Disclaimer

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Practical Approaches to Improving Diversity in Clinical Trials

Wednesdays
11AM – 12noon ET

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

LEANING IN: A WEBINAR SERIES

Recording available	Community Awareness, Access, Knowledge
Recording available	Workforce Development
Recording available	Study Design, Eligibility, Site Selection & Feasibility
Recording available	Study Conduct (Recruitment, Retention)
January 13, 2021	Data Standards and Analysis
January 27, 2021	Stakeholder Roles and Responsibilities
February 10, 2021	Role of Data in Diversity: Genetics & Real World Data

Data Standards and Analysis

January 13, 2021
11AM –12noon ET

Sarah White, MPH
Moderator
Executive Director,
MRCT Center

Roberto Lewis-Fernández , MD
Guest Speaker
Professor of Clinical Psychiatry,
Columbia University; Director, NYS Center
of Excellence for Cultural Competence,
NYS Psychiatric Institute; Co-Director,
Anxiety Disorders Clinic, NYSPI

Steve Snapinn, PhD
Guest Speaker
Statistical Consultant,
Seattle–Quilcene Biostatistics LLC.

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LEANING IN: A WEBINAR SERIES
Practical Approaches to Improving Diversity in Clinical Trials

The Multi-Regional Clinical Trials Center (MRCT Center)

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.

DEVELOP STANDARDS

ESTABLISH BEST PRACTICES

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

IDENTIFY OPPORTUNITIES FOR IMPROVEMENT

IMPROVE TRANSPARENCY

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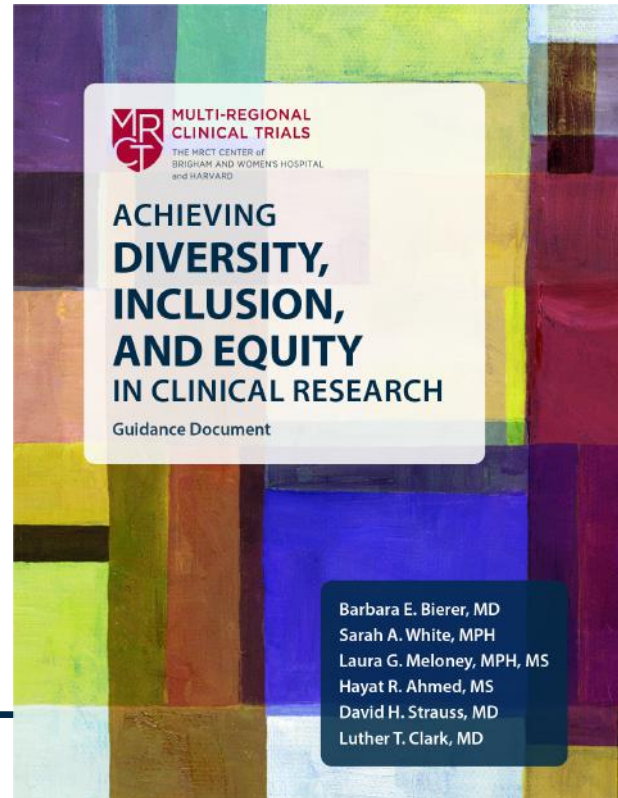and HARVARD

MRCTcenter.org

Leadership and Guidance

- RADM Richardae Araojo, PharmD, MS, U.S. FDA
- Barbara E. Bierer, MD, MRCT Center
- Luther T. Clark, MD, Merck & Co., Inc.
- Milena Lolic, MD, U.S. FDA
- David H. Strauss, MD, Columbia University
- Sarah White, MPH, MRCT Center

MRCT Center staff:
- Carmen Aldinger, PhD, MPH
- Hayat Ahmed, MS
- Laura Meloney, MS, MPH
- Joshua Smith-Sreen, MBE

Achieving Diversity, Inclusion, Equity In Clinical Research

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

ACHIEVING DIVERSITY, INCLUSION, AND EQUITY IN CLINICAL RESEARCH

Guidance Document

Barbara E. Bierer, MD
Sarah A. White, MPH
Laura G. Meloney, MPH, MS
Hayat R. Ahmed, MS
David H. Strauss, MD
Luther T. Clark, MD

And the invaluable contributions of >50 workgroup members, representing:

- Patients, Patient Advocates
- Academia
- Pharmaceutical companies
- CROs
- Non-profit organizations
- Trade associations
- Government agencies
- Research institutes

Each serving in their individual capacity.

Guidance Document

- Multi-stakeholder contributions and consensus

- Practical and actionable recommendations

- Accountability section considers how each stakeholder can change the paradigm

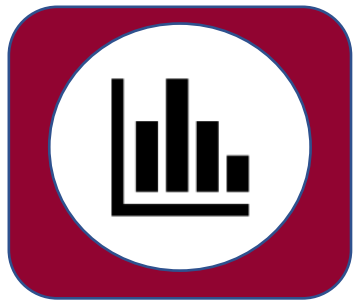- Toolkit provides adaptable resources not easily found elsewhere
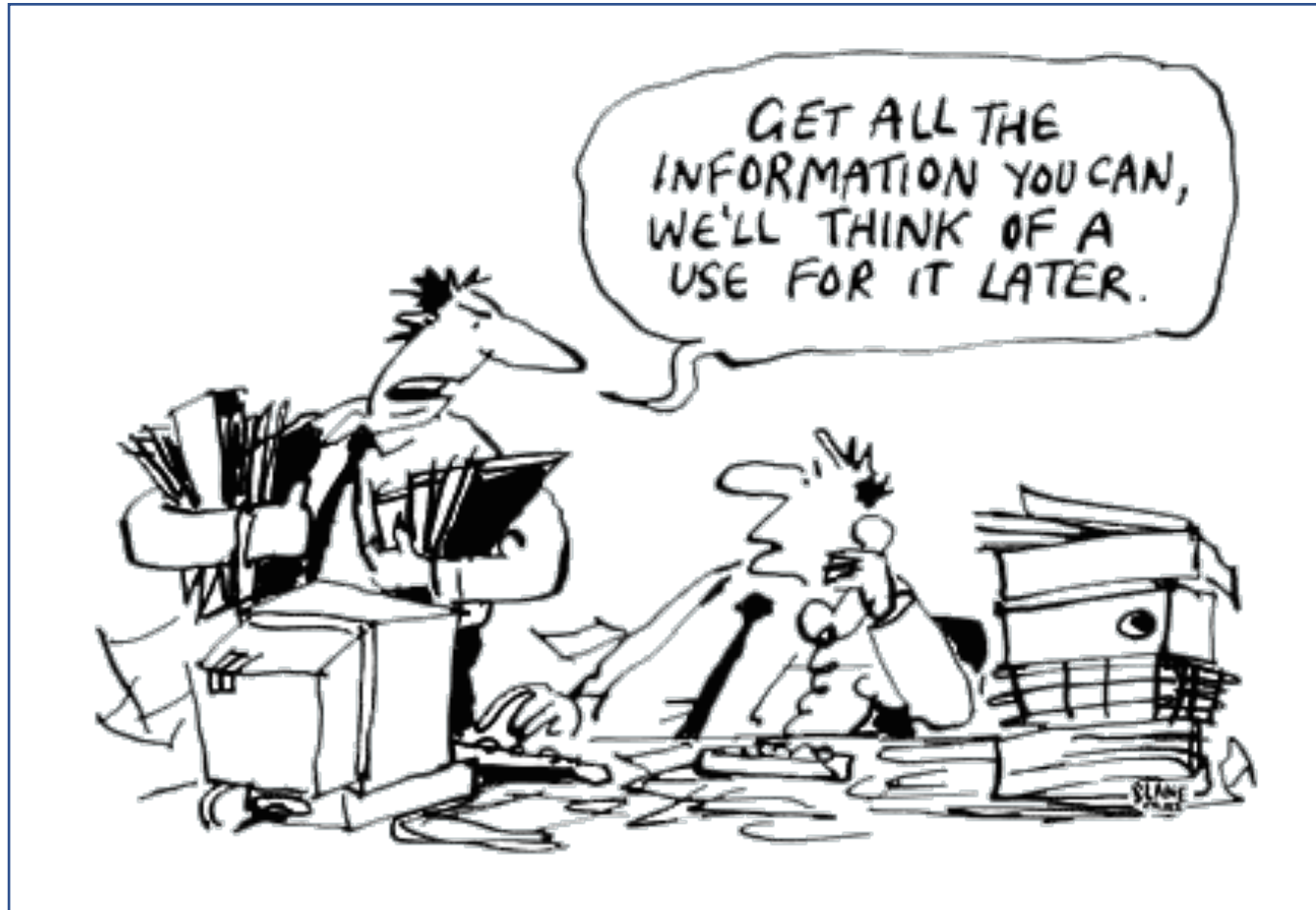
The Problem:

- Lack of uniform data collection
- Lack of interoperability
- Data analysis is dependent on data collection

Data Standards and Analysis

- **Data collection**
  - Collection in most granular form

- **Data reporting**
  - Biologically relevant categories

- **Data Analysis**
 - Meaningful subgroup analysis

- **Consequences of poor data collection:**
  - Data integrity
  - Failure to reach outcome measures
 - Mis-informed analysis
  - Failed analysis

Data Variables & Collection

Need to be:

- Disease and intervention specific

- Pre-determined
  - Part of study question
  - Biological significance relating to intrinsic and extrinsic factors

- Considered at study design phase:
  - What data
  - How collected
  - Are there regulatory authority, funder, sponsor, and/or institutional requirements
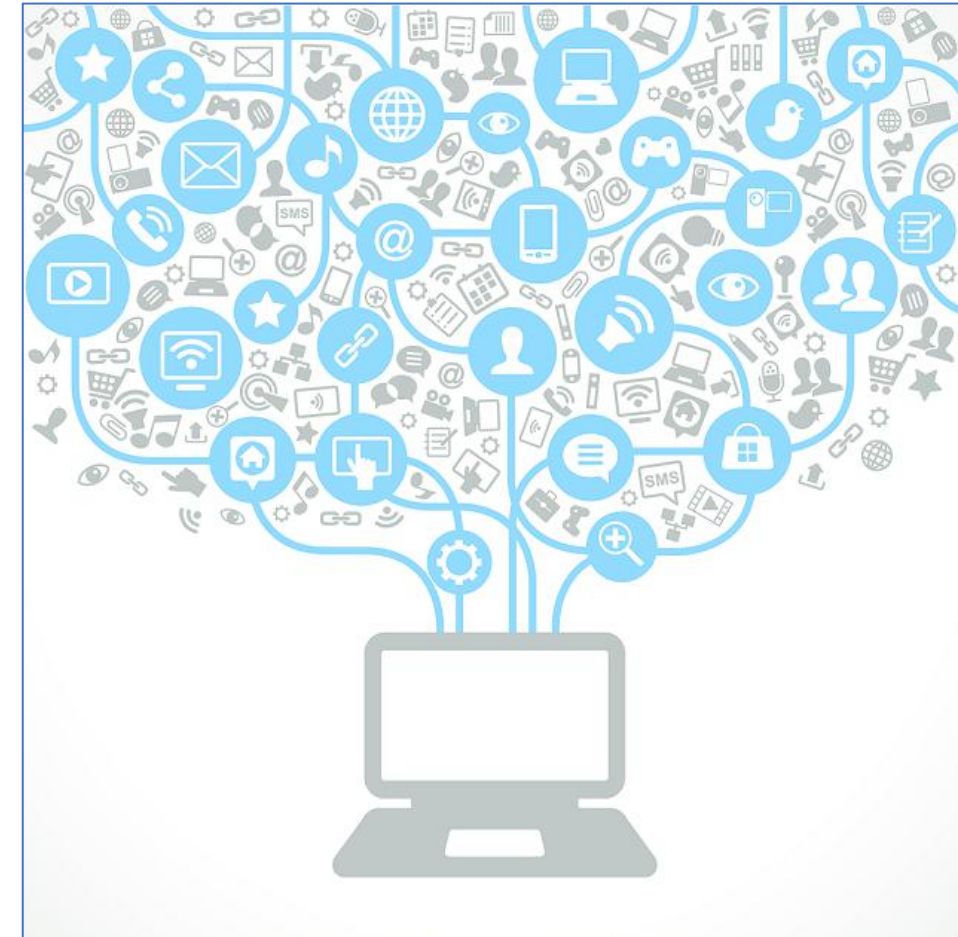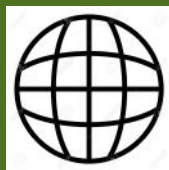
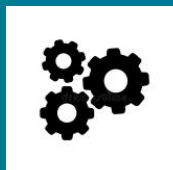# Challenges of data collection and reporting
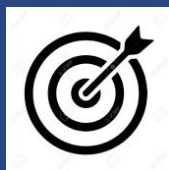
Discrete vs. Continuous
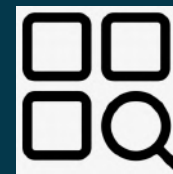
Categorization

Global harmonization

Interoperability

Data Collection and Reporting: Age

- Data should be collected at the most granular form: date of birth

- Be specific as to order of terms (MM/DD/YYYY or DD/MM/YYYY)

- Then can be categorized, shared, aggregated in different ways for different purposes of data reporting

- As per regulatory authorities

Data Collection for Age: date of birth

SUBGROUP	APPROXIMATE AGE RANGE
In Utero	
Preterm newborn	Gestational age < 37 weeks
Newborns	0-27 days
Infants & toddlers	28 days – 23 months
Children	2-11 years
Adolescents	12-17 years
Adult	18-64 years
Old Adult	65-84 years
Older Adult	Over 85 years

Clinical Data Interchange Standards Consortium

- CDISC creates data standards and controlled terminology for collection of safety and efficacy variables

- Goal to enable data interoperability in clinical and translational research

- Required by US and Japan regulatory authorities; recommended in Europe and China

- CDASH = Clinical Data Acquisition Standards Harmonization (CDASH)
  - Foundational standard created to collect research data consistently across studies and sponsors

A Four Stage Approach to Data Collection

Key Consideration #1 – Identify Relevance

Which data variables (demographic and non-demographic) are most biologically important to the disease area and study question? What data will be used to define the planned analyses?

What should be collected?

Key Consideration #2 – Define Granularity

What is the most granular level at which this data variable can be, or is recommended to be, collected from participants?

Key Consideration #3 – Standard Collection Format

What are the available standardized formats for collection of this variable? Does the sponsor, funder, or regulatory authority request different formats?

Key Consideration #4 – Aggregate for Reporting

What are the aggregate categories that could be used to report these variables, i.e., per regulatory standards?

Data Collection Tool for Baseline Demographic Variables

Study ID:

Participant Study ID:

Date of data collection: ___(specify MM/DD/YYYY or DD/MM/YYYY)

AGE
Instructions: Provide your date of birth to the best of your ability

Date of birth: ___(specify MM/DD/YYYY or DD/MM/YYYY)

Corresponding Age: __(specify units: hours, days, months, years)

Note:
- Collect age as a continuous variable, in order to summarize and/or report as re[quired by] regulatory authority.
- Collect age in hours, days, months, years. Age may be grouped into categories [based on] important age-related distinctions or underlying biological differences.
- If there are limitations to collecting date of birth (often related to national- or [local] privacy laws), data can be collected as year of birth and corresponding age. Speci[fy units:] years, months).
- See Section *Achieving Diversity, Inclusion, and Equity in Clinical Research Guid[ance]* 11.2.1 – 11.2.3 regarding data standards for specific age categories including [neonatal,] elderly.

SEX
Instructions: Select your biological sex at birth. Sex is defined as the different physiological and biological characteristics of males and females, such as reproductive organs, chromosomes, hormones, etc.[6]

SEX	
	○ Male
	○ Female
	○ Unknown or undifferentiated. Intersex is included in the term undifferentiated.

GENDER
Instructions: Select the gender you most closely identify with. Gender is defined as the socially constructed characteristics of women and men – such as norms, roles and relationships of and between groups of women and men. It varies from society to society and can be changed.[7]

GENDER[8]		
	○ Male	○ Gender non-conforming
	○ Female	○ Different Identity: Please specify_____
	○ Trans-male	○ Chose to not answer the question
	○ Trans-female	

Note:
- The collection of gender is sensitive. The individual collecting this information should be sensitive that this may make a participant uncomfortable and use scripted questions to ensure questions are asked in a respectful way.

Aggregate Reporting Tool

Study ID: Baseline Demographics, Aggregated Data				
Demographic Variables	**Treatment Group(s)**		**Control Group**	**Total**
	Group 1, N (%)	**Group 2, N (%)**	**N (%)**	**N**
Age				
>=18 - <65 years				
>=65 - <74 years				
>=75 - <84years				
>= 85 years				
Sex				
Male				
Female				
Unknown/Undifferentiated				
Gender				
Male Gender				
Female Gender				
Trans-Male				
Trans-Female				
Gender Nonconforming/ Unknown				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Not Reported				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Not reported/unknown				
Other/More than one				

Data Analysis and Diverse Populations
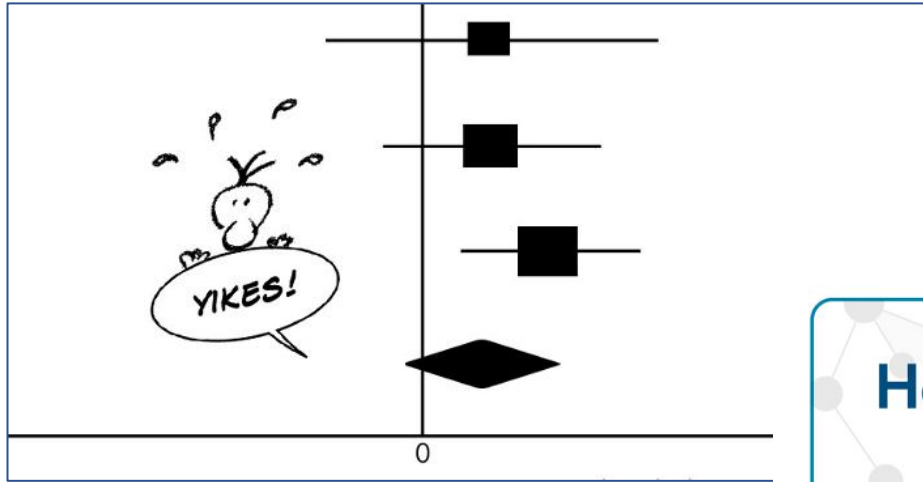
Example of a Forest Plot

Heterogeneity of Treatment Effects in Clinical Trials: Methods and Innovations

NOVEMBER 30, 2020 - DECEMBER 1, 2020
8:30am-1pm ET

Virtual Conference hosted by
MRCT Center in collaboration with FDA

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FDA

https://www.youtube.com/watch?v=7tQonkq_bhk&feature=youtu.be

"Will it work for me?"

- The more homogenous the study population
  - ➢ more likely the results will apply to others exactly like them, but not a heterogeneous population
- The greater the diversity in the trial
  - ➢ the more variability and heterogeneity the result, and less applicable to the individual patient
- What matters in the end:
  - o Whether an intervention works
  - o Whether the benefit is likely to outweigh the potential risk of harm
- The healthcare provider must choose and prescribe
- The patient must trust the provider and the system

Roberto Lewis-Fernández, MD

Professor of Clinical Psychiatry, Columbia University

Director, NYS Center of Excellence for Cultural Competence, NYS Psychiatric Institute

Co-Director, Anxiety Disorders Clinic, NYSPI

Social Determinants of Health:
Research Methods

Roberto Lewis-Fernández, MD

Professor, Department of Psychiatry, Columbia University
Director, NYS Center of Excellence for Cultural Competence,
and Hispanic Treatment Program,
Co-Director, Anxiety Disorders Clinic,
New York State Psychiatric Institute

NEW YORK STATE OF OPPORTUNITY.

New York State Psychiatric Institute
Center of Excellence for Cultural Competence

Overview

- Importance of social determinants of health in clinically relevant research

- Practical questions
  - What do we need to know?
  - What measures do we need?
  - How do we administer them?

Social Determinants of Health
WHO definition

Employment

Housing

Education

Social Support
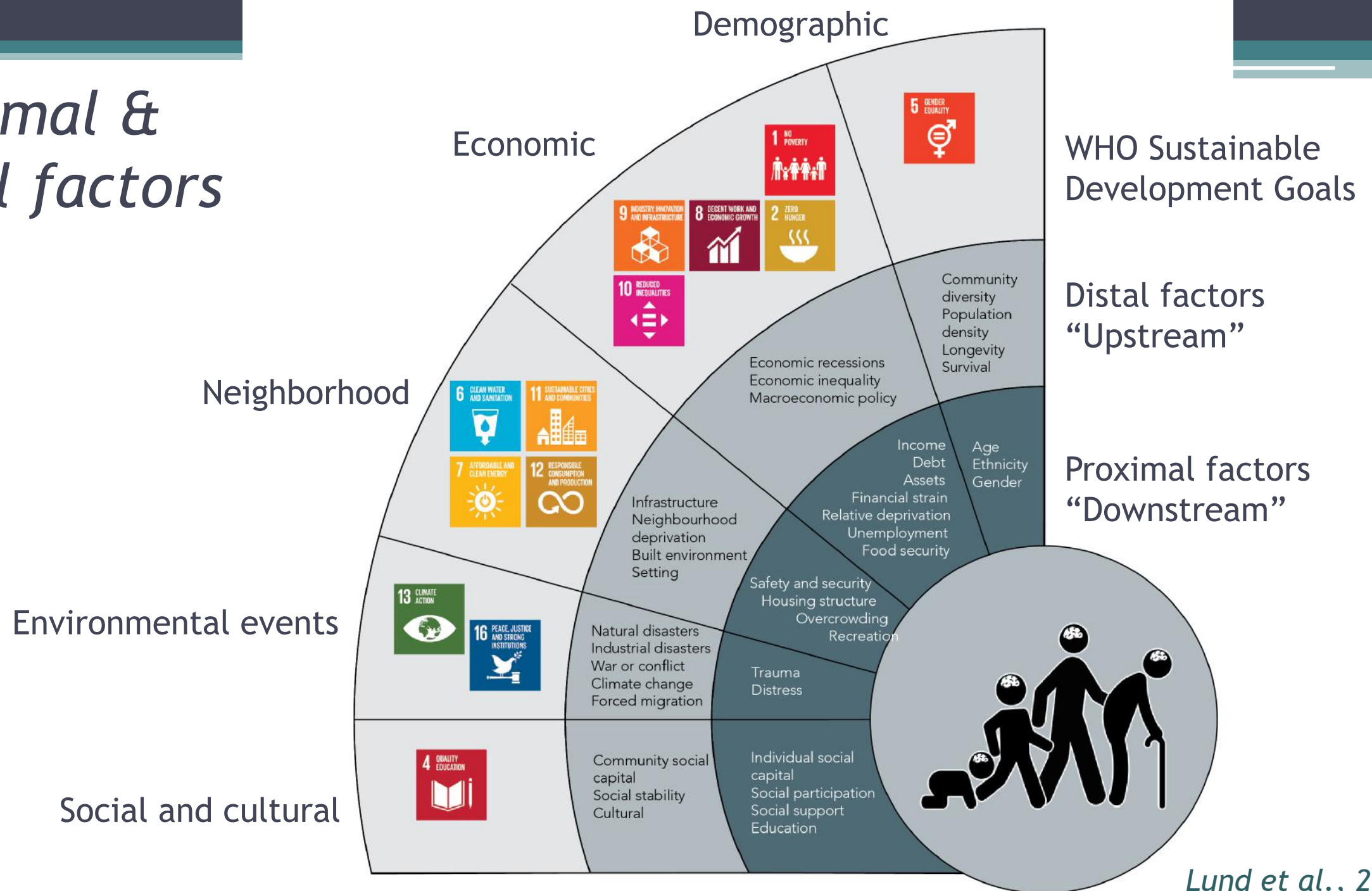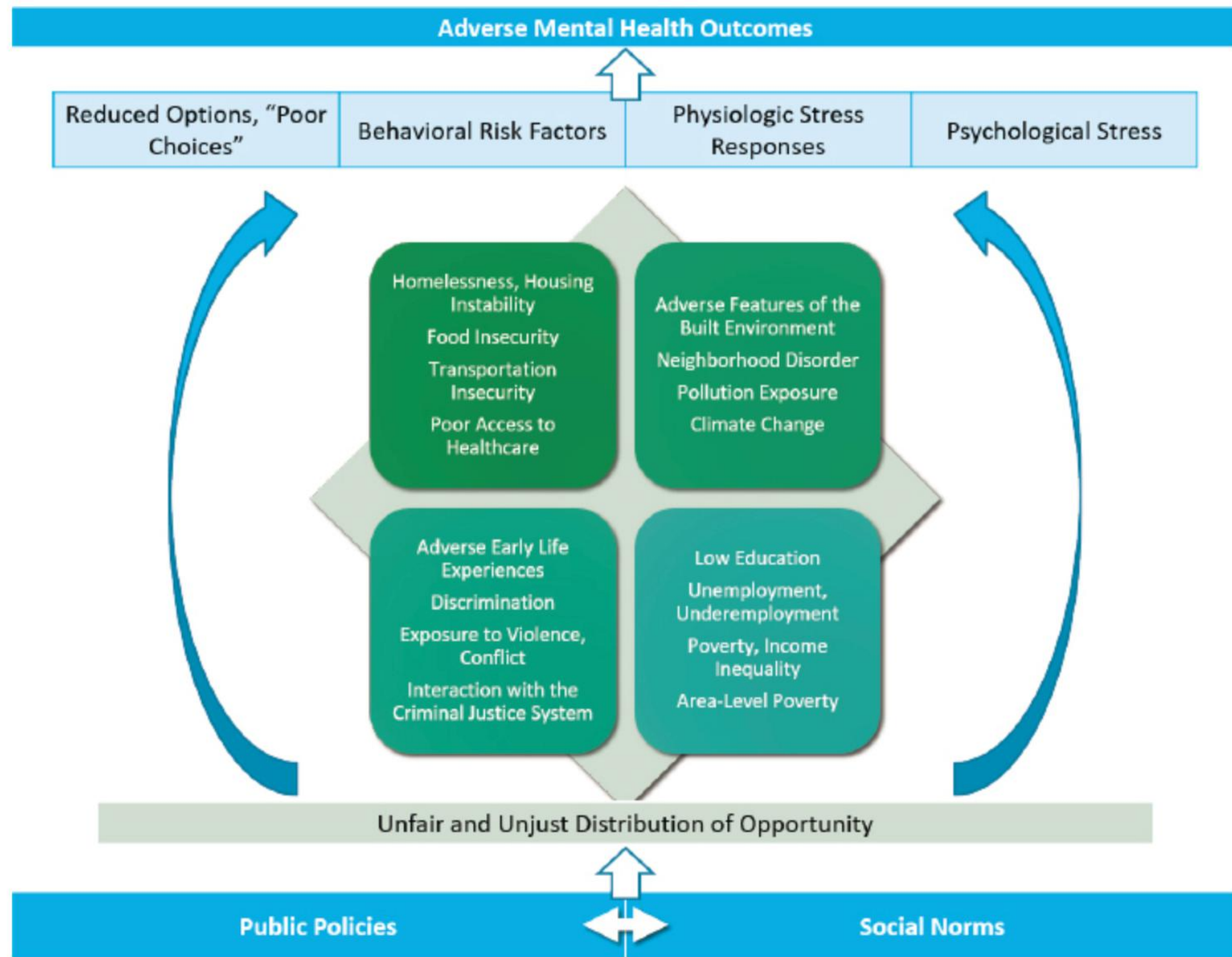
Income

Health Care

Those factors that impact upon health and well-being: the circumstances into which we are born, grow up, live, work, and age, including the health system.

These circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels, which are themselves influenced by policy choices.

WHO Commission on SDOH, 2008

Proximal & distal factors SDoH

Demographic

Economic

Neighborhood

Environmental events

Social and cultural

WHO Sustainable Development Goals

Distal factors "Upstream"

Proximal factors "Downstream"

Community diversity
Population density
Longevity
Survival

Economic recessions
Economic inequality
Macroeconomic policy

Income
Debt
Assets
Financial strain
Relative deprivation
Unemployment
Food security

Age
Ethnicity
Gender

Infrastructure
Neighbourhood deprivation
Built environment
Setting

Safety and security
Housing structure
Overcrowding
Recreation

Natural disasters
Industrial disasters
War or conflict
Climate change
Forced migration

Trauma
Distress

Community social capital
Social stability
Cultural

Individual social capital
Social participation
Social support
Education

Lund et al., 2018

SDoMH

Compton & Shim, 2020

What do we need to know?

- Relevance of specific SDoH to a particular study
  - E.g., impact on heterogeneity of effects (HTE)?
- Anticipate factors that can clarify complex outcomes
- Prepare for subgroup analyses
- Supplement required data
  - E.g., what aspect of "race/ethnicity" is relevant?
    - Impact of racism and ethnic discrimination?
    - Genetic ancestry?
    - Variations in exposure to adversity?
- Select parsimonious list of SDoH

Ex: HTE in asthma studies

- 2019 systematic review of 30 cluster-randomized trials
  - 8 subgroup analyses: 3 positive (incl. 1 of 1 demographic analysis)
- Multiple possible causes for HTE
  - Genetic, environmental, physiologic, demographic, inflammation, others
- Signif. effect of housing interventions suggest it is a key SDoH
  - 3 asthma studies in US and UK: housing improvements (e.g., ventilation):
    - **Lower** asthma symptom score or severity, healthcare visits, cost
- But none of the 30 CRT studies included housing items

- **REC: Include SDoH item(s) on housing to clarify asthma HTE**

Carr & Bleecker, 2016; Starks et al., 2019; Taylor et al., 2016

What measures do we need?

- "Sweet spot" of number and length of measures
- Prepare for various levels of data aggregation
  - E.g., Use continuous measures if possible
    - E.g., age as DOB if allowed, if not as # years
- Local validity of measures
  - E.g., race and ethnicity; income/wealth/financial strain
- Tension between harmonization and brevity
  - NIH Toolkit
  - Briefer measures

PhenX Toolkit

Social Determinants of Health Collections

Social Determinants of Health Project
Social Determinants of Health Collection

Social Determinants of Health Research 🏠🏠

Release Date: 5/11/20

View Supplemental Information ❓   View Scope

View Social Determinants of Health WG Roster

Core Collection

➕ Add to My Toolkit   Social Determinants of Health: Core

Specialty Collections

➕ Add to My Toolkit   Individual Social Determinants of Health

➕ Add to My Toolkit   Structural Social Determinants of Health

https://www.phenxtoolkit.org/collections/view/6

PhenX Toolkit

Individual Social Determinants of Health

+ Add to My Toolkit 270101 Access to Health Services

+ Add to My Toolkit 280401 Access to Health Technology

+ Add to My Toolkit 210302 Discrimination

+ Add to My Toolkit 280101 Disparate Health Care Quality

+ Add to My Toolkit 270201 English Proficiency

+ Add to My Toolkit 270301 Food Insecurity

+ Add to My Toolkit 270401 Health Literacy

Structural Social Determinants of Health

+ Add to My Toolkit 290101 Air Quality Index

+ Add to My Toolkit 290201 Concentrated Poverty

+ Add to My Toolkit 290301 Educational Attainment - Community

+ Add to My Toolkit 290401 Environmental Justice

+ Add to My Toolkit 290501 Food Swamp

+ Add to My Toolkit 290601 Percent Unionized for Non-Agricultural Labor Force

+ Add to My Toolkit 211403 Race/Ethnic Residential Segregation - American Community Survey

+ Add to My Toolkit 211404 Race/Ethnic Residential Segregation - Separation (S) Index, Unbiased

+ Add to My Toolkit 211402 Race/Ethnic Residential Segregation - U.S. Census

+ Add to My Toolkit 290701 Social Vulnerability

https://www.phenxtoolkit.org/sub-collections/view/29

https://www.phenxtoolkit.org/sub-collections/view/30

Alternative measures

The Accountable Health Communities Health-Related Social Needs Screening Tool

- 5 domains (10 items total) on housing instability, food insecurity, transportation problems, utility help needs, interpersonal safety
- Supplementary modules on financial strain, employment, family and community support, education, physical activity, substance use, mental health, disabilities

https://nam.edu/wp-content/uploads/2017/05/Standardized-Screening-for-Health-Related-Social-Needs-in-Clinical-Settings.pdf.

Alternative measures

Upstream Risks Screening Tool & Guide

- 14 domains (1-4 questions each) on education, employment, social connection & isolation, physical activity, immigration, financial strain, housing insecurity, food insecurity, dietary pattern, transportation, exposure to violence, stress, civic engagement

https://sirenetwork.ucsf.edu/tools-resources/mmi/healthbegins-upstream-risk-screening-tool

Alternative measures

Protocol for Responding to and Assessing Patient Assets, Risks, and Experiences

- 14 domains (21 items total) on personal characteristics, family & home, money & resources, social & emotional health, optional additional questions (correctional involvement, refugee status, neighborhood safety, domestic violence)

https://www.nachc.org/research-and-data/prapare/

How to administer the measures?

- Ensure validity of responses
  - Standardized scripts
    - That work for all populations studied
    - Ordering of measures, like ethnicity before race
  - Trusted interviewers
  - Engage/activate participants
    - Community involvement over time
    - What is in it for the community, not only for individuals?

Conclusions

- Importance of SDoH as moderators and mediators of disease and treatment effects

- Need to anticipate:
  - Domains and measures
  - Best administration methods for populations studied

- Tension btw parsimony and sufficient data to explain HTE

- Develop long-lasting relationship w/ patient populations to maximize validity and engagement

Steve Snapinn, PhD
Statistical Consultant
Seattle-Quilcene Biostatistics LLC

Outline

- Power/Sample Size Calculations and Diverse Populations
  - Prognostic Factors and Predictive Factors

- Examples of Heterogeneity of Treatment Effects (HTE)

- Difficulty Detecting HTE

- Shrinkage Estimation as a Conceptually Appealing Approach

- Concept of power: probability of obtaining a statistically significant result, in the overall population, if the drug works as expected

- Two key factors influence power
  - The between-patient variability in the outcome measurement
    - High variability makes it hard to separate signal from noise and leads to larger sample size requirement
  - The magnitude of the treatment benefit

- **The diversity of the population can have an important impact on both of those factors**

- A **prognostic factor** is one that is related to a patient's likely outcome
  - Suppose we are investigating a treatment to slow the progression of a disease, with time-to-progression as the primary outcome measurement
  - Suppose that in an untreated population this outcome has a distribution as below

Rate of Progression

mrctcenter.org/diversity-in-clinical-trials

- A **prognostic factor** is one that is related to a patient's likely outcome
  - Suppose we are investigating a treatment to slow the progression of a disease, with time-to-progression as the primary outcome measurement
  - Suppose that in an untreated population this outcome has a distribution as below
 - Now suppose that men and women tend to progress at different rates

Rate of Progression
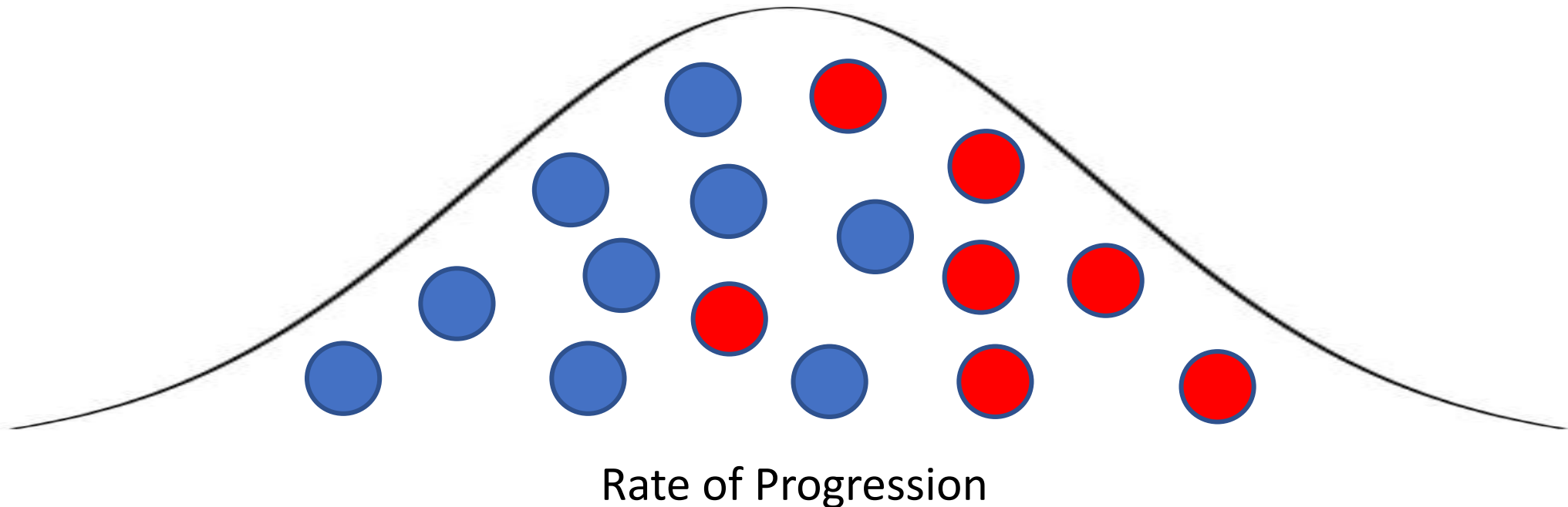
Patient Characteristics Can Be **Prognostic Factors** That Affect Variability

- You can see that a diverse population leads to greater variability, which leads to greater sample size requirement than a uniform population

- However, prognostic factors can be accounted for and this affect on power neutralized

- Design stage: stratified randomization

- Analysis stage: stratified analysis or covariate adjustment

- Requires knowledge of which factors are prognostic, and accurate assessment of them

Rate of Progression
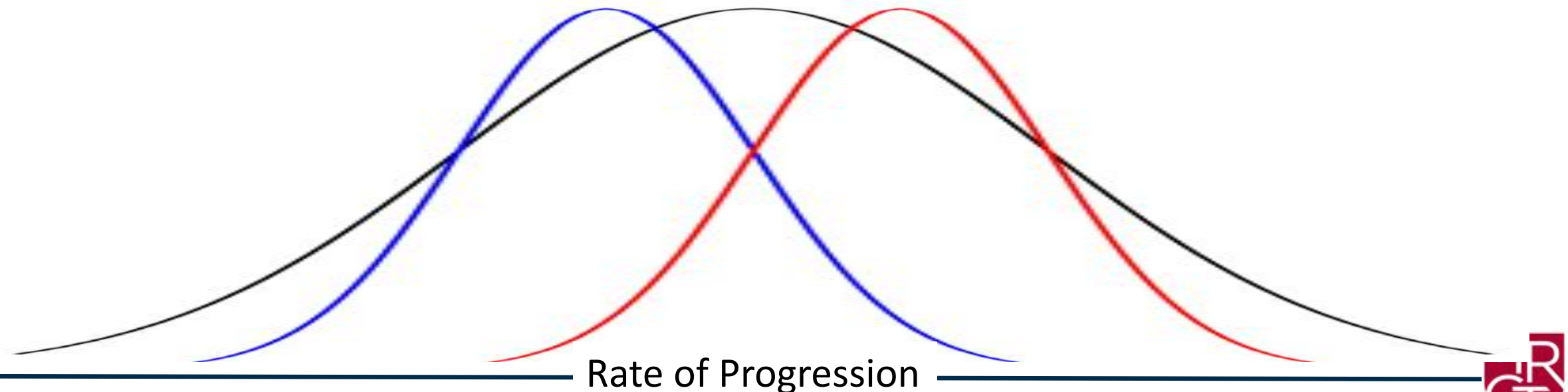
Patient Characteristics Can Be **Predictive Factors** That Affect the Magnitude of Treatment Benefit

- A **predictive factor** is one that is related to the likelihood of treatment benefit

- We refer to this situation as heterogeneity of treatment effects (HTE)

- Generally not accounted for at the design stage (one single magnitude of benefit assumed)

- Critically important to learn at the analysis stage whether HTE exists

- Two types of HTE
  - The treatment is effective in all subgroups, but to different degrees: "Quantitative Interaction"
  - The treatment is effective in some subgroups, but not effective or harmful in others: "Qualitative Interaction"

Example: MERIT-HF

- Challenges of Subgroup Analyses in Multinational Clinical Trials: Experiences From the Merit-HF Trial; Wedel et al 2001
- Apparent lack of effect on total mortality in the US

All Patients Randomized

	Total Mortality No. of deaths Meto CR/XL/Plac	Total Mortality/Any Hosp. No. of events Meto CR/XL/Plac	Total Mortality/CHF Hosp. No. of events Meto CR/XL/Plac
Belgium	3/13	31/31	13/21
Czech Republic	9/17	35/50	25/36
Denmark	11/11 (2.3)	58/60	24/28
Finland	0/2 Not estimable	6/4 (4.6)	2/3 (2.9)
Germany	19/31	88/100	44/63
Hungary	16/29	57/72	31/48
Iceland	2/2 (7.3)	6/10 (2.0)	3/4 (3.6)
Norway	6/11	41/48	17/28
Poland	8/8 (2.6)	26/25	16/18
Sweden	2/9	15/27	5/14
Switzerland	0/1 Not estimable	5/4 (4.5)	1/3 (2.9)
The Netherlands	14/25	63/91	28/52
UK	4/9	26/29	11/12 (2.0)
USA	51/49	184/216	91/109
All countries	145/217	641/767	311/439

Favors Meto CR/XL — Favors Placebo

Relative risk and 95% confidence interval (0.0, 1.0, 1.8)

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Example: PLATO

- Statistical Evaluation and Analysis of Regional Interactions: The PLATO Trial Case Study; Carroll and Fleming 2013

- Apparent lack of effect or harm in North America

Characteristic	Total Patients	KM at Month 12		HR (95% CI)	Interaction p-values
		Tic	Clop		
Geographic Region					
Asia / Australia	1714	11.4	14.8	0.80 (0.61, 1.04)	
Cent / Sth America	1237	15.2	17.9	0.86 (0.65, 1.13)	0.045
Euro / Md E / Afr	13859	8.8	11.0	0.80 (0.72, 0.90)	0.01
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	

0.5 1.0 2.0

Ticagrelor Better — Clopidogrel Better

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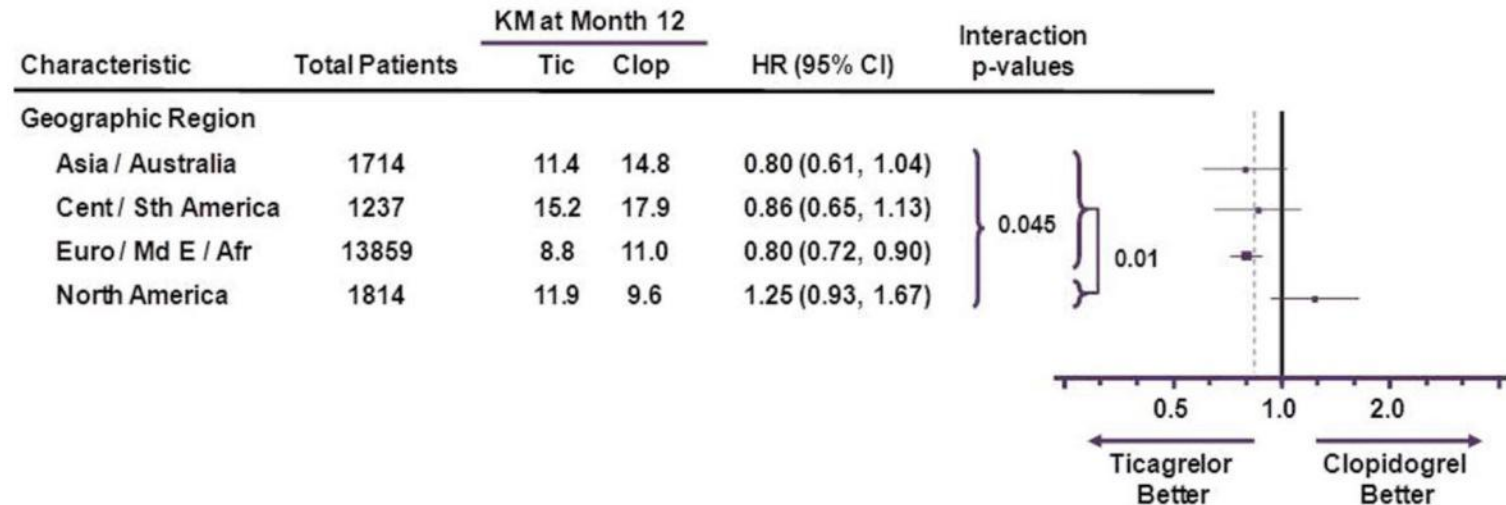
The Subgroup Problem Is Difficult

- Analyses within subgroups are valid and provide unbiased estimates of treatment effects
- The problem is that the play of chance frequently causes apparent HTE when none exists
  - Brilliantly illustrated by subgroup analysis of ISIS-2 by zodiac sign
  - Focusing on extreme estimates leads to **random high bias**; related to regression-to-the-mean
  - Many cases of failure to replicate HTE in follow-up studies
  - "Subgroup analyses in clinical trials — fun to look at, but don't believe them!" Sleight 2000
- Real HTE is important to detect, but can be swamped by multiple instances of spurious HTE

# A Bayesian Approach Can Better Address This Problem

o Bayesian subgroup analysis distinct from Bayesian analysis of trial results
  ▪ *Bayesian analysis of trial results*: Prior distribution for magnitude of treatment effect
  ▪ *Bayesian subgroup analysis*: Prior distribution for consistency of effect, regardless of magnitude
o Bayesian thinking (prior belief in consistency of effect) is pervasive
  ▪ "In order to … design … a clinical trial, it is necessary to assume that the effect of the treatment will be relatively consistent across subgroups of potential importance…. If substantial heterogeneity of the treatment effect across subgroups is suspected at the design stage, then the whole basis of the trial is undermined." (Grouin et al 2005)
  ▪ "[Subgroup analyses] are commonly overinterpreted and can lead to further research that is misguided or, worse, to suboptimal patient care." (Lagakos 2006)
  ▪ "Thus the best estimate of the treatment effect … for any subgroup is the estimate … for the overall trial." (Wedel 2001)

Bayesian Shrinkage Estimators Are Sensible

o Shrinkage estimators combine observed estimate with prior belief in consistency

  ▪ Shrinkage estimate falls between observed treatment effect and overall treatment effec

  ▪ Addresses "random high bias"

o Degree of shrinkage depends on degree of consistency

  ▪ Greater consistency leads to more shrinkage

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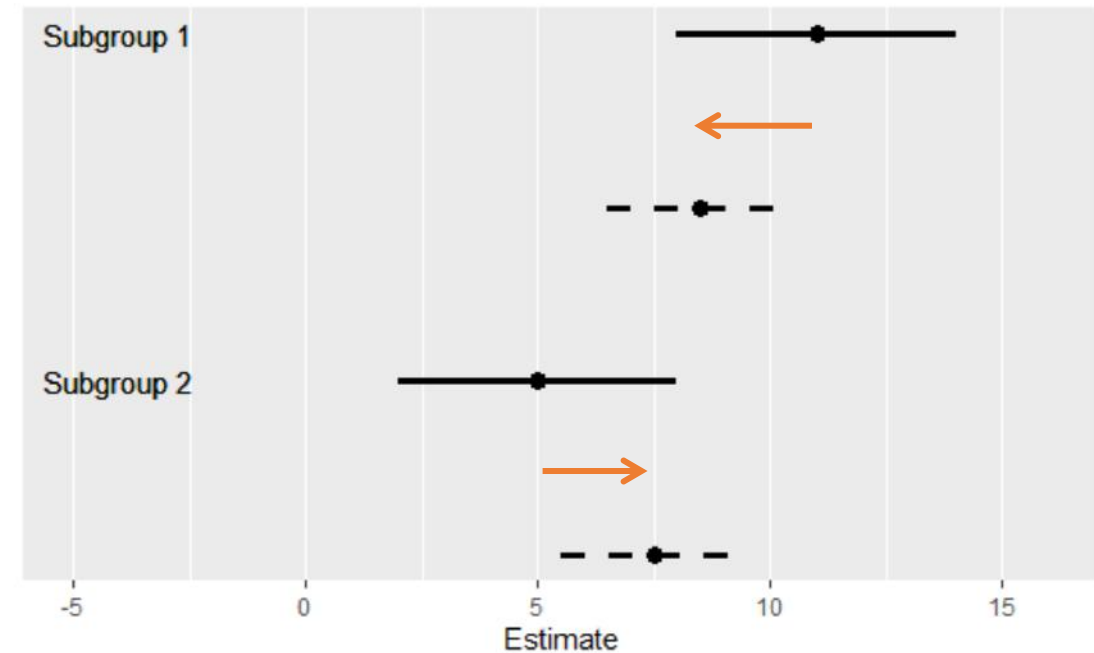
Shrinkage Estimator Applied to the PLATO Trial
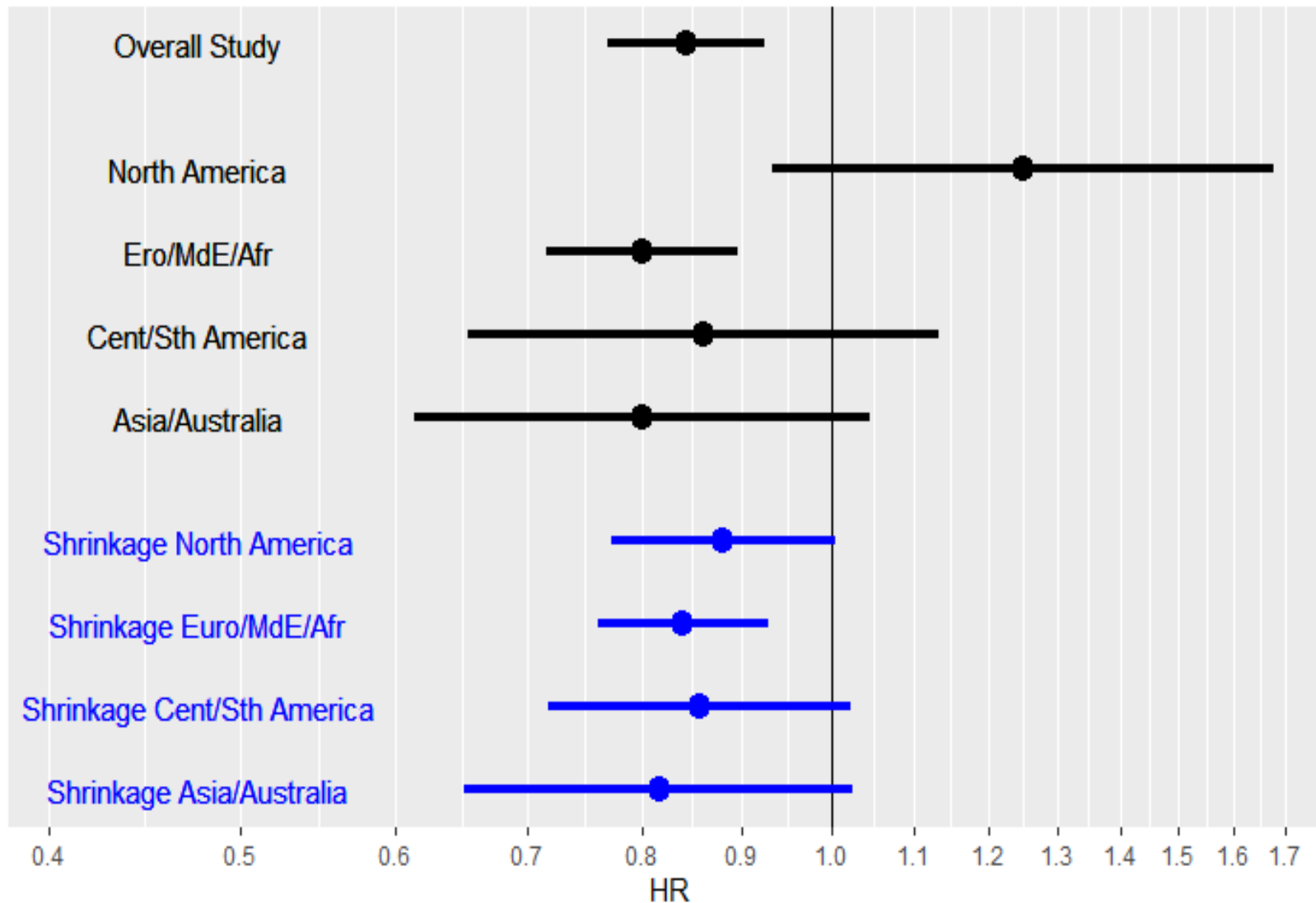
Summary

- Many Patient Characteristics are Prognostic Effects
  - Adds Variability to Efficacy Assessment; Increases Sample Size Requirement
  - Can Be Accounted for by Stratified Randomization and Analysis
- Some Patient Characteristics are Predictive Effects
  - Referred to as Heterogeneity of Treatment Effects (HTE)
- Detection of HTE is Critically Important But Extremely Difficult Using Standard Methods
- Shrinkage Estimators Have Great Potential

Practical Approaches to Improving Diversity in Clinical Trials

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MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

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Recording available	Community Awareness, Access, Knowledge
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Recording available	Study Design, Eligibility, Site Selection & Feasibility
Recording available	Study Conduct (Recruitment, Retention)
January 13, 2021	Data Standards and Analysis
January 27, 2021	Stakeholder Roles and Responsibilities
February 10, 2021	Role of Data in Diversity: Genetics & Real World Data