A USA perspective on diversity and inclusion

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Disclaimer:

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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.
Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.
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 (age, sex, race), disease severity, disease duration, PK, comorbidities, concomitant drug use, etc. may affect responses to treatment.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>BiDil (ISDN/Hydralazine)</td>
<td>VHeFT 1 and VHeFT 2 suggested; AHeFT demonstrated strong benefit in self-identified Blacks with heart failure; Explanation unknown</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>Hypertension in Blacks less responsive; Angioedema more common, greater risk</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Less efficacious in persons with CYP2C19<em>2 or CYP2C19</em>3 allele; higher frequencies in East Asians, Native Hawaiians, other Pacific Islanders</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>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</td>
</tr>
</tbody>
</table>

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

Black Patients Miss Out On Promising Cancer Drugs

A ProPublica analysis found that black people and Native Americans are under-represented in clinical trials of new drugs, even when the treatment is aimed at a type of cancer that disproportionately affects them.

by Caroline Chen and Riley Wong, Sept. 19, 5 a.m. EDT
## Multiple myeloma: Demographics and clinical trial drug development

### New Cases of Multiple Myeloma, Per 100,000 People

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>6</td>
</tr>
<tr>
<td>Black</td>
<td>14</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
</tr>
<tr>
<td>Native American</td>
<td>6</td>
</tr>
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</table>

### Darzalex

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>76%</td>
</tr>
<tr>
<td>Black</td>
<td>10%</td>
</tr>
<tr>
<td>Asian</td>
<td>6%</td>
</tr>
<tr>
<td>Native American</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

### Empliciti

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>84%</td>
</tr>
<tr>
<td>Black</td>
<td>4%</td>
</tr>
<tr>
<td>Asian</td>
<td>10%</td>
</tr>
<tr>
<td>Native American</td>
<td>&lt;1%</td>
</tr>
</tbody>
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### Farydak

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>63%</td>
</tr>
<tr>
<td>Black</td>
<td>3%</td>
</tr>
<tr>
<td>Asian</td>
<td>33%</td>
</tr>
<tr>
<td>Native American</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
FDA: Clinically Relevant Enrollment

- FDA expectations are that sponsors enroll participants who reflect the demographics for clinically relevant populations 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?

Drug Trials Snapshots

DRUG TRIALS SNAPSHOTS at a GLANCE

Drug Trials Snapshots provide consumers and healthcare professionals with concise information about who participated in clinical trials that supported the FDA approval of new drugs.

- Drug Trials Snapshots are part of an overall FDA effort to make demographic data more available and transparent.
- The information in the Snapshots also highlights where the trials were conducted and whether there were any differences in the benefits and side effects among different demographic groups.

Contact Us at Snapshots@fda.hhs.gov

https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots
**Drug Trials Snapshots: Summaries (2015)**

<table>
<thead>
<tr>
<th></th>
<th>WOMEN</th>
<th>BLACK OR AFRICAN AMERICAN</th>
<th>ASIAN</th>
<th>WHITE</th>
<th>OTHER</th>
<th>AGE 65 AND OLDER</th>
<th>AGE 75 AND OLDER**</th>
<th>AGE 80 AND OLDER**</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>40%</td>
<td>5%</td>
<td>12%</td>
<td>79%</td>
<td>4%</td>
<td>37%</td>
<td>15%</td>
<td>6%</td>
</tr>
</tbody>
</table>

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*


* The percentages of the categories “American Indian or Alaska Native (AI/AN),” “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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<td>40%</td>
<td>5%</td>
<td>12%</td>
<td>79%</td>
<td>4%</td>
<td>37%</td>
</tr>
<tr>
<td>2016</td>
<td>48%</td>
<td>7%</td>
<td>11%</td>
<td>76%</td>
<td>7%</td>
<td>21%</td>
</tr>
<tr>
<td>2017</td>
<td>55%</td>
<td>7%</td>
<td>11%</td>
<td>77%</td>
<td>14%</td>
<td>32%</td>
</tr>
<tr>
<td>2018</td>
<td>56%</td>
<td>11%</td>
<td>10%</td>
<td>69%</td>
<td>14%</td>
<td>15%</td>
</tr>
</tbody>
</table>

* The percentages of the categories “American Indian or Alaska Native (AI/AN),” “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.
Participation of Black/AAs in Clinical Trials for Oncology, Cardiology, and Psychiatry

- **Cardiovascular Disease**: Total Participants = 92,329, 2.50% (1,415) Black or African American, 97.50% (55,118) Some Other Race
- **Oncology**: Total Participants = 7,691, 2.74% (211) Black or African American, 97.26% (7,480) Some Other Race
- **Psychiatry**: Total Participants = 5,810, 24.18% (1,405) Black or African American, 75.82% (4,405) Some Other Race

Individual studies vary widely (2018)

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

- 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
Work Group Members

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Li Chen, Amgen
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Rhonda Facile, CDISC
Rachael Fones, IQVIA
Any Harry, GlaxoSmithKline
Melissa Heidelberg, Genentech/Roche
Quita Highsmith, Genentech/Roche
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Latha Palaniappan, Stanford University
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Claire Pigula, Biogen
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Crispin Woolston, Sanofi
Honghui Zhou, Johnson & Johnson

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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 Interventions
- Access
- Recruitment
- Screening
- Awareness

Study Conduct
- Informed consent: Participant on study
- On study: Additional testing Randomization
- On-Study visits
- Participant Last visit: End of study treatment
- Follow-up period
- End of trial LPLV

Data, Data Analysis and Reporting
- Data Lock
- Data Analysis Complete And Reporting

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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
  o Bringing the trial to the participant (insofar as possible) & site location
  o Minimizing research procedures to absolutely necessary
  o Clinic hours outside of work hours and work days
  o Transportation arrangements
  o Childcare arrangements
  o Payment for reimbursable expenses and for time and burden of study
  o Disability access
  o 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
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
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
Comprehensive deliverables

- Identifying & addressing barriers
- Why is diversity important?
- Data collection & analysis considerations
- The role of genomics
- Case studies and lessons learned
- Making the business case