Reflections on how to ensure diversity in clinical practice and clinical trials

Marie von Lilienfeld-Toal
Universitätsklinikum Jena

Disclaimer

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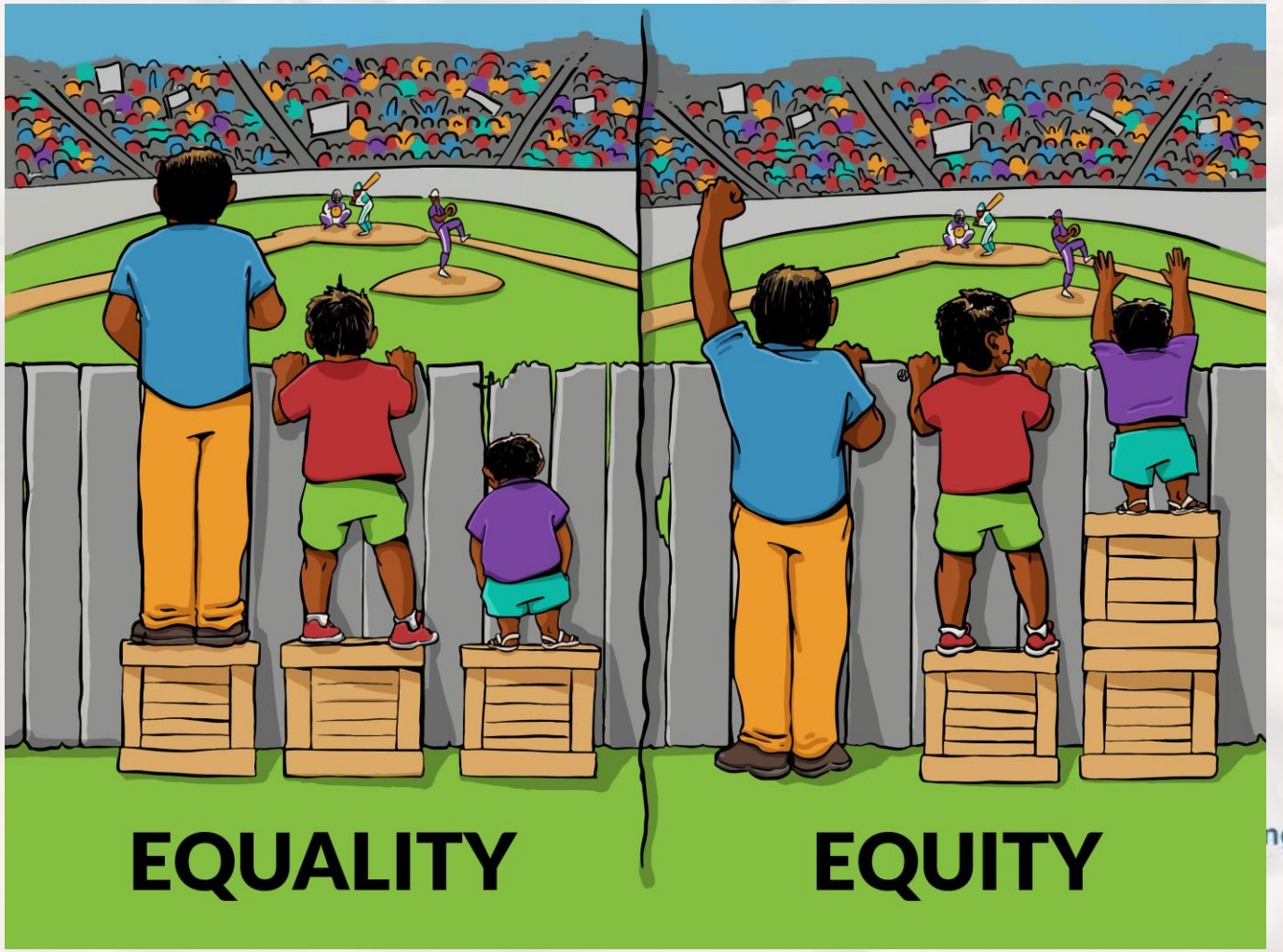
Overview

- What is the aim? To provide the best possible care
  - Representation of population at risk
  - Geographical representation
- Barriers in trial design
  - Definition of parameters/variables/risk factors
  - Eligibility
- Barriers on the side of the patient
  - Accessibility
- Barriers on the side of the physician
  - Commitment to diversity, equity and inclusion

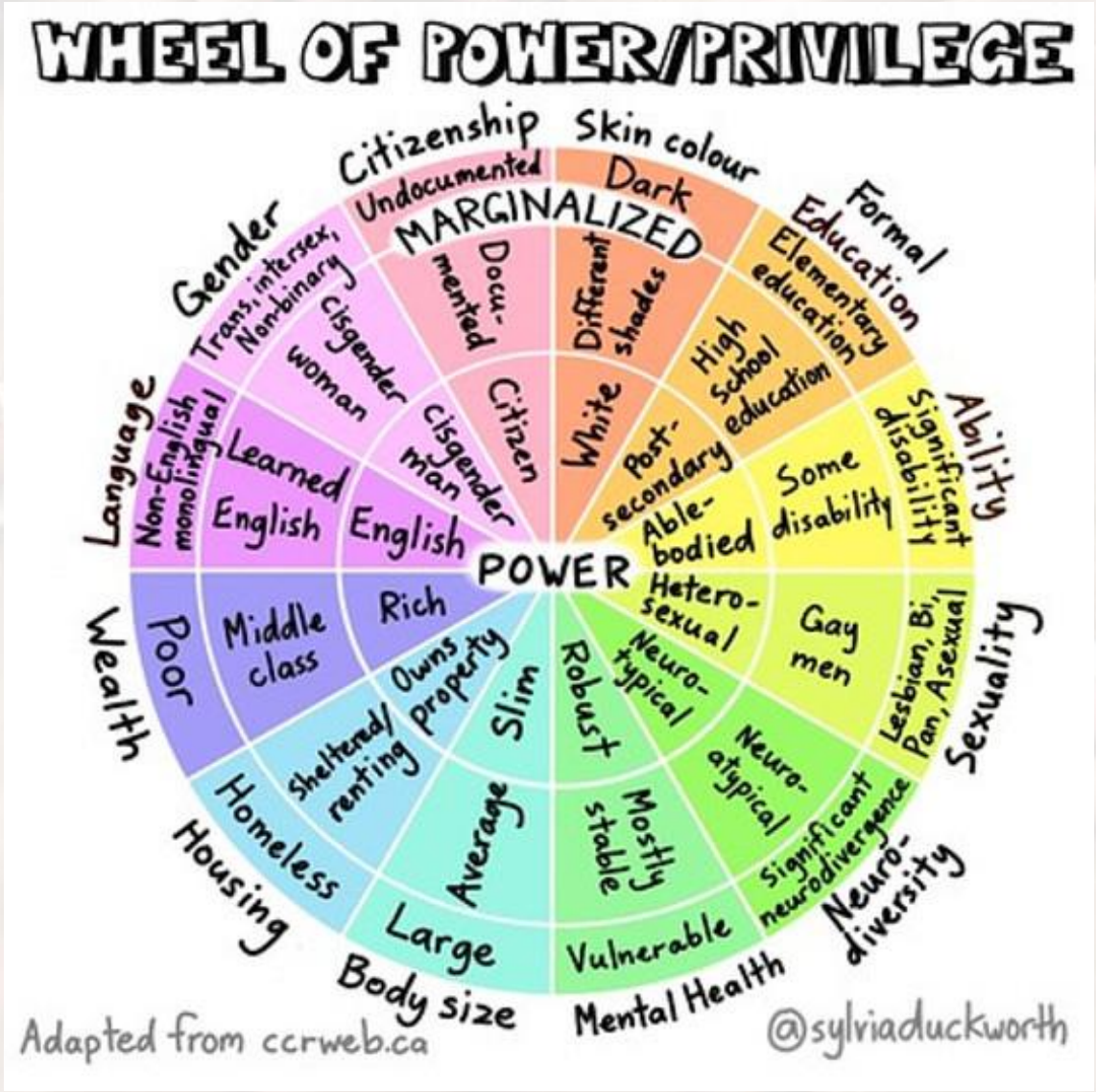
What is the aim?

To provide the best possible care to everyone everywhere

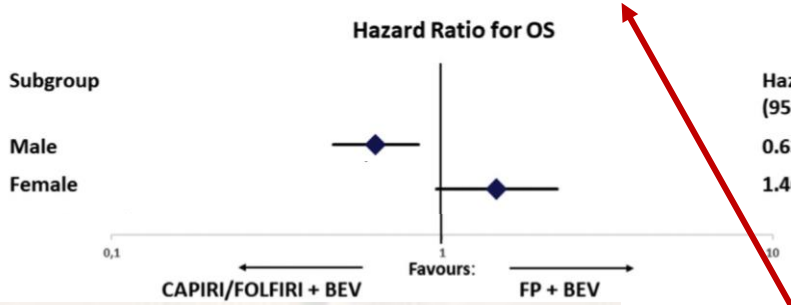


Interaction Institute for Social Change | Artist: Angus Maguire

What needs to be considered?



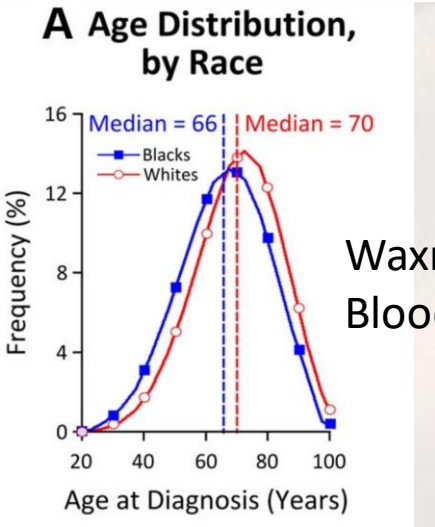
Triple-therapy for colorectal cancer only beneficial for men



Hazard Ratio
(95% confidence interval)
0.63 (0.47-0.85)
1.46 (0.96-2.24)

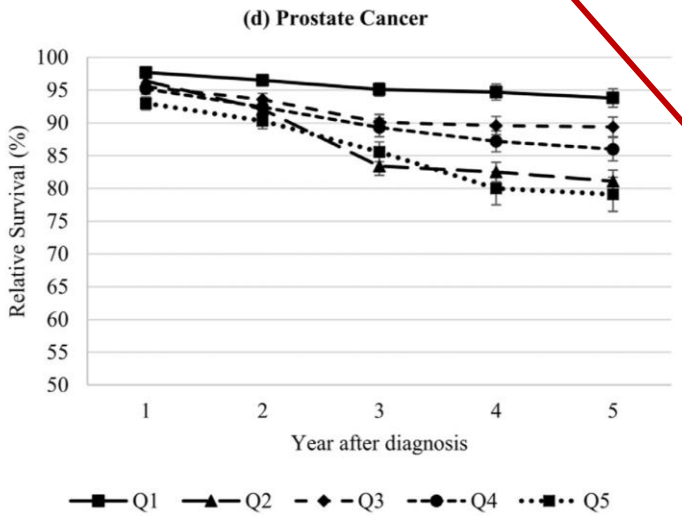
Heinrich et al., Eur J Cancer 2021

Multiple Myeloma 4 years earlier in Black people



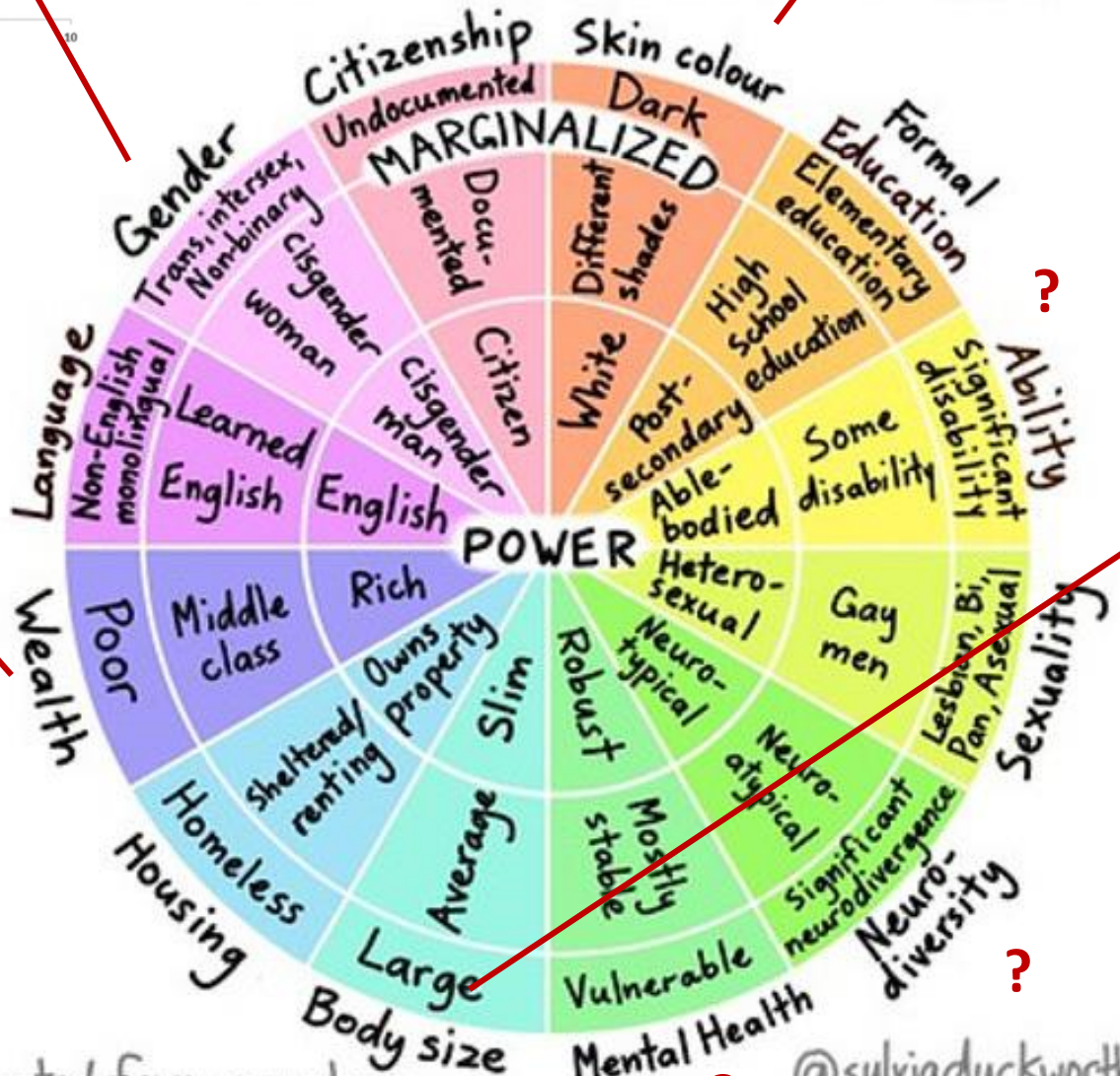
Waxman et al., Blood 2010

Prostate cancer in Germany: 5-y OS 15% lower in most deprived population



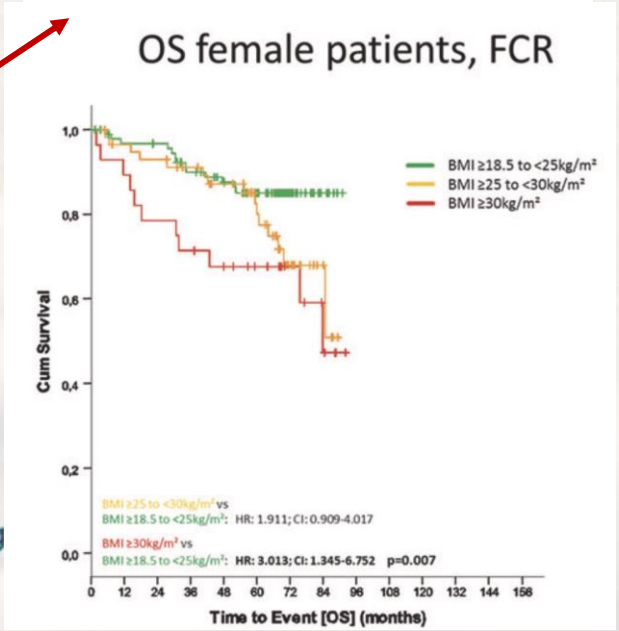
-2018 by socioeconomic deprivation quintile (Q1 – least deprived; Q5 – most deprived).

Jansen et al., Lancet Reg Health Eur 2021



Adapted from ccrweb.ca

Immune-therapy NHL only beneficial for slim women



Fürstenau et al., Leukemia 2020

What needs to be considered?

- Diversity, yes, in addition: geography…….

Geography

- Example: Pharmacogenomics Voriconazole

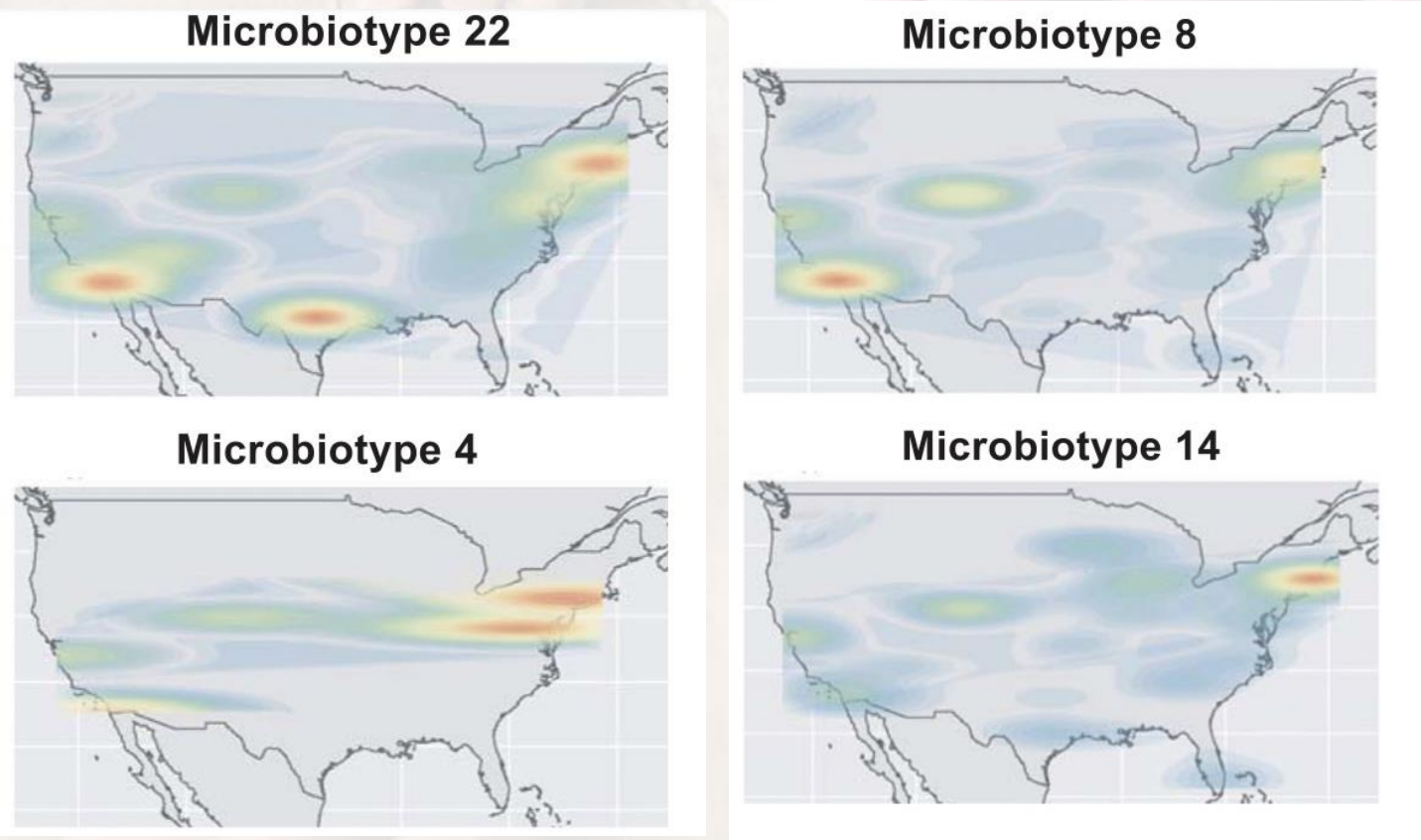
Frequencies of CYP2C19 phenotypes in biogeographical groups

Phenotype	African American/Afro-Caribbean	American	Central/South Asian	East Asian	European	Latino	Near Eastern	Oceanian	Sub-Saharan African
Ultrarapid Metabolizer	0.042943195	0.0074097984	0.029163336	0.00042194634	0.04641379	0.02774172	0.03664265	0.003249	0.030045323
Rapid Metabolizer	0.2373838	0.13638271	0.18567303	0.025343522	**0.2711846**	0.24136075	0.2573682	0.021329276	0.21080859
Poor Metabolizer	0.040512204	0.014819587	0.08156806	0.12978691	0.02387743	0.011408395	0.01858484	**0.5713864**	0.036714304
Normal Metabolizer	0.32805592	**0.62755567**	0.29552925	0.38055435	0.39611652	0.5249766	0.45192146	0.035006005	0.36977687
Likely Poor Metabolizer	0.007090685	0.0	0.0	0.0004349198	0.00020405183	0.0004440685	0.0	0.0	0.010332189
Likely Intermediate Metabolizer	0.027788177	0.0	0.0	0.00076989824	0.0011160374	0.003709162	0.0	0.0	0.042863965
Intermediate Metabolizer	0.31398684	0.21383229	0.40806636	0.45928204	0.26108757	0.19035932	0.2354828	0.36902928	0.29945874
Indeterminate	0.0022393465	0.0	0.0	0.0034064606	0.0	0.0	0.0	0.0	0.0

https://www.pharmgkb.org

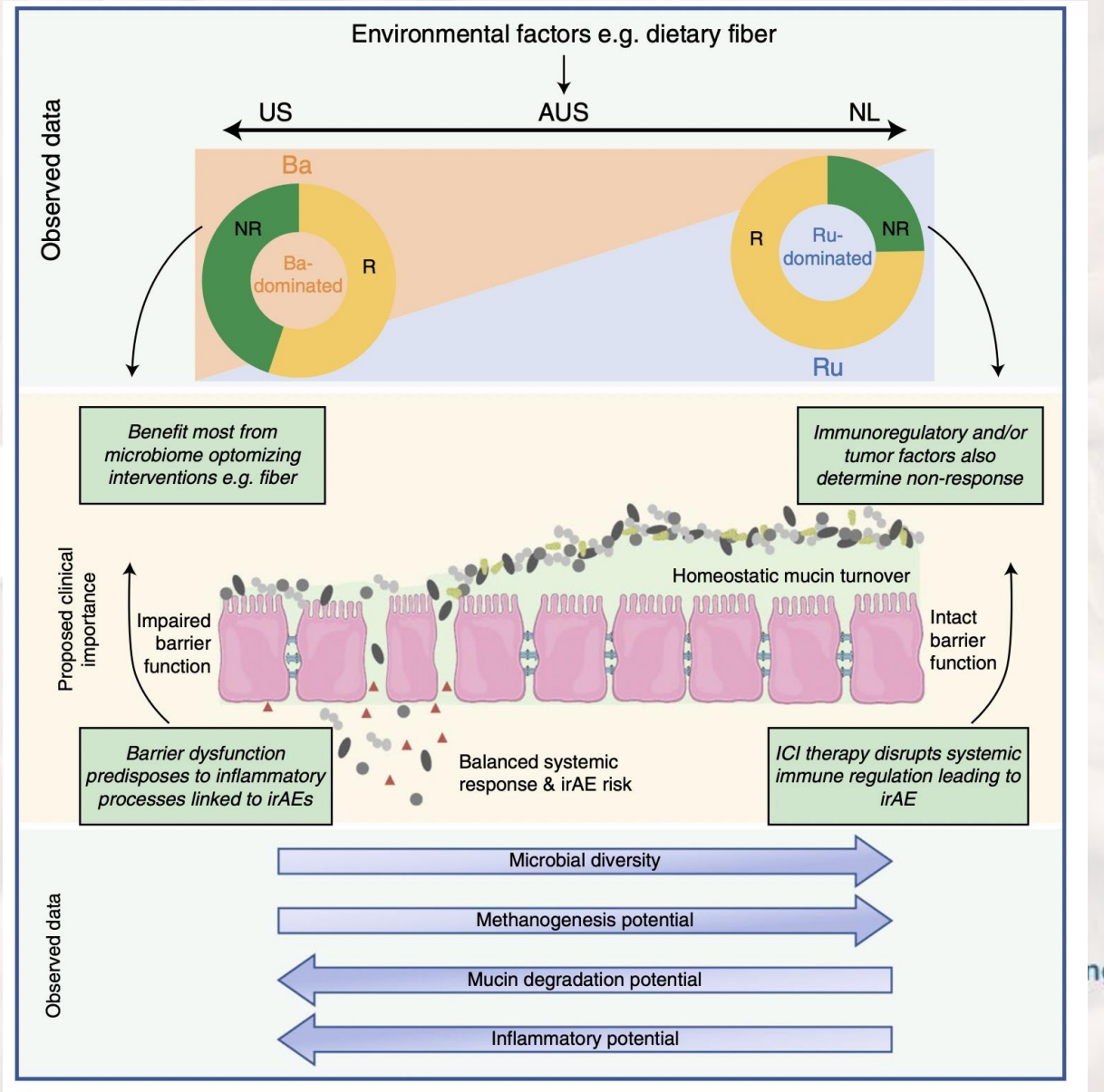
Geography

- Example: Diet, microbiota and immunotherapy



McCullock et al., Nat Med 2022

Geography



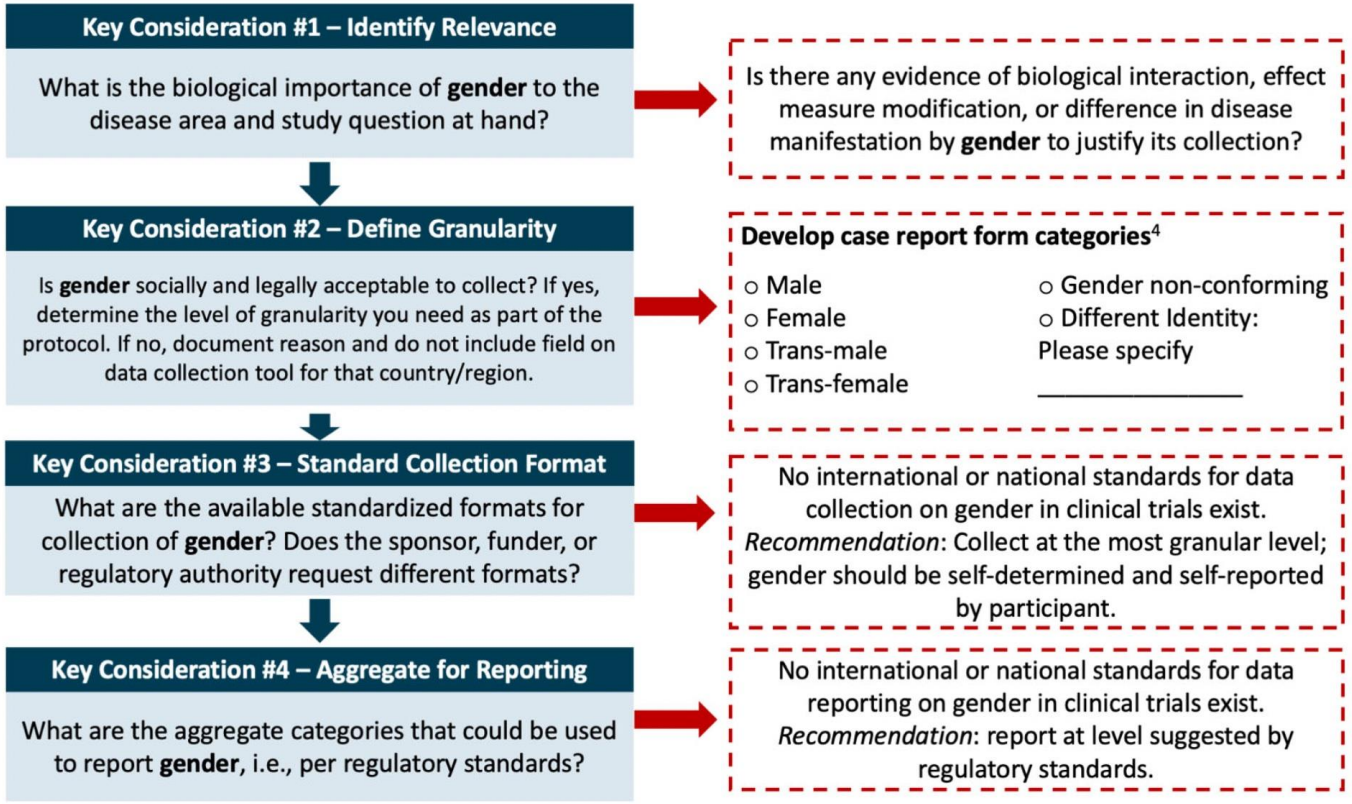
Simpson et al., Nat Med 2022

Trial Design - Variables

- Sex – or gender? Or both? And if so, how many? Including or excluding sexual orientation?
- Race? Ethnicity? Ancestry? Self-assigned? Tested?
- Class? Socioeconomic status? Income? Insurance? Education?

Trial Design - Variables

Figure 3: Key considerations for **gender**[3] as a data element during protocol development and study design



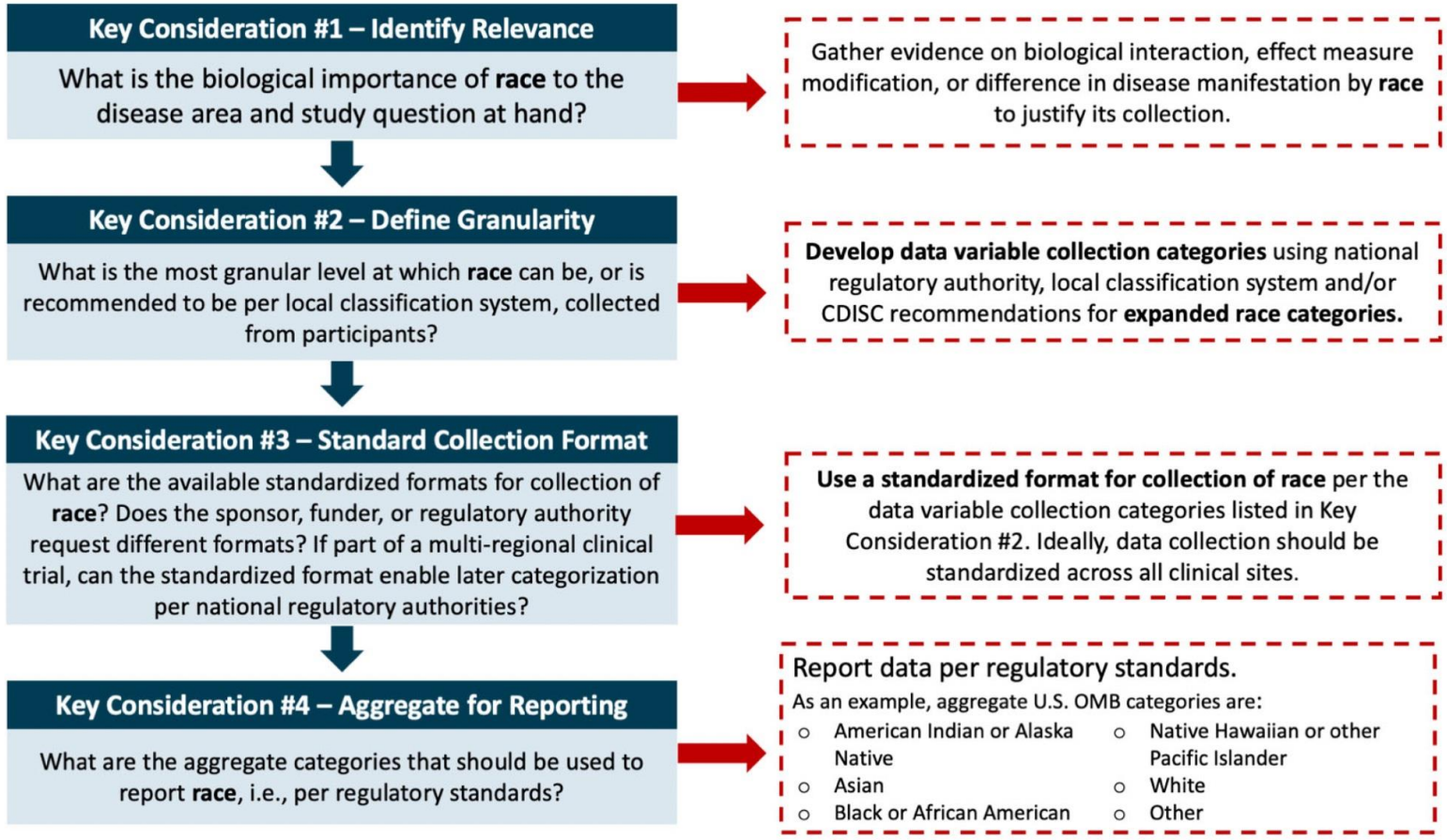
more often than not: yes

[3] 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. World Health Organization. Glossary of terms and tools [Internet]. WHO. Available online: https://www.who.int/gender-equity-rights/knowledge/glossary/en/ (accessed May 07 2020).

Bierer B.E. et al. (2021). *Achieving Diversity, Inclusion, and Equity in Clinical Research* Guidance Document Version 1.2. Cambridge and Boston, MA: Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center).
Available at: https://mrctcenter.org/diversity-in-clinical-trials/

Trial Design - Variables

Figure 2: Key considerations for **race** as a data element during protocol development and study design



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Differences attributable to what?

1 cohort

		Male n=179 (57%)	Female n=134 (43%)	p
Median age at SCT		59 (31-73)	59 (33-73)	0.523
Dose of Melphalan	MEL200	113 (63%)	79 (59%)	0.483
	MELRed	66 (37%)	55 (41%)	
Toxicity	Haem.	168 (94%)	132 (98%)	0.103
	Infections	131 (73%)	93 (69%)	0.527
	GI	91 (51%)	88 (66%)	0.107
	Mucositis	**39 (22%)**	**54 (40%)**	**0.001**
	Cardiovasc.	18 (10%)	13 (10%)	0.792
Response after SCT (≥VGPR)		157 (88%)	113 (84%)	0.410
Relapse (N=311)		99 (56%)	79 (59%)	0.504

?

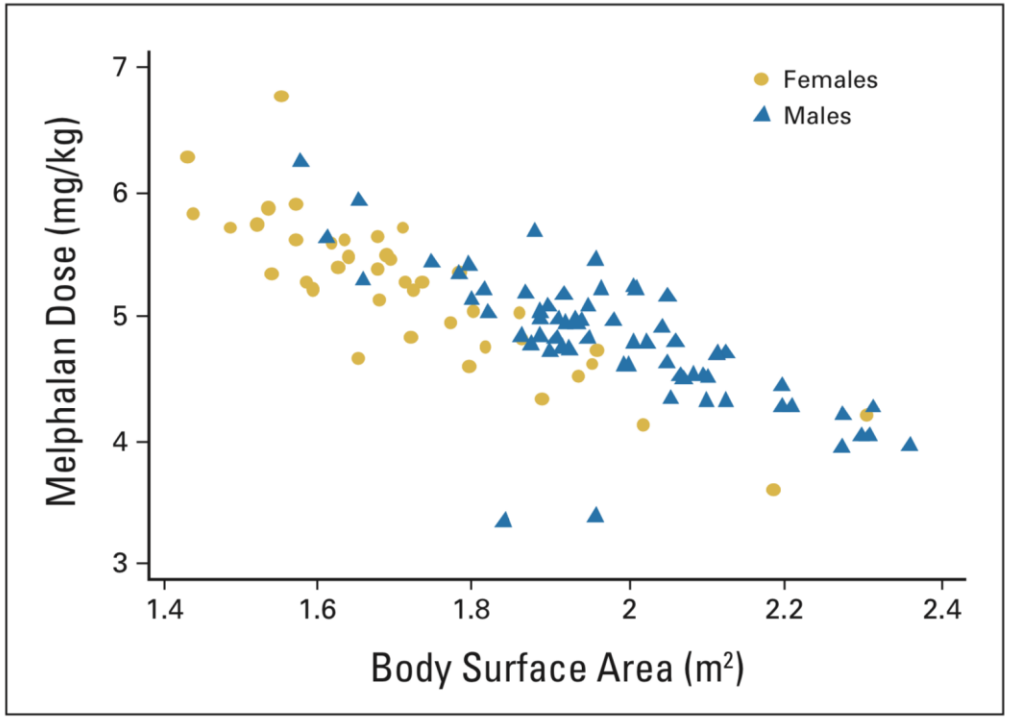
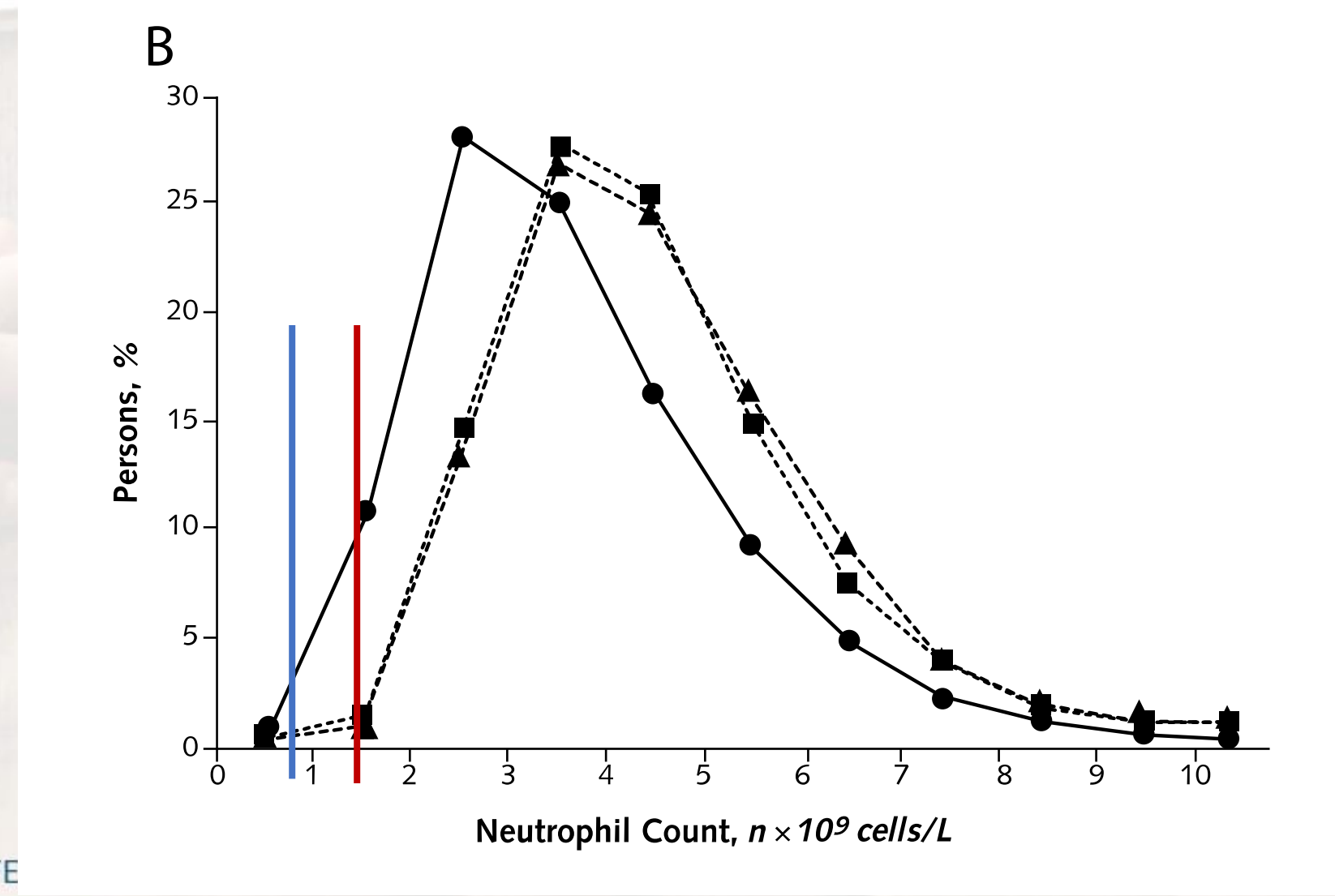


Fig 4. Scatterplot of melphalan dose in milligrams per kilogram of body weight and body-surface area in patients with multiple myeloma.

Brioli et al., Oncol Res Treat 2022

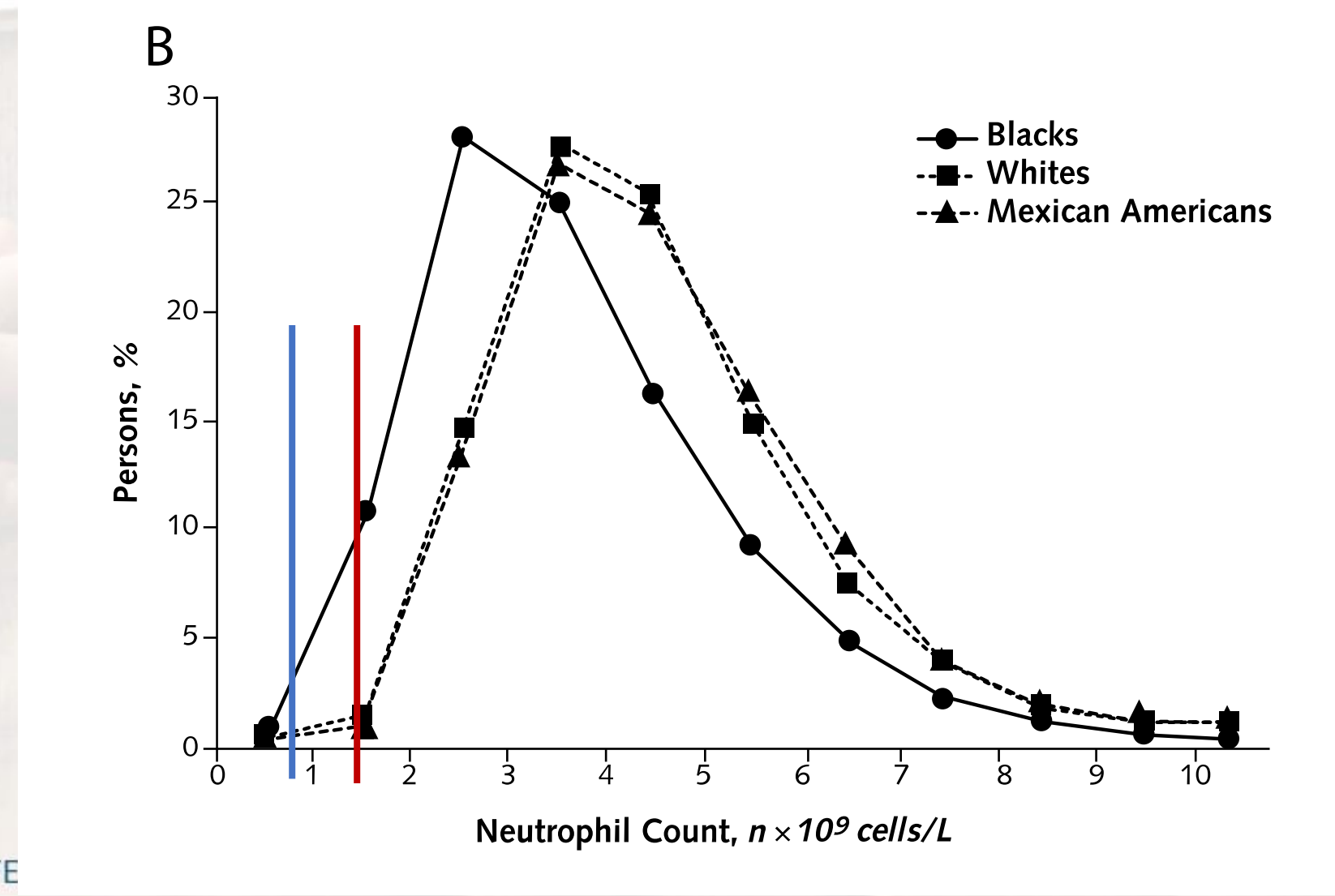
Blijlevens et al., J Clin Oncol 2008

Trial Design Eligibility Criteria



Hsieh et al., Ann Intern Med. 2007

Trial Design Eligibility Criteria



Hsieh et al., Ann Intern Med. 2007

American Society of Clinical Oncology Road to Recovery Report: Learning From the COVID-19 Experience to Improve Clinical Research and Cancer Care

Pennell et al., J Clin Oncol 2020

The specific goals are:

1. ensure that clinical research is accessible, affordable, and equitable;
2. design more pragmatic and efficient clinical trials;
3. minimize administrative and regulatory burdens on research sites;
4. recruit, retain, and support a well-trained clinical research workforce;
5. promote appropriate oversight and review of clinical trial conduct and results.

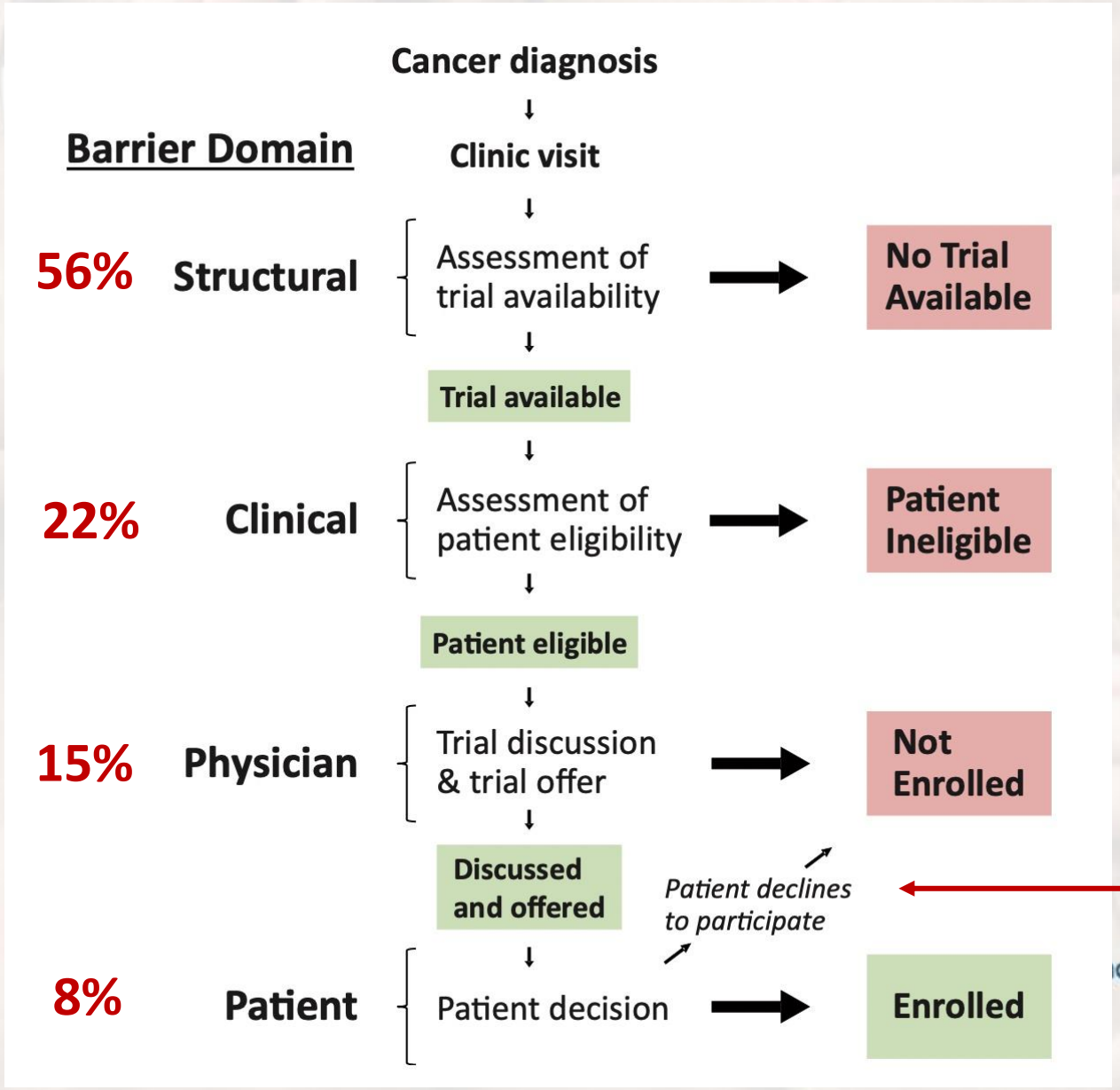
Pragmatic Approach to Eligibility

Eligibility criterion	Recommendation
Washout periods	• No time based washout periods unless scientifically justified • Instead use objective parameters (lab values/clinical findings)
Concomitant medication	• Only exclusion factor if relevant drug-drug interactions exist and potential toxicities will impact safety or efficacy
Prior therapy	• Only exclusion factor of potential interaction with study drug
Laboratory ranges	• Account for variations due to race, ethnicity, age, sex, and gender identity (i.e., due to surgical and/or hormonal changes • Only exclusion factor if potential safety concerns
Performance status	• ECOG PS eligibility criteria should be based on the patient population in which the intervention is expected to be used in clinical practice • PS should only be used as exclusion factor if scientific or clinical rationale • The rationale for exclusion should be justified and stated explicitly.

Kim et al., Clin Cancer Res 2021

Accessible Trials: Patient Barriers

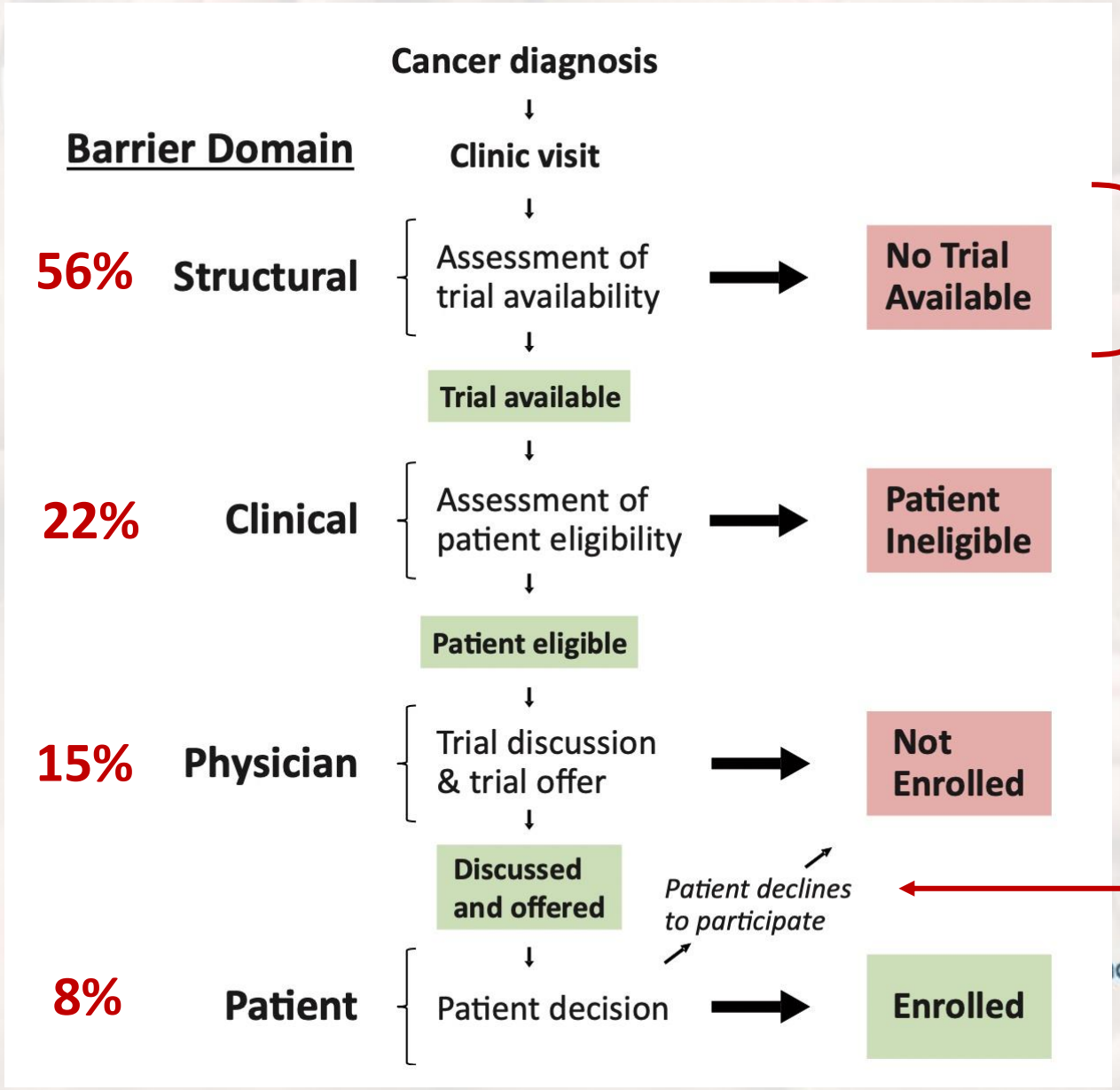
Meta-Analysis of 13 cancer trials with 8883 patients



- Lack of Trust
- Financial Barriers

Unger et al., JNCI 2019

Accessible Trials: Patient Barriers



Meta-Analysis of 13 cancer trials with 8883 patients

8% enrollment expected

That means, **80%** of patient population not reflected by trial population

Beware licensing for study population only!

- Lack of Trust
- Financial Barriers

Unger et al., JNCI 2019

If offered……

Table 4. Rates of agreement to participate if offered a trial by race and ethnicity

Comparison group	White	Black	Hispanic	Asian
All studies				
No. of studies	16	15	8	6
Rate, % (95% CI)	56.0 (47.3 to 64.5)	60.4 (49.5 to 70.8)	67.1 (57.4 to 76.2)	63.6% (39.2 to 85.3)
By study setting				
Treatment, % (95% CI)	53.4 (44.8 to 61.9)	57.6 (45.1 to 69.6)	64.9 (52.9 to 76.1)	61.7 (34.7 to 85.9)
Cancer control, % (95% CI)	75.9 (52.5 to 93.2)	70.4 (47.1 to 89.6)	72.5 (54.4 to 87.8)	79.8 (7.7 to 100)
P	.08	.33	.48	.65

Meta-Analysis
of 35 cancer trials (treatment and control) with participation offered to 9759 patients

Unger et al., JNCI 2020

Why is a trial not offered?

- Time constraint
- Limited ressources
- Implicit bias and lack of awareness

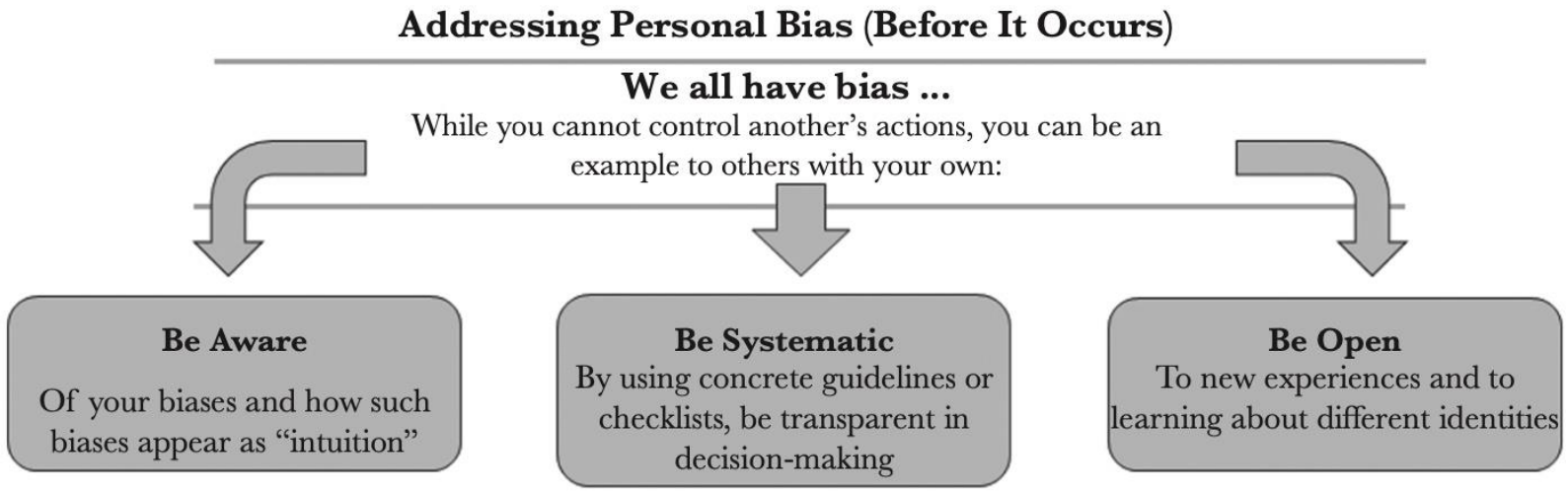
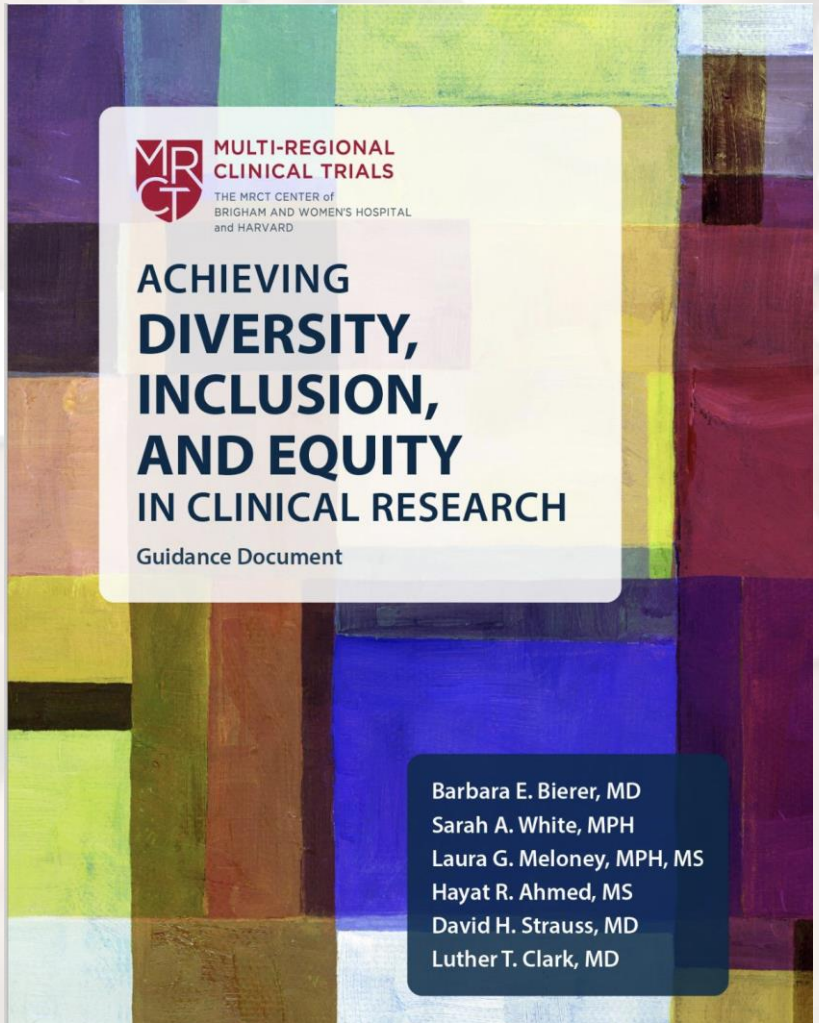


Figure 3. Strategies to address personal bias before and after it occurs.

What needs to be done?

- **Commit** to diversity, inclusion and equity
- Get **help:**



Available at:
https://mrctcenter.org/diversity-in-clinical-trials/

Personal View – some thoughts

- Personal Practice: mainly outpatient department, focus on multiple myeloma, university hospital

- **Barriers** towards better representation of focus population:
  - Focus population not well defined
  - Scientific question possibly of minor relevance
  - Studies not well designed (for example ePRO in rural elderly population)
  - Adverse culture in academic medicine that leads to underrepresentation in work force
  - Lack of money, lack of time, lack of people
  - Misinformation and lack of trust

Personal View – some thoughts

- Personal Practice: mainly outpatient department, focus on multiple myeloma, university hospital

- **Help** could come from:
  - Actually meaning what we say, i.e. commitment
  - Accountability
  - Enough ressources
  - Culture of reflexivity in medicine (Landy et al., Forum: Qualitative Social Research 2016)
  - Make personal career and self-esteem independent of study results and study conduct