Assessment of Potential Barriers to Inclusion in Randomized Clinical Trials Published in Top General and Internal Medical Journals

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Background

- Racial and ethnic minority groups are underrepresented in clinical research.
- Racially diverse individuals that speak languages other than English or have limited proficiency may be hindered from participation in randomized clinical trials (RCTs) through eligibility criteria. [1,2]

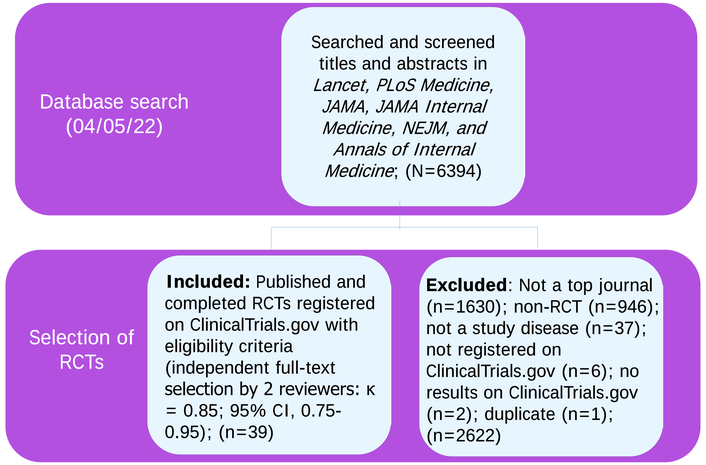
Objective

- To assess English language requirements for enrollment in registered and published RCTs as well as readability of eligibility criteria.

Design

- Cross-sectional study of RCTs on heart disease, stroke, cancer, asthma, influenza and pneumonia, diabetes, HIV/AIDS, and COVID-19 drug interventions retrieved from MEDLINE, Scopus, Epistemonikos, EBSCOHost, COVID-19 evidence, Web of Science Core Collection, and the WHO COVID-19 databases.
- Included published RCTs were:
  (1) within the top 10 first-quartile general and internal medicine journals in 2017 with at least 1 US site;
  (2) published between 2017 and 2022; and
  (3) registered on ClinicalTrials.gov with eligibility criteria in protocols.
- Eligibility criteria in protocols, informed consent forms, and ClinicalTrials.gov were assessed for indications that English was an enrollment requirement.
- Readability was assessed with Flesch-Kincaid grade (FKG) level (ranges from grades 0 to 18) and Gunning-Fog (GF) (ranges from grades 0 to 20 [college graduate]), where lower grades correspond to easier readability.
- Reporting of participant race and concordance between articles and ClinicalTrials.gov were determined

Figure 1. Database search and selection of eligible RCTs on top diseases in top journals



Results

- Total of 39 of 6394 RCTs from *Annals of Internal Medicine* (n = 1), *JAMA* (n = 14), *JAMA Internal Medicine* (n = 3), *Lancet* (n = 11), *PLoS Medicine* (n = 1), and *New England Journal of Medicine* (n = 8) [Figure 1].
- Trials mostly did not disclose which language was required for enrollment (Table 1) of participants reported as: American Indian (median [range], 0 [0-4]), Asian (14 [6-69], Black (median [range], 54 [36-106]), Latinx (45 [4-127]), and White (250 [108-513]).
- Regardless of funder and disease, median [IQR] FKG and GF of eligibility criteria were higher than the recommended sixth grade in protocols (11.5 [10.7-13.0] and 13.0 [11.7-14.5]) and ClinicalTrials.gov (13.0 [11.0-14.0] and 13.7 [11.7-14.7]), respectively.
- There were 17 (44%) RCTs that had at least 1 difference in the reporting of race in the article and ClinicalTrials.gov.

Table 1. Reporting of English Language Requirements for Trial Enrollment in Protocol Eligibility Criteria of Randomized Clinical Trials

	No. (%)			
Characteristic	Total (N = 39)	English language	Other language	No language requirement
Disease studied				
COVID-19	18 (46.1)	3 (7.7)	3 (7.7)	12 (30.8)
Heart disease	6 (15.4)	0 (0.0)	2 (5.1)	4 (10.3)
HIV/AIDS	6 (15.4)	0 (0.0)	1 (2.6)	5 (12.8)
Cancer	5 (12.8)	1 (2.6)	1 (2.6)	3 (7.7)
Diabetes	2 (5.1)	0 (0.0)	1 (2.6)	1 (2.6)
Asthma	1 (2.6)	0 (0.0)	1 (2.6)	0 (0.0)
Pneumonia	1 (2.6)	0 (0.0)	0 (0.0)	1 (2.6)
Funder type				
Industry	23 (56.4)	1 (2.6)	5 (12.8)*	17 (43.6)
Non-industry	16 (43.6)	3 (7.77)	5 (12.8)	8 (20.5)

*The frequency of language stipulations was determined separately from the protocol and informed consent document for one study.[3]

Conclusions

There was low explicit reporting of required languages for enrollment in RCT eligibility criteria; and readability levels of protocols were high. Ethics committees and funders should obligate inclusion of explicit reporting of languages and high readability of RCT information. Responsibility rests with ethics committees, funders, and trialists to conceive inclusive trials to strive toward health equity.

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References
1. George S, Duran N, Norris K. A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders. Am J Public Health. 2014;104(2):e16-e31. doi:10.2105/AJPH.2013.301706
2. Muthukumar AV, Morrell W, Bierer BE. Evaluating the frequency of English language requirements in clinical trial eligibility criteria: a systematic analysis using ClinicalTrials.gov. PLoS Med. 2021;18(9):e1003758. doi:10.1371/journal.pmed.1003758
3. Gillison ML, Trotti AM, Harris J, et al.. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet. 2019 Jan 5;393(10166):40-50. doi: 10.1016/S0140-6736(18)32779-X.