Setting diversity enrollment goals in clinical trials based on real-world data: challenges of multi-country demographics

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Abstract

- **Objectives:** Under the United States (US) Food and Drug Omnibus Reform Act of 2022, the Food and Drug Administration published draft guidance in April 2022 to improve participant diversity in clinical trials. Similarly, the United Kingdom's Medicines and Healthcare products Regulatory Agency is currently developing diversity guidance for clinical research. Researchers have proposed methods for setting diversity enrollment goals in trials using real-world data (RWD). This analysis examines potential diversity enrollment goals for two types of cancer (liver cancer and melanoma), for England and the US, to understand potential challenges for sponsors.
- **Methods:** The most recent accessible data on cancer incidence and census counts were used for each country. Cancer incidence by race and ethnicity was obtained from Public Health England for England and from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute for the US. Using methods proposed by Cullen et al, we calculated enrollment goals for common race/ethnic groups in England and the US.
- **Results:** Enrollment goals differed considerably between England and the US. The greatest differences were observed in Black patients (liver cancer: England: 4.2%, US: 13.7%; melanoma: England: 4.2%, US: 12.7%). There were also large differences in enrollment goals for White patients (liver cancer: England: ≤81.0%, US: ≤55.2%; melanoma: England: ≤81.0%, US: ≤58.3%) between the two countries. This was driven by a 19.4% enrollment goal for US Hispanic patients for both cancers, whereas there is no Hispanic category in England's census or PHE data source.
- **Conclusion:** There are many challenges with setting diversity enrollment goals, starting with identifying informative RWD sources that reflect the indicated population. These challenges increase with requirements from multiple countries with different population demographics. Cooperation across countries and coordinated guidance will be needed to assist sponsors in meeting multi-country diversity requirements for global studies.

Background

- Under the United States (US) Food and Drug Omnibus Reform Act of 2022, the Food and Drug Administration (FDA) published draft guidance in April 2022 to improve participant diversity in clinical trials with an intent to improve the strength and generalizability of the evidence for the intended use population[1]
  - This guidance expands on FDA guidance from 2016, Collection of Race and Ethnicity Data in Clinical Trials[2]
  - FDA advises sponsors to seek diversity in clinical trial enrollment beyond populations defined by race and ethnicity, including other underrepresented populations defined by demographics such as sex, gender identity, age, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity
  - Sponsors should define enrollment goals for underrepresented racial and ethnic participants as early as practicable in clinical development for a given indication in a Diversity Action Plan (DAP)
  - When there is information that the product may perform differentially across race or ethnicity, the DAP should specify the study design features that will support analyses to inform the safety and effectiveness of the product in the relevant racial and ethnic populations
  - When there is no information that race or ethnicity will impact safety or effectiveness, it is appropriate that clinical trial enrollment reflects the epidemiology of the disease
  - In certain situations (e.g., disease defined by the presence of a rare molecular aberration), it may be challenging to set an enrollment goal based on the epidemiology of the disease due to limited data to characterize the incidence and/or prevalence of the disease across diverse racial and ethnic populations
  - FDA encourages sponsors to leverage various data sources (e.g., published literature and real-world data [RWD]) to set enrollment goals; if this is not feasible, it may be appropriate to set the enrollment goal based on demographics in the overall population with the disease or condition
  - Goals should be specified for enrollment of underrepresented racial and ethnic participants, based on the epidemiology of the disease and/or based on a priori information that may impact outcomes across racial and ethnic groups; and where appropriate, leverage pooled data sources or use demographic data in the general population
  - In some cases, increased (i.e., greater than proportional) enrollment of certain populations may be needed to elucidate potential important differences
- Similarly, the United Kingdom's Medicines and Healthcare products Regulatory Agency is currently developing diversity guidance for clinical research[3]
- This creates the potential scenario where a sponsor of an international study may need to meet diversity goals for multiple countries
- Researchers have proposed a framework for setting diversity enrollment goals in trials which utilizes an algorithm for calculating enrollment goals based on RWD and weighting based on the US census or the epidemiology in the literature[4]

Objective

- The objective of this analysis is to examine potential diversity enrollment goals for two hypothetical trials (one in liver cancer, and another in melanoma) conducted in England and the US to understand potential challenges for sponsors when setting enrollment goals for global studies

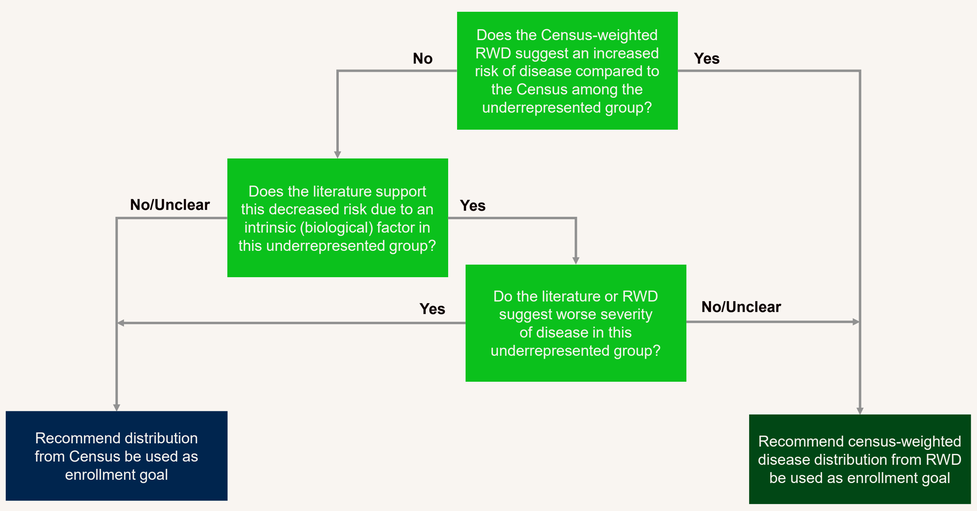
Methods

- Cancer incidence rates were obtained by racial and ethnic categories for **(Table 1)**:
  - England (from Public Health England)[5]
  - US (from Surveillance, Epidemiology, and End Results program of the National Cancer Institute)[6]
- Racial and ethnic categories were specific to England and the US as defined in the incidence data source:
  - England: Asian, Black, White, Mixed/Multiple
  - US: non-Hispanic American Indian or Alaska Native, non-Hispanic Asian or Pacific Islander, non-Hispanic Black or African American, non-Hispanic White, Hispanic, Mixed/Multiple
- The latest census distribution was obtained across racial and ethnic categories for England and the US **(Table 1)**[7,8]
- Census-weighted distributions of the incidence rates across racial and ethnic categories were calculated **(Table 2)**
- Using methods based on Cullen et al,[4] enrollment goals for the racial and ethnic categories were determined for England and the US **(Figure 1)**
- White category defaults to 100% minus the other racial and ethnic category percents

Results

- White patients comprised over 90% of the census-weighted percent for both liver cancer and melanoma in England and for liver cancer in the US **(Table 2)**
- Enrollment goals differed considerably between England and the US **(Table 2, Figure 2)**
- The greatest absolute differences were observed for Black patients **(Table 2, Figure 2)**:
  - Liver cancer: England: 4.2%, US: 13.7%
  - Melanoma: England: 4.2%, US: 12.7%
- There were also large absolute differences for White patients **(Table 2, Figure 2)**:
  - Liver cancer: England: ≤81.0%, US: ≤55.2%
  - Melanoma: England: ≤81.0%, US: ≤58.3%
  - Differences were driven by a 19.4% enrollment goal for US Hispanic patients for both cancers, whereas there is no Hispanic category in England's census or Public Health England data source

Figure 1. Algorithm for setting enrollment goals by racial and ethnic category[a]



RWD, real-world data

Adapted from Cullen MR et al (2023)

Table 1. Incidence of liver cancer and melanoma and census distribution in England and the US

Racial and Ethnic Category[a]	Crude Incidence (per 100,000)		Census Distribution (%)	
	England (2013-2017)	US (2021)	England (2023)	US (2023)
Liver Cancer				
White]	9.1	9.0	81.0	58.3
American Indian/Alaskan Native	–	12.5	–	0.7
Asian	5.3	9.9	9.6	6.4
Black	4.9	8.5	4.2	12.7
Hispanic	–	8.3	–	19.4
Mixed/Multiple	1.5	–	3.0	2.5
Other	–	–	2.2	–
Melanoma				
White	26.2	47.9	81.0	58.3
American Indian/Alaskan Native	–	9.6	–	0.7
Asian	0.5	1.4	9.6	6.4
Black	1.1	1.0	4.2	12.7
Hispanic	–	4.0	–	19.4
Mixed/Multiple	0.0	–	3.0	2.5
Other	–	–	2.2	–

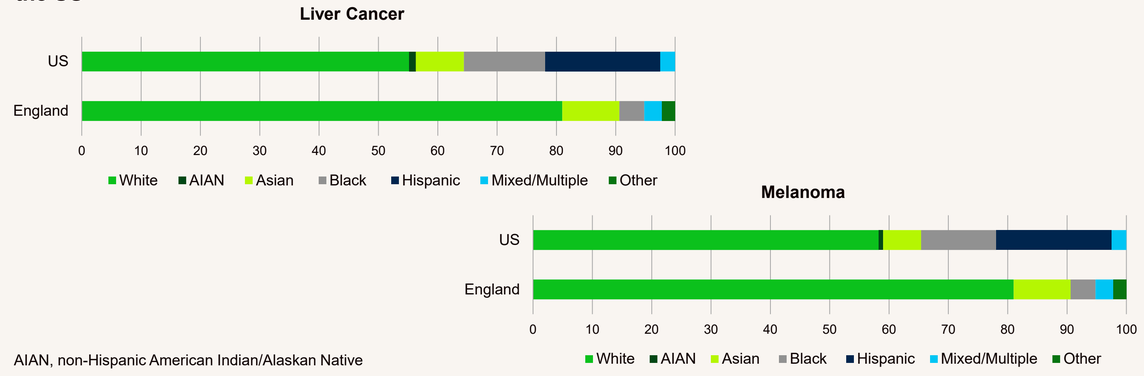
a Racial and ethnic categories are abbreviated. For the US: White=non-Hispanic White, American Indian/Alaskan Native=non-Hispanic American Indian/Alaskan Native, Asian=non-Hispanic Asian or Other Pacific Islander, and Black=non-Hispanic Black or African American, Mixed/Multiple=two or more races.
Real-world data sources: US – SEER Research Data, 17 Registries, Nov 2022 Sub (2000-2020) (Year 2021); England – Supplementary data available from Delon C, Brown KF, Payne NWS, Kotrotsios Y, Vernon S, Shelton J. Differences in cancer incidence by broad ethnic group in England, 2013-2017. *Br J Cancer.* 2022 Jun;126(12):1765-1773.
Census data: US – United States Census Bureau at https://www.census.gov/data/tables/time%1eseries/demo/popest/2020s%1enational%1edetail.html; England – Office for National Statistics at https://www.ons.gov.uk/datasets/create.

Table 2. Calculated census-weighted incidence distributions and enrollment goals for hypothetical trials in liver cancer and melanoma in England and the US

Racial and Ethnic Category[a]	Census-Weighted Incidence Distribution, %		Census-weighted Enrollment Goals, (%)		Absolute Difference Between Countries, %
	England (2013-2017)	US[b] (2023)	England	US	
Liver Cancer					
White	92.2	58.9	≤81.0	≤55.2	25.8
American Indian/Alaskan Native	–	1.1	0.0	1.1	1.1
Asian	5.2	8.1	9.6	8.1	1.5
Black	2.1	13.7	4.2	13.7	9.5
Hispanic	–	18.2	0.0	19.4	19.4
Mixed/Multiple	0.4	–	3.0	2.5	0.5
Other	–	–	2.2	0.0	2.2
Melanoma					
White	99.6	96.2	≤81.0	≤58.3	22.7
American Indian/Alaskan Native	–	0.3	0.0	0.7	0.7
Asian	0.2	0.4	9.6	6.4	3.2
Black	0.2	0.5	4.2	12.7	8.5
Hispanic	–	2.7	0.0	19.4	19.4
Mixed/Multiple	0.0	–	3.0	2.5	0.5
Other	–	–	2.2	0.0	2.2

a Racial and ethnic categories are abbreviated. For the US: White=non-Hispanic White, American Indian/Alaskan Native=non-Hispanic American Indian/Alaskan Native, Asian=non-Hispanic Asian or Other Pacific Islander, and Black=non-Hispanic Black or African American, Mixed/Multiple=two or more races.
b Weighted using the US December 2023 population distribution, projected from 2020 census. The weights for race and Hispanic origin accounted for persons of two or more races by allocating the percent of the population of two or more races to the Black, AIAN, and API race categories proportionately.
Real-world data sources: US – SEER Research Data, 17 Registries, Nov 2022 Sub (2000-2020) (Year 2021); England – Supplementary data available from Delon C, Brown KF, Payne NWS, Kotrotsios Y, Vernon S, Shelton J. Differences in cancer incidence by broad ethnic group in England, 2013-2017. *Br J Cancer.* 2022 Jun;126(12):1765-1773. Census data: US – United States Census Bureau at https://www.census.gov/data/tables/time%1eseries/demo/popest/2020s%1enational%1edetail.html; England – Office for National Statistics at https://www.ons.gov.uk/datasets/create.

Figure 2. Differences in enrollment goals for hypothetical trials in liver cancer and melanoma in England and the US



AIAN, non-Hispanic American Indian/Alaskan Native

Conclusions

- Applying the proposed methodology by Cullen et al[4] for determining enrollment goals results in considerable differences in the targets for England and the US
- There are many challenges with setting diversity enrollment goals, starting with identifying informative RWD sources that reflect the indicated population
- These challenges increase with requirements from multiple countries with different population demographics
- Cooperation across countries and coordinated guidance will be needed to assist sponsors in meeting multi-country diversity requirements for global trials

FDA draft guidance updates

- Most recently, following the submission of this abstract to ISPOR, the FDA updated its draft guidance on diversity action plans[9]
- Key changes in the 2024 draft guidance include:
  - Enrollment by age group, sex, and other non-demographic characteristics (e.g., socioeconomic status, geographic location), going beyond race and ethnicity
  - Detailed recommendations on operationalizing diversity in studies, including a template showing what data the DAP should include, in up to a maximum of 10 pages
  - A strong emphasis on accountability with a focus on sponsors' meeting diversity goals, encouraging sponsors to add their enrollment goals to their websites and be more transparent when clinical studies are open
  - Three required parts: 1) enrollment goals, disaggregated by age group, sex, race, and ethnicity of clinically relevant study populations, 2) rationale for sponsor's enrollment goals, 3) explanation of the sponsor's plans for meeting its enrollment goals; removing prior guidance to provide: overview of the disease/condition, scope of medical development program, and status of meeting enrollment goals
- The 2024 draft guidance does not address challenges of setting enrollment goals for global studies; the addition of other factors to consider beyond race and ethnicity increases these challenges

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