A2: Does Diversity Matter in the Conduct of a Clinical Trial?
Owen Garrick and Barbara Bierer
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Disclosure: Barbara E. Bierer, MD

I have no relevant personal/professional/financial relationship(s) with respect to this educational activity

Other than a personal and professional commitment to the topic
Learning Objectives

1. Explore lessons that can be extrapolated into how to build a diverse research community
2. Discuss what a good academic/community research partnership looks like
3. Contemplate an example of a necessary use of deception in research
4. Explore diverse representation in clinical trials
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Background: Statement of the problem

- Efficacy and safety of drugs and biologics can vary depending on intrinsic and extrinsic ethnic factors.
  - sex, gender, age, race and ethnicity, genomic background, social determinants of health (socioeconomic status, level of education, lifestyle, diet, geographic region, etc.)

- Regulatory approvals for investigational products are based on carefully designed, usually blinded, randomized clinical trials
  - But study populations do not reflect diversity in a manner that permits analysis of treatment outcome by subgroup
  - When these subgroups are represented, the sample sizes are often too small for robust analysis
  - The failure to achieve meaningful diversity limits information about drug response and measures of safety and efficacy in the underrepresented populations

- Lack of diversity is challenge to access to medicines, inclusion, and public trust

Imprecise use of race and ethnicity data as population descriptors in genomics research has the potential to miscommunicate the complex relationships among an individual’s social identity, ancestry, socioeconomic status, and health, while also perpetuating misguided notions that discrete genetic groups exist.

The challenge that scientists and medical journal editors must address is how to report human genomic variation without inappropriately describing racial and ethnic groups as discrete population groups. It will be necessary to build consensus about how race and ethnicity data should and should not be used in biomedical research and publications.
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

“The very relationship of race to drug development is fraught with controversy. Race is primarily seen as a social concept, rather than as a product of measurable biological traits. Yet there’s growing evidence that, whether for environmental or genetic reasons, drugs may have different effects on different populations.”

“Pharmaceutical companies contacted by ProPublica all said diversity in clinical trials is important to ensure that drugs meet patients’ needs. The issue “is not elevated high enough in the discussion on clinical studies,” said John Maraganore, chair of the industry group Biotechnology Innovation Organization. But he added that enrolling minorities is challenging, often for reasons beyond the manufacturer’s control, and that it would require a ‘public-private partnership, working with the FDA and NIH [National Institutes of Health].’ ”

https://www.propublica.org/article/black-patients-miss-out-on-promising-cancer-drugs
“Sex is recognized implicitly as an important factor in clinical research. More work is needed to standardize the way sex and gender are reported and elucidate the way these characteristics function independently and together to influence health and health care.”
Ethical Principles Underpinning Attention to Diversity

- **Respect for persons**
  "Incorporates two ethical convictions: 1) individuals should be treated as autonomous agents, and 2) persons with diminished autonomy are entitled to protection"

- **Beneficence**
  “an obligation to not harm and to maximize possible benefits and minimize possible harms”

- **Justice**
  “fairness in distribution” on who bears the burdens and who receives the benefits of research
Ethical foundation

The concept of justice and fairness as *access to the benefits* of research for subgroups who have been understudied, whether systematically or incidentally, is at the core of current concerns about diversity in clinical trials. Further, given the (unintended) exclusion of certain populations, we argue that reparative justice—to confront the harm done and transcend historical inequity—may serve to restore that equity and, importantly, the health for all individuals.
Multiple Directives (1)

U.S. Food and Drug Administration

- While there is no statutory or regulatory requirement to include demographic subgroups as participants in clinical trials, FDA guidance recommends and regulations require that the sponsors or applicants submit:
  1) Data on enrollment of demographic subgroups (including race) in Investigational New Drug (IND) annual reports
  2) Analyses of safety and effectiveness data by demographic subgroups in the new product applications.¹

- 2016: The Year of Diversity in Clinical Trials

Multiple Directives (2)

National Institutes of Health Guidelines

- NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research
  The purpose of this Notice is to inform the research community that NIH is amending its NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research to include a requirement that recipients conducting applicable NIH-defined Phase III clinical trials ensure results of valid analyses by sex/gender, race, and/or ethnicity are submitted to Clinicaltrials.gov.

- Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects
  The purpose of this Notice is to inform the research community that NIH is revising its NIH Policy and Guidelines on the Inclusion of Children. Changes to the policy include (1) the applicability of the policy to individuals of all ages, including children and older adults; (2) clarification of potentially acceptable reasons for excluding participants based on age; and (3) a requirement to provide data on participant age at enrollment in progress reports.

Extent of the problem

- Treatment outcomes may vary significantly between patient subgroups.

- According to a recent review approximately one-fifth of new drugs approved by the FDA between 2008-2013 demonstrated differences in exposure and/or response across racial/ethnic groups, translating to population-specific prescribing recommendations in a few cases.¹

  - Pharmacokinetic and pharmacodynamic differences across different racial/ethnic groups may lead to different dosing recommendation.

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FDA Drug Trials Snapshots

WHAT IS THE PURPOSE OF DRUG TRIALS SNAPSHOTS?

Drug Trials Snapshots provide consumers with information about who participated in clinical trials that supported the FDA approval of new drugs. The information provided in these Snapshots also highlights whether there were any differences in the benefits and side effects among sex, race and age groups. Drug Trials Snapshots is part of an overall FDA effort to make demographic data more available and transparent.

HOW TO USE SNAPSHOTS:

Each Snapshot contains information about the drug in a question and answer format. At the end of each section of the Snapshot, there is a shaded bar with the words “MORE INFO”. Click the “MORE INFO” bar for more technical and detailed content. At the bottom of each Snapshot, there is a link to the drug’s Package Insert as well as the medical review.

LIMITATIONS OF SNAPSHOTS:

www.fda.gov/drugtrialssnapshot
**Geography**

**Where are Participants From?**

The country contributing the most clinical trial participants was the United States. Compared to the population of the entire world (7.4 Billion), the US (0.35 Billion) makes up a little more than 4% of the world population.

**Trial Participants by US vs Non-US**

Total Participants = 131,749

- United States: 31%
- Rest of World: 69%

**Population of US vs Non-US**

Total People = 7,403,227,777

- United States: 4%
- Rest of World: 96%
Gender

How does Gender Participation differ by Geographic Location?

Gender composition at non-US sites was majority male, whereas gender composition at US sites was closer to 50:50.

Global
Total Participants = 131,747*
*Gender missing for 2 US participants

Rest of the World
Total Participants = 90,914

United States
Total Participants = 40,833
How does Racial Participation differ by Geographic Location?

The majority of Asian trial participants were at non-US sites. The representation of Black or African American participants at US sites is similar to the US general population, which is 13% Black or African American (2011-2015 Census).
Participation of Black/AAs in Clinical Trials for Oncology, Cardiology, and Psychiatry

- **Cardiovascular Disease**
  - Total Participants = 92,329
  - 97.50% (55,118)
  - 2.50% (1,415)

- **Oncology**
  - Total Participants = 7,691
  - 97.26% (7,480)
  - 2.74% (211)

- **Psychiatry**
  - Total Participants = 5,810
  - 75.82% (4,405)
  - 24.18% (1,405)
Examples of recommendations provided in the FDA-approved product labeling that are directed at specific races/ethnicities*

<table>
<thead>
<tr>
<th>Recommendation in FDA approved Labelling</th>
<th>Example Drug</th>
<th>Racial/Ethnic Information in the Labeling</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicated for a specific racial population</td>
<td>Isosorbide dinitrate/hydralazine</td>
<td>Indicated for self-identified blacks</td>
<td>Based on retrospective analyses, an effect on survival was supported in blacks, with little evidence to suggest effect in whites</td>
</tr>
<tr>
<td>Contraindicated in case of G6PD deficiency which is present in a higher frequency in specific racial populations</td>
<td>Rasburicase</td>
<td>Contraindicated in G6PD deficiency. Screen patients at a higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting therapy</td>
<td>Recommendations to screen patients at a higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting therapy because of the increased risk of hemolysis in patients with G6PD deficiency</td>
</tr>
<tr>
<td>Warnings and precautions directed at a specific racial population</td>
<td>Carbamazepine</td>
<td>Boxed warning for HLA-B*1502 in Asian Patients</td>
<td>Incidence of adverse event and prevalence of genetic factor are higher in Asian Populations</td>
</tr>
<tr>
<td>Recommendations for considering alternative therapy for a specific racial population</td>
<td>ACE inhibitors or Angiotensin II antagonists, e.g., candesartan and losartan</td>
<td>A general statement for African-American/blacks in the labeling of a number of drugs belonging to this class because of the smaller effect size observed</td>
<td>Pathophysiologically, hypertension is driven less by renin-angiotensin-aldosterone system in African-Americans/Blacks</td>
</tr>
<tr>
<td>Different dosing recommendation for a specific racial population</td>
<td>Rosuvastatin</td>
<td>Lower initial starting dose in Asians</td>
<td>Based on clinical observation of ~2 fold higher exposure in Asians compared to Caucasians</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td>Higher dose in African-American transplant patients</td>
<td>Based on clinical observation; metabolized by CYP3A5 and African-American/Black populations have low prevalence of reduced function variants compared to Caucasians</td>
</tr>
</tbody>
</table>

Sex Differences in Adverse Event Reporting

• Sex-related differences in the frequencies of adverse events reporting may be due to pharmacokinetic or pharmacodynamic factors, polypharmacy, or differences in reporting patterns.

• Males and females may differ in specific drug pharmacokinetics and pharmacodynamics. It is, therefore, essential to understand those sex differences in drug disposition and response, as they may affect drug safety and effectiveness.

### Table 4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacokinetic parameter</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>Area under the concentration-time curve</td>
<td>The concentration-time profile is larger in women, suggesting greater therapeutic and potential side effects</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Clearance, half-life</td>
<td>Aspirin is cleared more rapidly from women</td>
</tr>
<tr>
<td>Benzylamine</td>
<td></td>
<td>Following transdermal absorption, women excrete 3 times more than men</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>Oral clearance lower in women, lower volume of distribution in women resulting in higher systemic exposure</td>
<td>The greater reduction in blood pressure in women was due to pharmacokinetic and not pharmacodynamic differences</td>
</tr>
<tr>
<td>Atenolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Clearance</td>
<td>Clearance is decreased in women</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Clearance</td>
<td>Clearance is lower in women</td>
</tr>
<tr>
<td>Cipodoxine</td>
<td>Clearance</td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
<td></td>
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<tr>
<td>Cephradine</td>
<td></td>
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<tr>
<td>Clozapine</td>
<td></td>
<td></td>
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<tr>
<td>Diazepam</td>
<td>Plasma binding</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>Volume of distribution, clearance, and first-pass metabolism</td>
<td>When ethanol is ingested, men metabolize more in first pass metabolism; in addition the volume of distribution is smaller in women</td>
</tr>
<tr>
<td>Ferrous Sulfate</td>
<td>Absorption</td>
<td></td>
</tr>
</tbody>
</table>
Scientific/biological issues

- PK differences
- Pharmacogenomic differences: Racial/ethnic differences in genetic alleles or mutations
- Functional variants are common for phase I drug metabolizing cytochrome P450s, phase II enzymes, drug transporters, and genes associated with drug response
- Other

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.

- Academic credibility
- Trusted collaborator
- Independent convener
Define guiding ethical principles, establish standards of approach and practice, and explore solutions to common scientific and sociocultural barriers to meaningful diversity in clinical trials.

Convene a workgroup of diverse stakeholders

- Academic
- Industry
- Non-profit
- Patients and advocates
- Regulatory officials

Moving the needle?
Barriers to Recruitment, Enrollment and Retention
Barriers to participation

- Costs of participation
- Inadequate reimbursement
- Lack of child care support or services
- Research visits schedule
- Research center feasibility
- Research center location
- Other

- Inclusion/Exclusion criteria that exclude diverse populations
- Unconscious bias

**Awareness**
- Language barriers and inadequate translation
- Low health and research literacy among underserved communities
- Cultural differences
- Lack of community engagement
- Research advertisements fail to reach populations

**Access**
- Poor/Inconsistent relationship between underserved communities and researchers
- Deep mistrust of academic medical research model
- Lack of cultural competency and representation among research faculty and staff
- Perceived operational/timeline costs to having representation mimicking general population
Workgroup:
Diverse representation in clinical trials

Issues approached by workgroup

- Identifying & Addressing Barriers
- The Role of Genomics
- Why diverse representation is important
- Case Studies & Lessons Learned
- Making the Business Case
- Collection & Analysis Consideration

Diversity in Clinical Trials
Questions?
Thank You