

Reporting clinical trial patient population representativeness in publications – new requirements, future directions

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Introduction

- Diversity in clinical research promotes equity in health outcomes; however, most randomized clinical trials are not representative of patients in everyday practice¹
- Underrepresented groups include those with increased disease burden relative to their representation in the general population²
- Clinical trials often use standard organ function eligibility criteria regardless of the drug under investigation and its potential toxicities, despite differences in organ function reference values between ethnic/racial groups^{3–5}
- Further, ineligible patients based on organ function have been found to have worse outcomes and be more likely to die from disease progression than therapy-related complications^{3,5,6}
- The U.S. Food and Drug Administration (FDA) draft guidance ensures there is a race and ethnicity diversity plan for all medicinal products in the future and recognizes the need to consider gender identity, age, socioeconomic status, disability, pregnancy/lactation status and comorbidities⁷
 - This builds on the existing guidance, Collection of Race and Ethnicity Data in Clinical Trials (October 2016)⁸
- Transparency in reporting of clinical trial representativeness may reinforce the need for trial recruitment of representative participants²
- Recent International Committee of Medical Journal Editors (ICMJE) guidelines recommend authors comment on study population representativeness without providing detailed best practices⁹
- We evaluated journal requirements for representativeness reporting and how these requirements are perceived by health care providers (HCPs) to understand broader implications for health equity and data dissemination

Methods

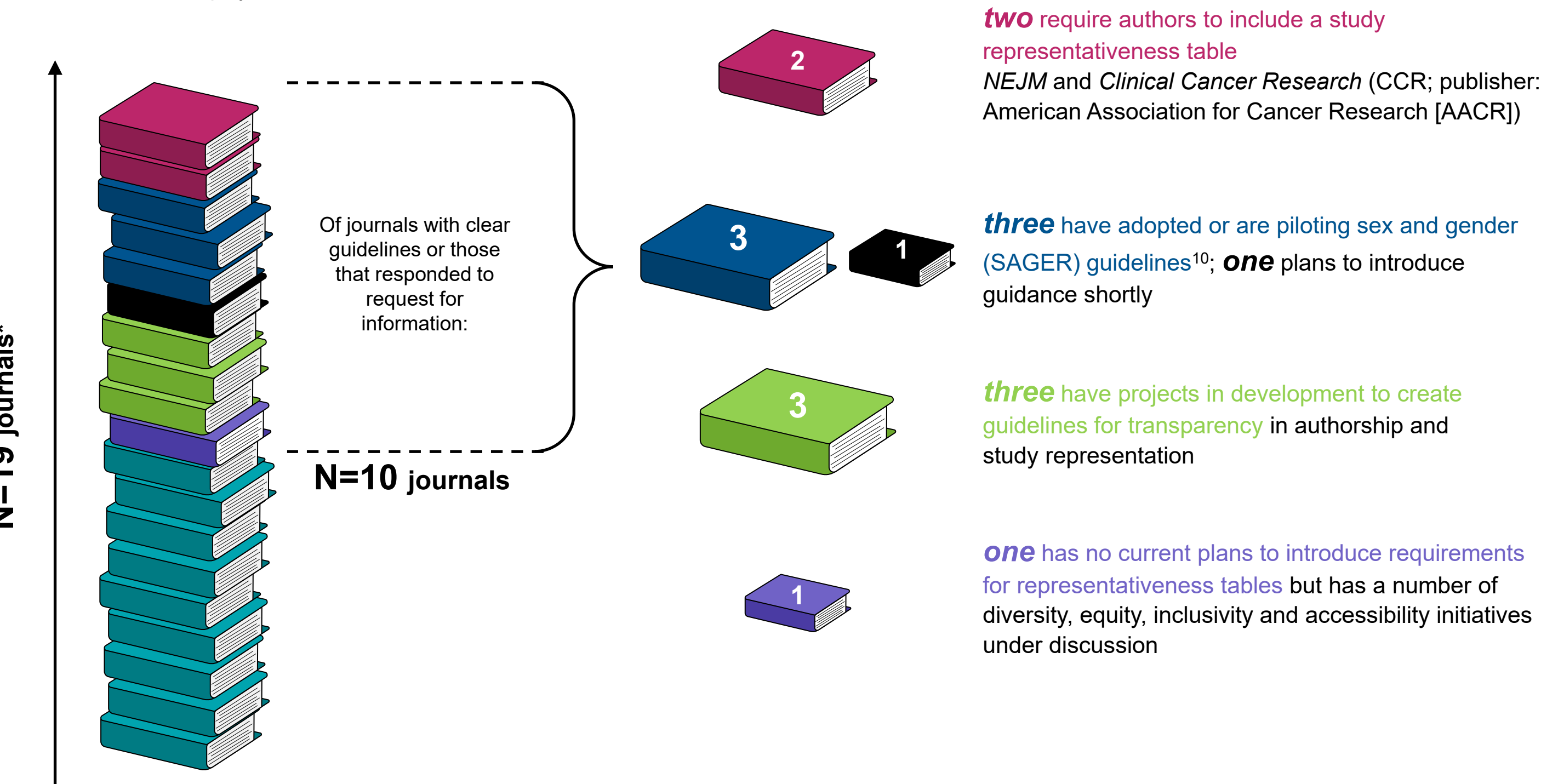
- Journal representativeness requirements
 - We conducted desk research to evaluate guidance and current practice for publishing clinical trial patient population representativeness in key journals, with a focus on hematological oncology
 - We reviewed requirements in 19 journals, representing 15 publishers. We based our selection on the *New England Journal of Medicine (NEJM)* Journal Watch Oncology and Hematology list to reflect a range of general and specialist journals with differing impact factors and from different publishing houses
 - If representativeness requirements were not clearly stated in author guidelines, we contacted journals for further information
 - For journals that had tables of representativeness requirements, we reviewed published examples to see the type of information presented and the sources used
- Survey of HCP perspectives
 - Targeted, high-level insights were collected via a short online survey tool, Sermo
 - HCPs were asked to complete a series of questions to better understand their experience with published tables of representativeness and how additional diversity and inclusion data might support their clinical practices
 - The full list of survey questions can be found in the supplementary materials via the QR code (see lower right hand corner)

Results

Journal/publisher perspectives: Current initiatives to improve transparency in journal clinical trial publications

Figure 1: Summary of journal patient representativeness reporting requirements (hematological oncology therapy area)

- Most of the 19 evaluated journals have a clear commitment to Diversity, Equity and Inclusion stated on their websites with some drawing specific attention to collections of selected publications that highlight related topics (Figure 1)
 - Journal of the National Cancer Institute* has a special collection; Diversity, Equity and Inclusion¹¹
 - The Lancet* published a themed issue on advancing women in science, medicine, and global health in 2019¹² and in 2022 appointed an International Racial Equity Advisory Board to guide the generation of a special issue¹³
 - Journal of the American Medical Association (JAMA)* published a collection of papers on health disparities,¹⁴ on Equity, Diversity and Inclusion,¹⁵ and an editorial on Equity¹⁶



*Am J Hematol, Ann Intern Med, Ann Oncol, Blood, Br Med J, Br J Clin Pharmacol, Br J Haematol, Clin Cancer Res, Future Oncol, Haematologica, Hemasphere, JAMA, J Clin Oncol, J Natl Cancer Inst, J Thromb Haemost, Lancet, Nature, New Engl J Med, and Ther Adv Hematol

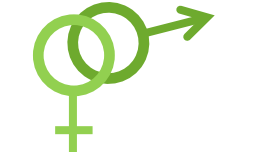
- Journals that encourage or require representativeness reporting do not provide guidance on appropriate sources of epidemiological data
- In journals with no current guidance, manuscripts (October 2022 onwards) including representativeness tables/statements are rare

References
1. Kennedy-Martin T, et al. Trials 2015;16:485.
2. Rubin E, N Engl J Med 2017;376:1029-30.
3. Khurana A, et al. J Clin Oncol 2021;39(15):1641-49.
4. Lim E, et al. Hematol J Med Public Health 2015;7409:302-10.
5. Metz LE, Aschew M, Blood 2021;137(1):13-5.
6. Khurana A, et al. Blood 2022;140(Suppl 1):2056-58.
7. US Food and Drug Administration. Diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials guidance for industry. Draft Guidance. Accessed April 2023. <https://www.fda.gov/media/157635/download>.
8. US Food and Drug Administration. Collection of race and ethnicity data in clinical trials. Guidance for industry and food and drug administration staff. October 26, 2016. Accessed April 2023. <https://www.fda.gov/media/174533/download>.
9. ICMJE. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Updated May 2022. Accessed January 2023. <https://www.icmje.org/>.
10. Heider S, et al. Res Integr Peer Rev 2016;1:2.
11. Journal of the National Cancer Institute. Diversity, Equity, and Inclusion Statement. Accessed April 2023. <https://academic.oup.com/jnci/pages/diversity-equity-inclusion>.
12. The Lancet. Lancet 2019;393(10171):P493.
13. The Lancet. Lancet 2022;400(10368):P2007.
14. JAMA Network. Health disparities. Accessed April 2023. <https://jamanetwork.com/collections/5679/health-disparities>.
15. JAMA Network. Equity, Diversity and Inclusion. Accessed April 2023. <https://jamanetwork.com/collections/46387/equity-diversity-and-inclusion>.
16. Fontanarosa PB, et al. JAMA 2021;325(1):18-20.
17. SEER. Surveillance, Epidemiology, and End Results Program. Accessed April 2023. <https://seer.cancer.gov/>.
18. Yuma T, et al. BMJ 2022;381:n803095.
19. Radtke AJ, et al. Nat Med 2022;28(8):1518-20.
20. Organisation for Economic Co-operation and Development. Statistics and data directorate. Accessed April 2023. <https://data.oecd.org/document/SDD/DOC2018/en.pdf>.

Comparison of publisher requirements

- When comparing the information requested for tables of representativeness in *NEJM* and *CCR* (Table A), the criteria were largely the same, with notable differences in requirements to refer to the table in the main manuscript text
- The sources used for representativeness data varied widely with only three referencing The Surveillance, Epidemiology, and End Results (SEER) Program, which provides information on cancer statistics among the U.S. population¹⁷

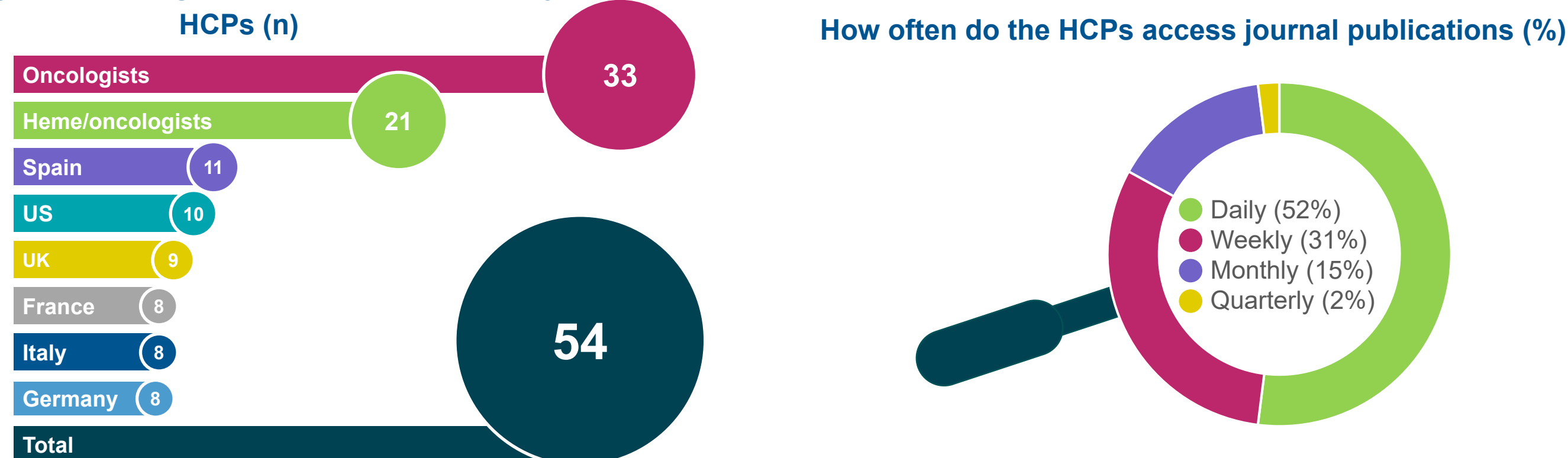
Table A: Summary of representativeness criteria requested by *NEJM* and *CCR*

Similarities	Differences
Parameters requested by the journals for the table of representativeness: Disease, problem, condition, cancer type/subtype/stage Special considerations related to:	
	
Sex and gender	
	
Age	
	
Race or ethnic group	
	
Geography	
Overall representativeness	
Tables are cited in the supplementary materials	Only <i>NEJM</i> request that the table is referenced in the manuscript including a comment about the representativeness of the trial population

HCP perceptions of tables of representativeness

- Figure 2 shows the number, expertise and geographic spread of the HCPs who completed the survey

Figure 2: Demographics of the HCPs surveyed



- More than 50% of HCPs surveyed read journal publications every day and 61% said they always checked the trial populations versus their own patients
- HCPs were shown an example of a table of representativeness from a journal?
 - 41% said they had seen one before and felt it was very useful in understanding how the trial patients related to their own patients
 - 72% agreed/strongly agreed that the table would help with assessing the results with respect to their own patients
 - 89% agreed/strongly agreed that all publications should include tables of representativeness

Quotes from HCPs related to the shared example representativeness table from *NEJM*



- When assessing the impact of the diversity data on the interpretation of the published study:
 - 68% of HCPs surveyed agreed/strongly agreed that differences between the table of representativeness and the trial data would modify their interpretation of the findings
 - 65% of HCPs surveyed agreed/strongly agreed that providing representativeness tables and having transparency of diversity were important advances towards health equity for patients

Acknowledgements

The authors thank Victoria Crossland of Takeda Development Center Americas, Inc., for the valuable insights on challenges and considerations for reporting clinical trial representativeness in medical publications.

Disclaimer

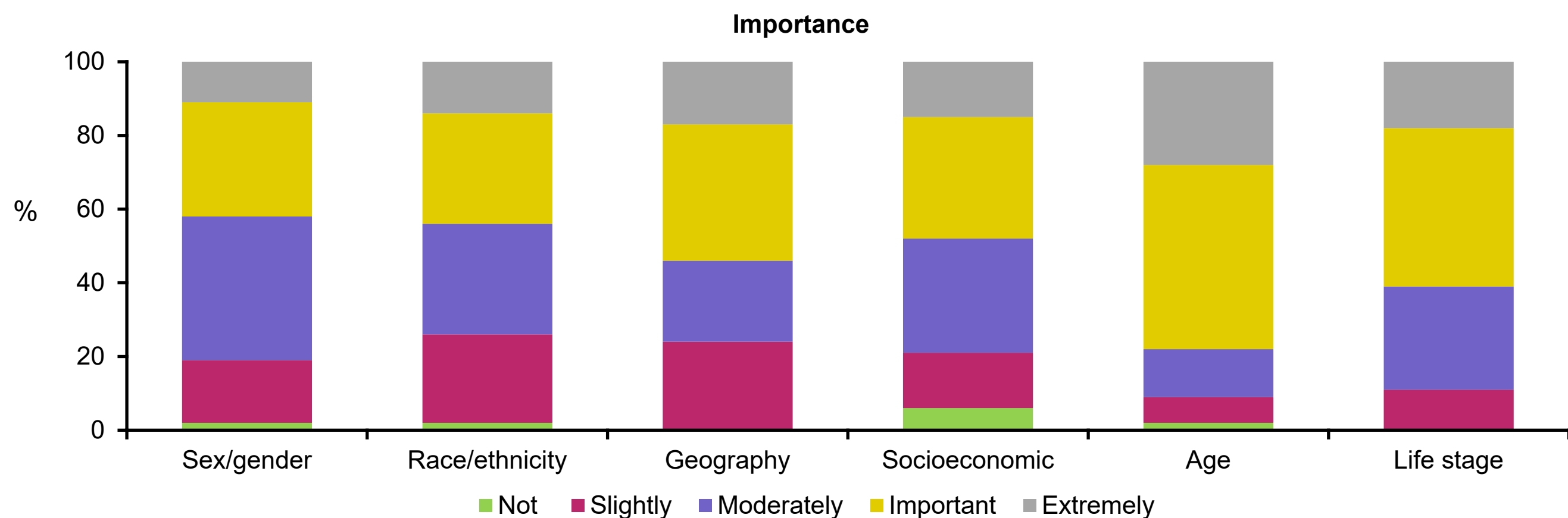
The views and opinions expressed in this poster are those of the authors and do not necessarily reflect those of Takeda or Ashfield MedComms.

Funding

This research was funded by Ashfield MedComms, an Inizio company, and Takeda Pharmaceuticals U.S.A., Inc., Lexington, MA, USA.

- HCPs were asked to rank the diversity characteristics they deemed important when considering the relevance of published data to their patients (Figure 3)

Figure 3: The importance of diversity parameters when assessing relevance of clinical data



- When asked what additional parameters would be helpful when assessing the relevance of the clinical trial data, most HCPs that were surveyed felt the example table covered their needs, with only additional comorbidities data highlighted by two HCPs

Challenges of commenting on how representative the study sample is of the larger population of interest

- A fair inclusion score has been developed and tested on oncology pivotal trials; however, this is not yet available for other therapeutic areas¹⁸
- In early phase and in rare disease trials, patient numbers may be small⁴
- The belief that early phase clinical trials should have more stringent inclusion and exclusion criteria to improve internal validity of results may lead to deferment of efforts to improve enrollment of diverse populations until later phase 2 and 3 studies¹⁹, as well as reporting of trial representativeness data
 - Moreover, if any inclusion or exclusion criteria are more common in certain populations, the criteria may lead to their underrepresentation
- Although epidemiological data are widely available for cancer¹⁷, non-oncology epidemiological data at a local or regional level may be sparse
- Currently, many population-based cancer registries do not collect any data on race, ethnicity, or socioeconomic status of their population¹⁹, making comparisons with clinical trial data difficult at a country level
- In some countries, race and ethnicity are defined differently, and nationality may be collected instead²⁰
- Relevant global and regional demographic and disease characteristic data may not be collected in the trial⁴

Considerations for reporting of clinical representativeness in medical publications

- Data may be stratified by geography for global clinical trials
- Real-world data sources for comparison with trial data should be selected carefully to ensure they are representative of the population
 - Depending on the local healthcare system, if claims data are used to determine the real-world patient population where epidemiological data are sparse, it would not capture patients who are not insured
- Based on the feedback of the surveyed HCPs that the tables of representativeness were important for understanding the generalizability of data to their patient populations, journals should consider if the table should be moved from the supplement to the main manuscript
- Ensuring quality and consistency in presenting trial representativeness data may not be feasible even with standardized guidance, as considerations for determining clinical trial representativeness vary between therapeutic areas
- Given the lack of standardized guidance, consultation with clinical trial diversity and inclusion experts in the publication process may increase quality of trial representativeness reporting; any such contributions should be acknowledged appropriately

Conclusions

- Of the journals evaluated, few currently require inclusion of representativeness data, despite ICMJE guidance
- Journals that have requirements for representativeness data provide limited guidance on how to present the data in a transparent and meaningful way
- Considering that oncology is one of the main therapeutic areas in which randomized controlled trials and real-world populations have been compared, consistent findings of limited journal guidance are expected across disease areas
- The value of greater transparency in clinical trial patient diversity was recognized by the oncology HCPs who were surveyed and would likely be mirrored by other health experts
- Additional considerations from other disease areas should be incorporated into representativeness reporting guidance
- Standardized guidance or best practices may not be feasible, so medical publication professionals should consider consulting with clinical trial diversity and inclusion experts to ensure that trial representativeness is reported in meaningful way to clinicians