#### **Evolving science in clinical trials in special populations**

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# Agenda

- Introduction to MRCT Center
- Does diversity and inclusion matter?
- Do we (the US) have a problem? (By the way, the answer is yes)
- Barriers and approaches
- Solving for inclusion

(A meta-regulatory perspective)

• Evaluation of diversity in safety



#### Leadership:

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- Barbara E. Bierer, MD, MRCT Center, Harvard
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- Milena Lolic, FDA
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### **Our Mission**

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





- Academic credibility
- Trusted collaborator
- Independent convener



# 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, Weight, etc.
    - Region (e.g. urban v rural, region and country)
    - Other extrinsic factors
- Diverse populations may be underrepresented in research and underserved, but are not necessarily vulnerable populations (who are also underrepresented in research and underserved.)

#### Focus on inclusion



## Today's perspective

- In this context, diverse representation in clinical trials is important for many reasons
  - Biological response to interventional therapies (heterogeneity of treatment effect)
  - Health equity
  - Trust in the system
- Focus today on variability of biological responses by subgroup, the principal regulatory concern
- Responses are impacted by both demographic, genetic, and non-demographic factors:
  - Race/ethnicity (e.g. BiDil, ACE inhibitors)
  - Genetic (e.g. Clopidogrel)
  - Non-demographic (e.g. polypharmacy, comorbidities, etc).
- Product development should focus on population for whom the intervention is intended.



# Demographics and clinical trial drug development: one example





# **Drug Trials Snapshots: Summaries**

	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%



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 (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



#### <sup>29</sup> https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots

# Drug Trials Snapshots: Summaries (2015 - 2018)

	WOMEN	BLACK OR AFRICAN AMERICAN	ASIAN	WHITE	OTHER	AGE 65 AND OLDER
2015	40%	5%	12%	79%	4%	37%
	WOMEN	BLACK OR AFRICAN AMERICAN	ASIAN	WHITE	OTHER	AGE 65 AND OLDER
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	HISPANI C	AGE 65 AND OLDER
2018	56%	11%	10%	69%	14%	15%



FDA Guidance Recruitment plan "for discussion" required by end Phase 2

#### Improvement over time, but variability exists. Data transparency is helpful.



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# Participation of Black/AAs in Clinical Trials for Oncology, Cardiology, and Psychiatry (2015-2016)



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



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# **Diversity Lacking In Genomic Databases**

- Ethnic minorities underrepresented in genomic databases
- Lack of diversity impacts understanding of the relationships of genes and disease in under-served and under-studied populations
- 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. Numbers of genomewide association studies and genotype and phenotype studies, by disease area and study population demographic group, 2017



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



# Work Group Members

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# A short list of challenges: real and perceived



Regulators/ Institutions/ Sponsors



Investigators/ Referring Physicians





Data & Data Analysis



Patients// Communities

- Regulatory expectations for review and approval variable
- Uncertain scientific utility
- Inclusion/exclusion criteria limiting enrollment
- Data collection and reporting variable
- Data analysis methodologies inconsistent
- Inaccuracy of feasibility assessments
- Inadequate staffing and time constraints of PIs, staff
- Trial time and cost, inertial forces
- Recruitment and retention challenges
- Limited health literate communications and education
- 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



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Research Staff







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# Participant's Clinical Trial Journey



Patient Engagement Study Design Data standards **Community Engagement** Informed consent simplification Standardized data collection Education & Health Literacy Post-trial access to medicines Logistical issues **IRB** Tools Decentralized and siteless trials End of study communications Feasibility Assessment Return of results Payment Transportation, Child care, etc. **Eligibility Criteria** Referring physician engagement



# Data, Data Analysis, and Reporting: A meta-regulatory perspective

- Data standards and data collection
- Eligibility requirements
- Recruitment plans
- Data Analysis
- Results reporting
- Further potential regulatory actions: Safety





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## Data standards and data collection

- Global cooperation on definitions and required questions to self-report
  - e.g. race/ethnicity, confounding in US and not relevant globally (Hispanic v Spanish)
  - Gender (sex typically defined, gender not)
  - Scripted investigator questions to elicit responses, likely varying by country/culture
    - Country/culture comparisons until validation
  - All questions required on case report forms
  - Documentation of failure to respond
  - Build into CDISC and other standards
- Case report forms reviewed for inclusion of all required elements
  - If standardized, then reliance in regulatory review is possible



# **Eligibility criteria**

- Global cooperation on definitions and required questions to self-report
  - Race/ethnicity, confounding in US and not relevant globally (Hispanic v Spanish)
  - Gender (sex typically defined, gender not)
  - All questions required on case report forms
- All I/E criteria should include scientific rational and justification, and reviewed
- Elimination of "investigator discretion" (~source of bias) as an eligibility criterion and, if included, explanation documented
- Laboratory reference intervals based on race, ethnicity, and geography, as well as for sex, age, and body mass index should be developed and used
  - sCr overestimates mild/moderate kidney injury in some, and overestimates in others
  - WBC count differs in Black/African-American populations
- Broaden age inclusion (adolescents and elderly when appropriate)
- If product not metabolized by kidney or liver, expand eligibility criteria
- Other (eliminate language-specific requirements when appropriate)
- Early planning for progressive inclusion, including recruitment plan



## **Recruitment Plan**

- Current recruitment plans suggested, but not required
- Regulatory review variable

To consider:

- Required recruitment plan with (1) product development plan and (2) trial protocol
- Proactive planning for failure to meet recruitment plan with corrective measures outlined
- Review of case report forms for alignment with international standards
- Required reporting of actual to planned recruitment
- Concurrent collection and evaluation of real world data (e.g. EHR, PROs, claims) during product development, to enable post-trial data collection and extension of understanding of risk/benefit



# Data analysis: conduct to impact label

- Control eligibility (I/E) to narrow population
- Manage inclusion/exclusion criteria, but insufficient recruitment, thereby ensuring large confidence intervals



• Label permissive to all included populations



# Data analysis: an example

- Losartan Intervention For Endpoint (LIFE) Study for hypertension
- Primary analysis: overall, the risk of the primary composite end point (cardiovascular death, stroke, myocardial infarction) was reduced by 13% (p = 0.021) with losartan, with similar blood pressure (BP) reduction in both treatment groups.



#### LIFE Study:

Interaction existed between the dichotomized groups (black/non-black) and treatment (p 0.005); a test for qualitative interaction significant (p 0.016). The hazard ratio (losartan relative to atenolol) for the primary end point favored atenolol in black patients (1.666 [95% confidence interval (CI) 1.043 to 2.661]; p 0.033) and favored losartan in non-blacks (0.829 [95% CI 0.733 to 0.938]; p 0.003).

Julius et. al. JACC, 2004.43:1047 doi:10.1016/j.jacc.2003.11.029



## Data analysis and Results Reporting

- Bayesian methods developing, assumptions need clarifying
- "Borrowing" from likely similar populations reasonable
  - E.g. Norway more similar to Sweden than to Japan
  - African Americans more similar to Caribbean-African Americans than Australians
  - 17 year old more similar to 21 year old than 85 year old
- Standardize analyses where possible
  - E.g. Analysis of age: pairwise by group versus regression analysis
- Require results reporting, and unique DOI of analyzed data to develop results
- Particularly important as study designs evolve (e.g. adaptive, platform)
- Require registration of observational trials



# When in development phase should diversity be addressed?

Concerns differ over the time course of product development

But innovative study designs and novel therapies (e.g. gene therapy, advanced therapy) medicine products) challenge the historical design



- Early market approval, limited or conditional
- Dynamic and continuous scientific analysis and dialogue
- Periodic B/R reassessment, using RWD, with regulatory review, and anticipated revision including label and/or approval
- Real world data and observational studies should be considered in the continuum of understanding of the product, and therefore built into development
- Development plan and analysis of heterogeneity of treatment effect should • intentional and planned ©MRCT Center

# Aligning Post-market Safety Reporting

The Problem:

- PSURs/PBRERS require significant effort, especially for larger companies, to compile and produce
- Uncertain utility, if countries reporting AERs in real-time when identified
- Varying requests from different countries
  - Data lock point
  - International birth date
  - Frequency and timing of reports
  - Specific country-specific reports and appendices
- Data and data analyses are not shared
  - Among companies each of whom have products of same active substance
  - Among regulatory agencies during or after review
- Limited transparency between countries, companies, and reports CONFIDENTIAL - DO NOT CIRCULATE © MRCT Center



# The Opportunity: Aligning Post-market Safety Reporting

- Companies currently collect by country with demographic and nondemographic data, but each somewhat differently, and analyses differ
- Demographic and non-demographic data not analyzed unless requested
- Common data standards and required elements would permit a more rigorous—and cooperative—analysis
  - Safety reports by region and country, if requested
  - Demographic comparisons
  - Analysis by drug class, across companies
- Regulatory reliance or cooperative review
  - e.g., EMA currently submits reports to substantive Pharmacovigilance
    Risk Assessment Committee (PRAC) review:
  - Other regulatory agencies could rely or cooperate, or subject to subsequent review
- Required transparency– but after all, this is safety





# Aligning Safety Reporting: the Model

The Solutions:

- Global or near-global adoption
  - Particularly helpful for under-resourced agencies
  - Allows multi-national companies to focus on deep analysis of safety events
  - Permits detailed analysis and cooperative or reliant review
- Needed:
  - Common data model, structured data, and in a common format
    - Potential to develop common database for comparison
  - Acceptance of data lock point
  - Acceptance of International birth date
  - Determination of necessary risk-based frequency of reports
  - (accepting 'gap reports' for specific countries if necessary)
  - Set standard report structure for the gap report format
  - Governance considerations
  - Transparency



# Proactive Safety Surveillance – a Global Initiative

The Problem(s):

- Spontaneous adverse event reporting works but is retroactive, inconsistent, and incomplete
- Lack of common data model and data terms restricts alignment across countries and regions
- Limited collaboration and cooperation between regulatory agencies
- Limited or no access to primary data or analyses





# Proactive Safety Surveillance – a Global Initiative

The Solution:

- A global approach to pharmacovigilance
- Recognition and commitment from regulators and industry

- Improved collaboration and transparency
- Use of RWD to augment and compliment current PV systems





# Comprehensive deliverables







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