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The Impact of Demographic Diversity on Efficacy Outcomes in Clinical Trials

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INTRODUCTION

- Clinical trials are the gold standard for organizations responsible for regulating and approving new drug treatments, yet women and racial minorities have historically been underrepresented in clinical trials[1]
- Relative efficacy, an outcome measure that compares the clinical endpoints of the intervention arm versus a control arm, is the crucial piece of evidence used to support the effectiveness of a new drug and its regulatory approval[2]
  - In oncology, overall survival (OS) hazard ratio (HR) is the key relative efficacy measure comparing the OS of the intervention arm versus the OS of the control arm
  - An OS HR <1 indicates the intervention arm is more effective than the control arm
- Given the importance of relative efficacy in drug approvals, we need evidence to determine whether the lack of representation of women and racial minorities in clinical trials may bias relative efficacy, which in turn, may bias drug approvals

OBJECTIVES

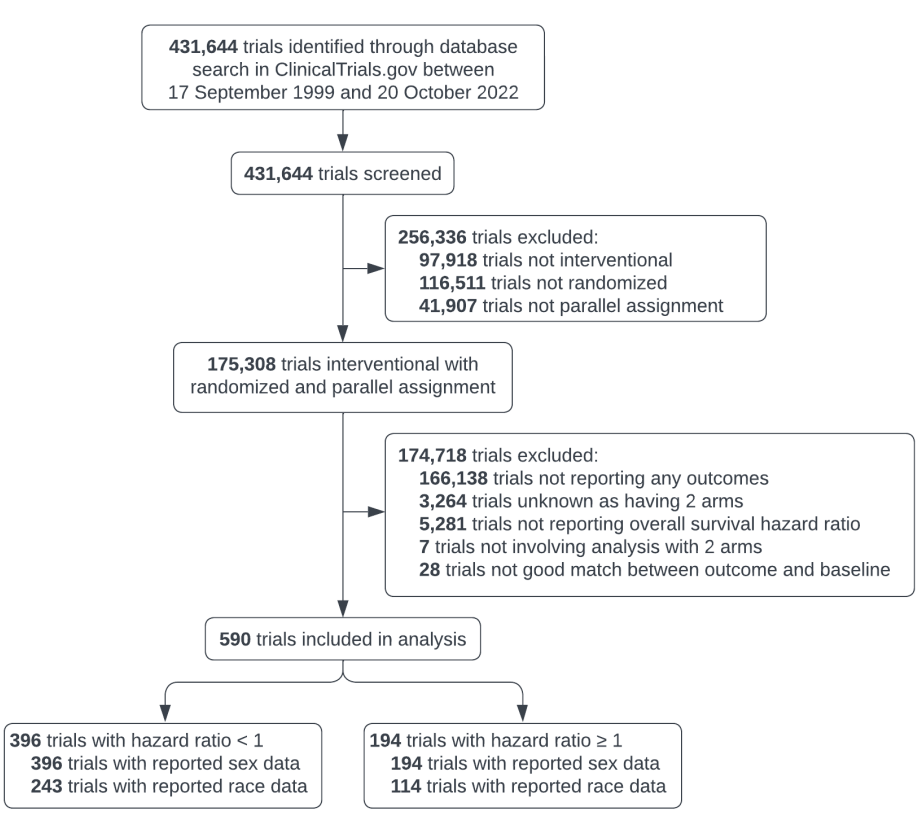
We aimed to investigate whether and how race and sex at baseline are associated with the relative efficacy of intervention drugs versus standard of care in clinical trials.

METHODS

Setting and trial identification

- We downloaded all clinical trials registered on ClinicalTrials.gov using the Aggregate Analysis of ClinicalTrials.gov (AACT) database[3]
- We filtered for all trials that were interventional with parallel and randomized assignment
- We further narrowed our selection to two-armed trials that reported an OS HR
  - OS HR is the most comparable relative efficacy measure across trials in various disease categories
  - All trials in our dataset are oncological given the focus on OS HR

Figure 1. PRISMA flow diagram of the trial selection procedure



Data extraction

- In this study, the primary outcome variable was whether OS HR <1. The secondary outcome variables were the OS HR itself and the p-value testing whether OS HR=1
- The primary exposure variables were the proportion of participants from each sex and race group
  - Sex: male, female
  - Race: White, Black, Asian, Other

Statistical analysis

- For primary outcome (HR <1 or not), we used multivariate logistic regression on each exposure variable controlling for all other trial-level covariates. Adjusted odds ratios (ORs) with 95% confidence intervals (CI) are reported
- For secondary outcomes (HR and its associated p-value), we used multivariate linear regressions on each exposure variable controlling for all other trial-level covariates. Regression coefficients with 95% CIs were reported
- We used three model settings for including exposure variables
  - Proportion of a given sex or race group separately included (base case)
  - Proportions of all race groups jointly included
  - Proportions of all sex and race groups jointly included

Table 1. Number of sample trials by whether hazard ratio < 1

	Full sample	Hazard ratios <1	Hazard ratios ≥1
Sex Reported	590	396 (67%)	194 (33%)
Race Reported	357	243 (68%)	114 (32%)
Phase			
2	168	95 (56%)	76 (44%)
3	419	298 (72%)	118 (28%)
4	3	3 (100%)	0 (0%)
Masking			
None (Open label)	330	219 (66%)	111 (34%)
Single	3	1 (33%)	2 (67%)
Double	106	66 (62%)	40 (38%)
Triple	45	32 (71%)	13 (29%)
Quadruple	106	78 (74%)	28 (26%)
Funding source			
Industry	478	331 (69%)	147 (31%)
Network	48	31 (65%)	17 (35%)
National Institutes of Health (NIH)	28	16 (57%)	12 (43%)
Other	36	18 (50%)	18 (50%)
Total participants			
<200	162	97 (60%)	65 (40%)
[200, 400)	126	83 (66%)	43 (34%)
[400, 600)	106	76 (72%)	30 (28%)
≥600	196	140 (71%)	56 (29%)

Note: Not all trial-level covariates are listed due to space constraints.

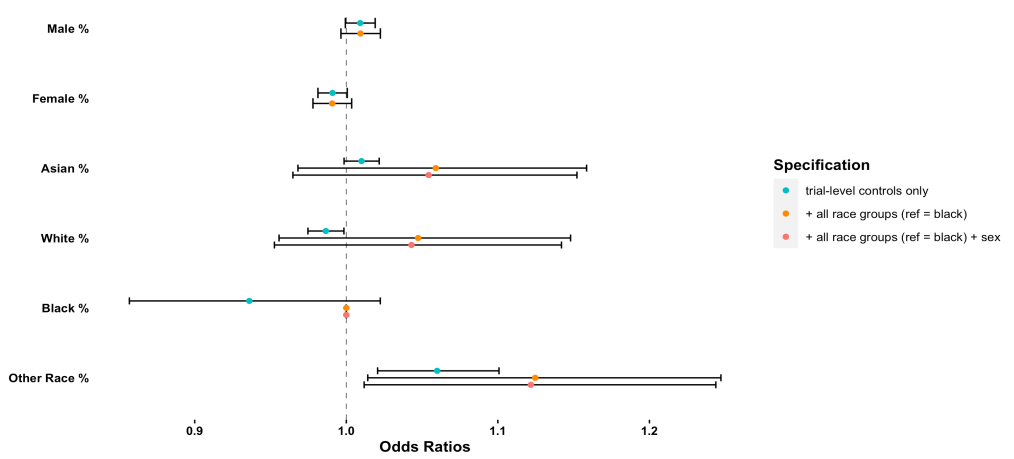
RESULTS

Base case regression results where proportion of a given sex or race group was separately included and all trial-level covariates were controlled:

- A higher proportion of male participants was **positively** associated with the odds of HR <1 (adjusted OR, 1.009; 95% CI, 0.996 to 1.022; P = 0.162)
- A higher proportion of White participants was significantly and **negatively** associated with the odds of HR <1 (adjusted OR, 0.986; 95% CI, 0.975 to 0.998; P = 0.027)
- A higher proportion of Black participants was **negatively** associated with the odds of HR <1 (adjusted OR, 0.936; 95% CI, 0.857 to 1.023; P = 0.143)
- A higher proportion of Asian participants was **positively** associated with the odds of HR <1 (adjusted OR, 1.010; 95% CI, 0.999 to 1.022; P = 0.088)

Results were similar across all three model settings and all secondary outcomes (see Figure 2)

Figure 2. Association of sex and race with whether hazard ratio < 1



DISCUSSION

- These results suggest two possible mechanisms:
  - Demographic sub-populations may have different relative efficacies in certain disease categories
  - Trials with more diversity may differ from trials with less diversity in unobserved ways
- Under-enrollment of women and racial minorities biases medical evidence towards the development, approval, and use of drugs with understudied efficacy and safety in certain sub-populations

CONCLUSIONS

- Sex and race composition at baseline were associated with relative efficacy as measured by the overall survival hazard ratio
- Increased participation from male or Asian participants in an oncological trial was associated with a higher chance of finding the treatment arm more effective. By contrast, increased participation from female, White, or Black participants was associated with a lower chance.

An electronic version of the poster can be viewed by scanning the QR code.

REFERENCES

1. US Food and Drug Administration. 2019. https://www.fda.gov/drugs/development-approval-process-drugs.
2. Kleijnen et al. Value in Health 2012; 15(6): 954-60.
3. Tasneem et al. PLOS ONE 2012; 7(3): e33677.

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