically competent strategies
- Community engagement
- Build and consistently maintain trust



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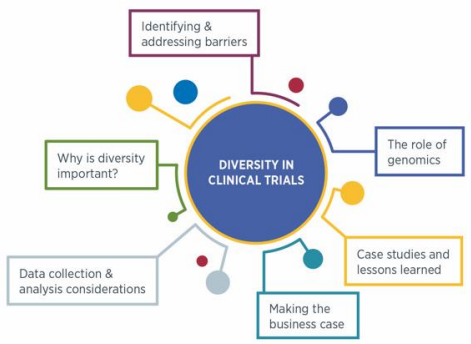
Comprehensive deliverables



MRCT Center
14 Story Street, 4th Floor, Cambridge,
MA 02138, USA
Telephone: (617) 496-9807
Email: mrct@bwh.harvard.edu

Barbara E. Bierer, MD
bbierer@bwh.harvard.edu

Mark Barnes, JD
Mark.Barnes@ropesgray.com

Sarah White, MPH
sawhite@bwh.harvard.edu