Inclusion of Diverse, Disparate, and Hard-to-Reach Populations

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Of all forms of *inequality*, injustice in *healthcare* is the most *shocking* and *inhuman*.

—Martin Luther King, Jr.

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Why is diversity crucial for clinical research?

- 1 in 5 FDA approvals differed in exposure / response as a function of racial / ethnic group (Ramamoorthy et al., 2015)
- Representation issues particularly acute in pain management (Anderson et al., 2009; Green et al., 2003; Meghani et al., 2012)
- Selection and survival biases skew estimates of causal factors (Mayeda 2018; Weuve 2015)
- What happens if we don't recruit *representatively*?

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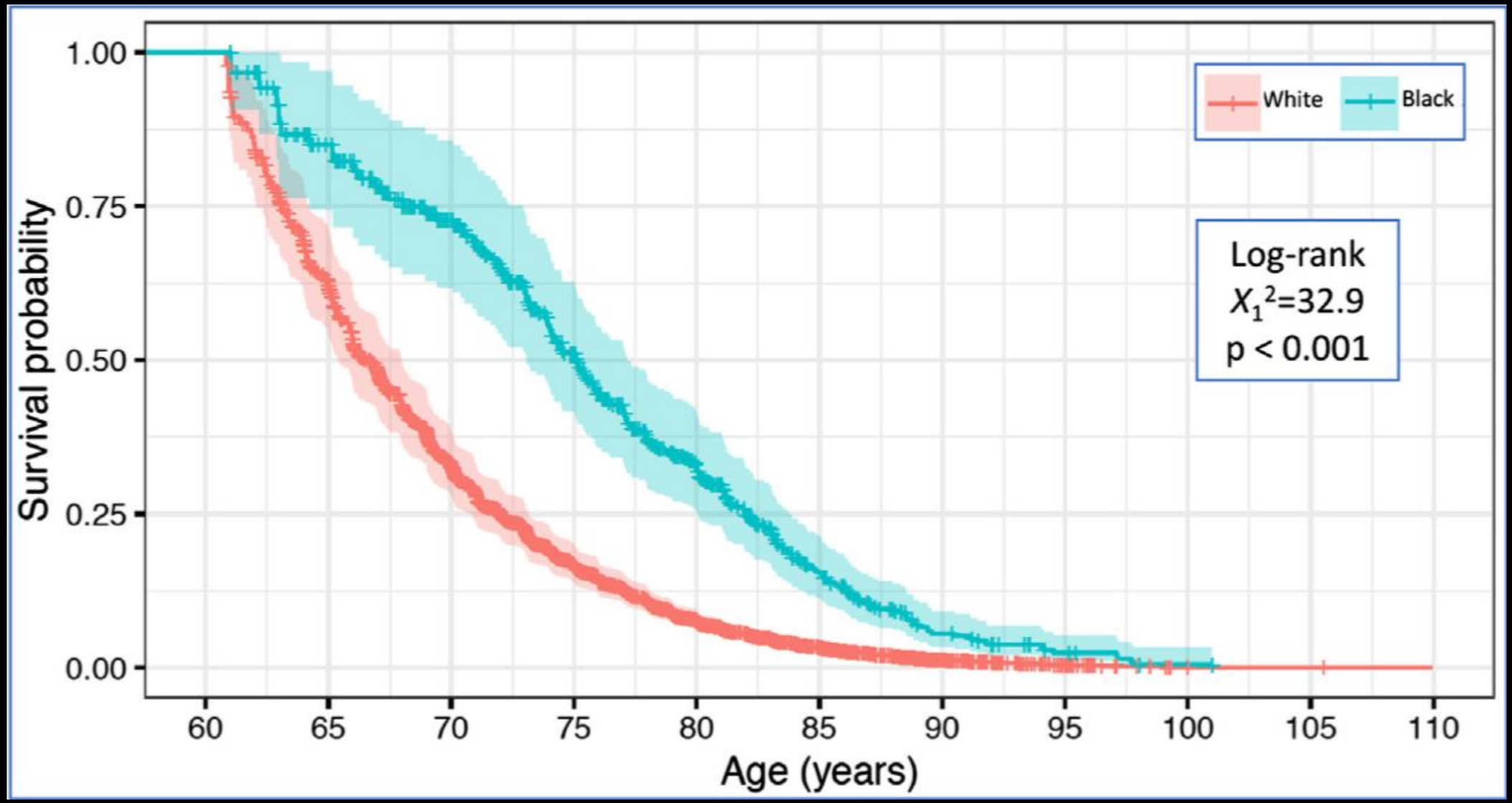
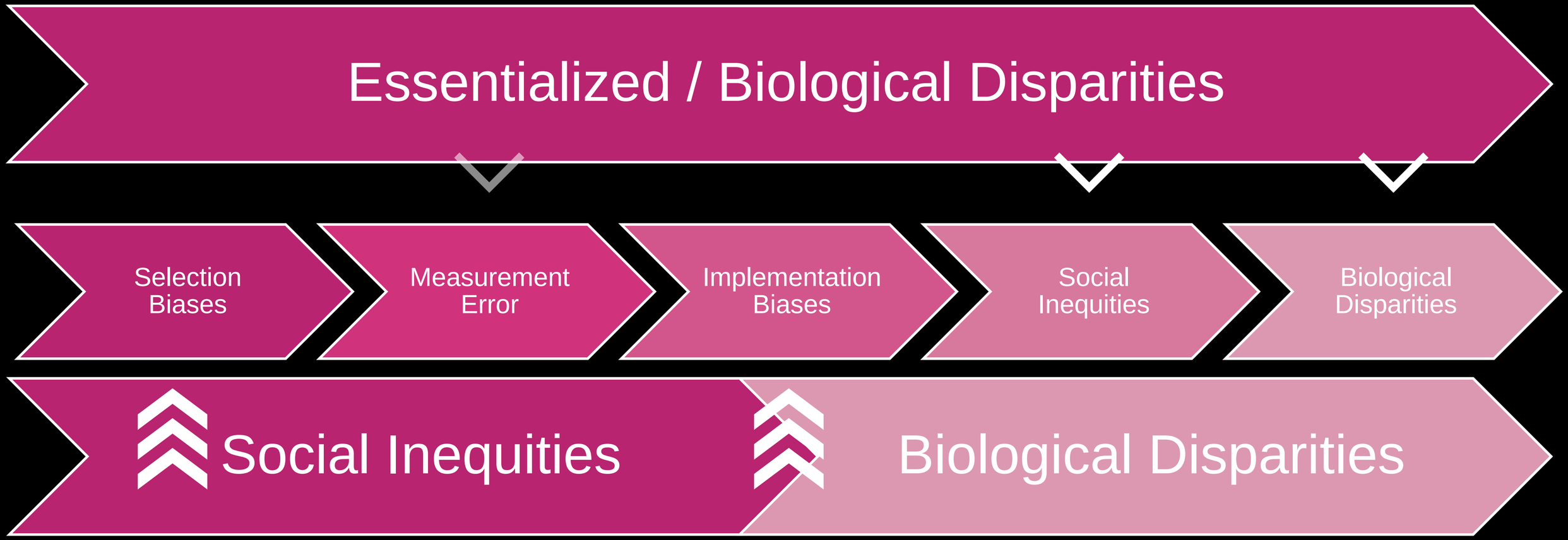
Current efforts in diverse recruitment



Gleason 2019 | Alz & Dementia

What do we mean by “disparities”?



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Why can’t we recruit diversely?

1. Lack of awareness of research opportunities
2. Deep mistrust of healthcare system and research studies
3. Confusion and concern over what research is
4. Limited transportation options / times
5. Inclusion / exclusion criteria (e.g., lumbar puncture, study partner)
6. Lack of plain language use in documents
7. Fear of placebo / fear of intervention
8. Health insurance coverage
9. Limited diversity on study staff
10. Insufficient return of value

Selected references:

Bonevski 2014 | BMC Med Res Method
Dunbar 2019 | Ped Neur
Ejiogu 2011 | The Gerontologist
George 2004 | Am J Public Health
Gilmore-Bykovskyi 2019 | Alz & Dem: TRCI
Gul & Ali 2009 | J Clin Nursing
Howell 2020 | Alz & Dem
Indorewalla 2021 | J Alz Dis
Oh 2015 | PLoS Medicine
Otado 2015 | Clin Trans Sci
Probstfield & Frye 2011 | JAMA
Robinson & Trochim 2007 | Ethn Health

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Diversity as a *workflow* problem

Sampling frame

Awareness

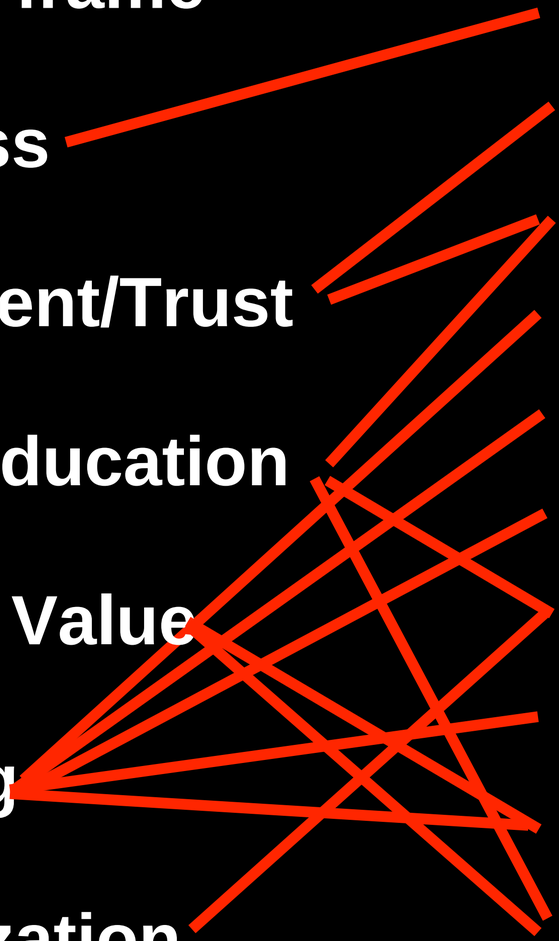
Engagement/Trust

Interest/Education

Return of Value

Screening

Randomization



Lack of awareness of research opportunities

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Confusion and concern over what research is

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Jackson | under review

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Study Design

Randomization

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Jackson | under review

Trends in
Molecular Medicine

CellPress

Science & Society

The Urgency of Justice in Research: Beyond COVID-19

Andrea Gilmore-Bykovskyi [1,*]
Jonathan D. Jackson,[2,3] and
Consuelo H. Wilkins[4,5]

The striking imbalance between disease incidence and mortality among minorities across health conditions, including coronavirus disease 2019 (COVID-19) highlights their under-inclusion in research. Here, we propose actions that can be adopted by the biomedical scientific community to address long-standing ethical and scientific barriers to equitable representation of diverse populations in research.

'Who ought to receive the benefits of research and bear its burdens? This is a question of justice…' - The Belmont Report

From 1932 to 1972, the US Public Health

yet comprise just 4% of participants in Moderna's Phase I/II severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) vaccine trial[i], with improvements promised for Phase III[ii] [1]. Similar trends exist for Latino and Indigenous Americans, with ~74 Latino deaths per 100 000 and 90 Indigenous deaths per 100 000[i]. Amid unprecedented urgency to accelerate the development of safe, effective SARS-CoV-2 vaccines, there is growing concern that trials will paradoxically fail to include those at greatest risk for contracting and dying from COVID-19 [2].

The time is long overdue to fulfill the Belmont Report's principle of justice: equitable distribution of risks and benefits of research[iii]. Despite good intentions, we propagate and maintain a system where non-white populations bear the burden of disease but do not reap the benefits of research advances. This phenomena is evident globally, whereby lower and middle income countries (LMICs), predominantly in Africa, Asia, and Latin America, experience higher burdens of disease and lower life expectancy yet remain under-represented in clinical trials [3]. In 2019, there were 27 461 trials regis-

represent 16% of the world's population, compared with 7743 trials in LMICs, which comprise the remaining 84% (Figure 1)[iv,v]. Conversely, therapeutic breakthroughs made possible by trials conducted in LMICs may remain inaccessible to segments of these populations despite their disproportionate disease burden; for example, despite ethically controversial studies on preventative interventions for vertical transmission of HIV conducted during the 1990s in Africa, regional disparities in access to antiretroviral medications persist[vi] [4]. Shifting demographics, both globally and within the USA, demonstrate that such imbalances are likely to accelerate because non-white US populations are projected to become majority demographics by 2044[vii].

The exploitation and neglect of non-white populations in biomedical research are not insular phenomena but rather a direct consequence of dominant social forces and the histories that shape them. Effectively addressing inequities in research participation requires us to acknowledge their existence as harmful and unethical, as addressable rather than immutable. We must question the status quo, which

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Justice: Belmont's Forgotten Pillar

- Strengthen compliance, reporting, transparency
  - Demographic / subgroup data often unreported, missing, despite requirements
  - Develop detailed, transparent reporting as well as accountability (enforcement)
  - End ongoing research abuses (yes, even after Belmont)
- Identify, measure, systemically address exclusionary research
  - Assess and address data burden
  - Model overlapping, currently unmeasured selection biases
  - Promote language equity, even for English speakers
  - End practices that exclude on the basis of researcher convenience
- Move beyond proportional representation
  - No scientific basis for representation at the level of census tracts
  - Focus on disease risk or burden
  - No basis for Whites as referent group

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Justice: Belmont's Forgotten Pillar

- Build sustained, reciprocal relationships with marginalized communities
  - Stop centering research goals on researcher / institution
  - Develop participant experience metrics
  - Broaden definition of "participation" in research
  - Don't lament mistrust – become trust*worthy*
- Develop science<u>s</u> of research participation and inclusion
  - Build evidence-based, mechanistic guidance for study design, recruitment, retention
  - Systemically identify and address research barriers
  - Remember that the plural of anecdote is not data, even for diverse recruitment
- Recognize connection between research and health inequities
  - Without justice in research, we cannot solve health inequities
  - Build an infrastructure to support measurement and intervention on justice pillar
  - If successful, will create daylight between *inequities* and *disparities*

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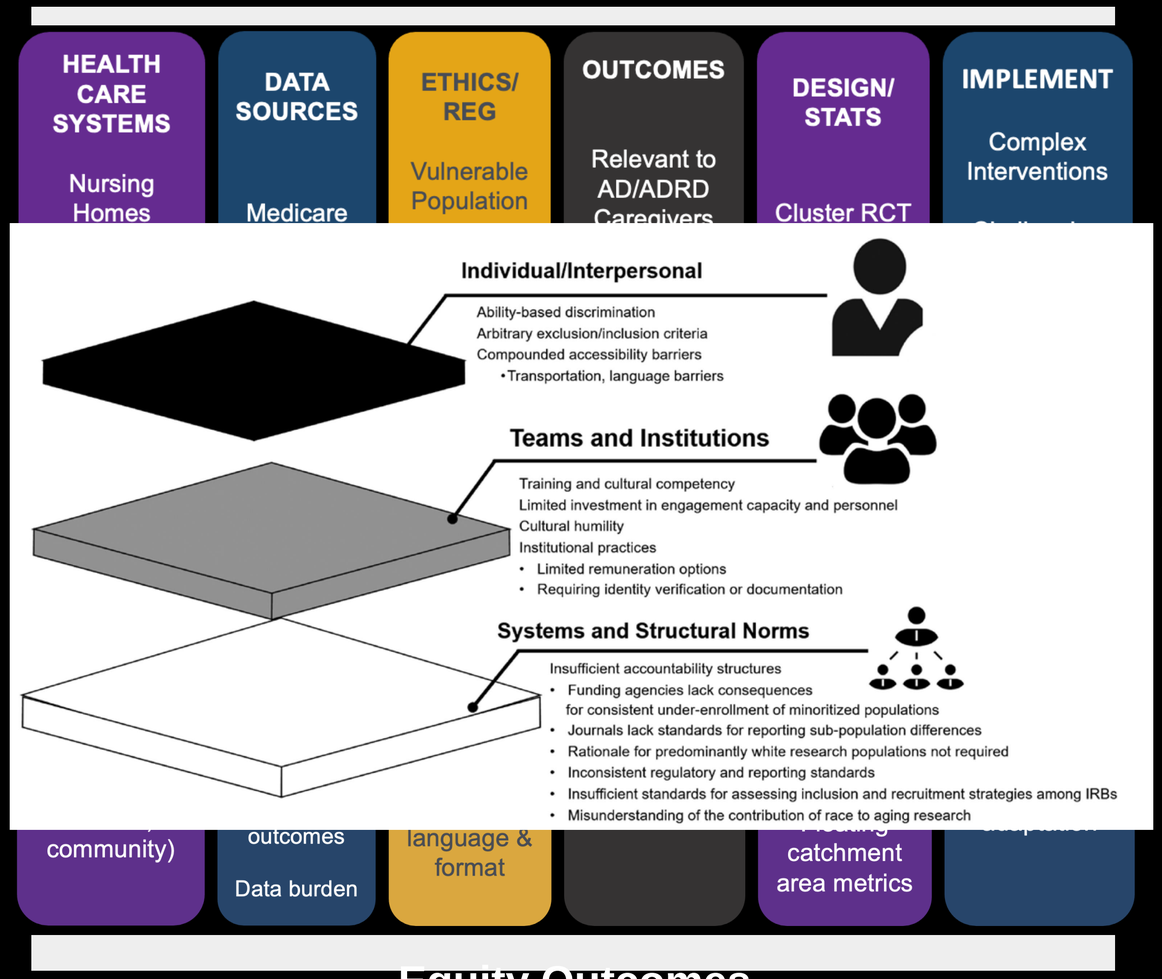
Patient centricity in pragmatic trials

Selection Biases → Measurement Error → Implementation Biases → Social Inequities → Biological Disparities

Traditional Outcomes



Equity Outcomes

- The PRECIS-2 framework for pragmatic trials
  - Nine domains to assess how pragmatic a trial is
  - Often considered strong real-world evidence
  - Randomizes health care systems rather than individuals
- However, need to integrate equity
  - Selection biases *still* occur at level of individual
  - In addition to selection effects at *any* level of randomization
- Proposed changes promoting equity & representation
  - Equity considerations at each domain
  - Additional domain of Value, to focus on Wilkins' Return of Value
  - Added dimension of stakeholder groups for each domain
    - Organizational level: Health care system
    - Team level: Clinician / Research team
    - Individual: Patient and care partner(s)
  - New metrics for each Core Working Group of IMPACT Collaboratory

Quiñones 2020 | J Am Ger Soc
Gilmore-Bykovskyi 2021| The Gerontologist

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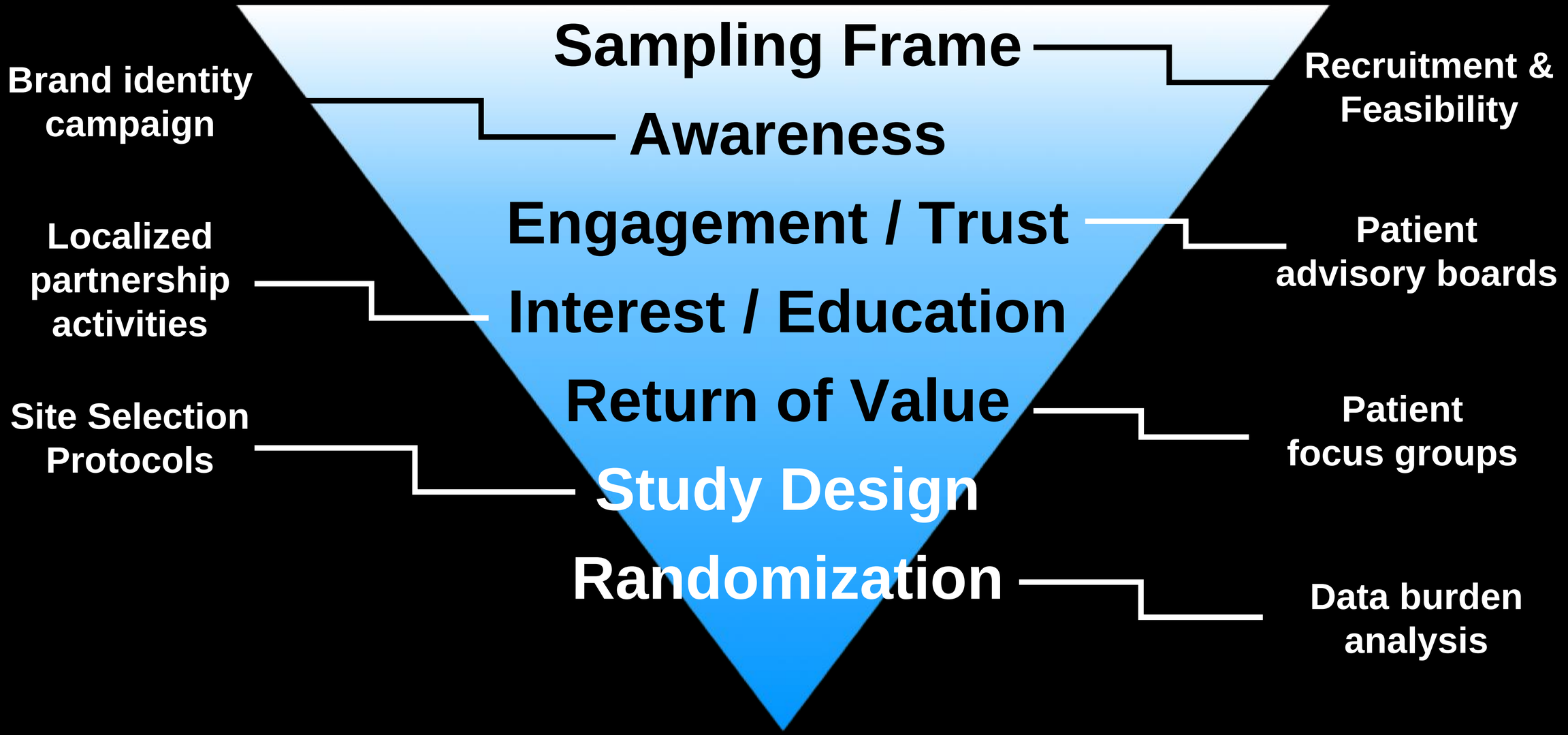
What We're Doing Now: EPPIC-Net



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When you measure
include the measurer.

—MC Hammer

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Bonus slides

(oh dear)

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Table 1. Demographic Subgroups in 2019

DEMOGRAPHIC SUBGROUPS	WOMEN	WHITE	BLACK or AFRICAN AMERICAN	ASIAN	HISPANIC	AGE 65 AND OLDER	UNITED STATES
AVERAGE	72%	72%	9%	9%	18%	36%	40%

*Data presented in this report are from 49 snapshots as one drug was approved for two indications.

Est US pop	50.8%	76.5%	13.4%	5.9%	18.3%	16.0%	
Median DTS	55%	78%	3%	5%	8%	11.5%	36%
CoV DTS (SD / mean)	0.47	0.35	1.64	1.44	0.85	1.10	0.80