



**MULTI-REGIONAL
CLINICAL TRIALS**

THE MRCT CENTER of
BRIGHAM AND WOMEN'S HOSPITAL
and HARVARD

ACHIEVING DIVERSITY, INCLUSION, AND EQUITY IN CLINICAL RESEARCH

Executive Summary

**Barbara E. Bierer, MD
Sarah A. White, MPH
Laura G. Meloney, MPH, MS
Hayat R. Ahmed, MS
David H. Strauss, MD
Luther T. Clark, MD**

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Executive Summary

Why, and to what extent, should study populations in clinical research represent the diversity of U.S. and global populations? Should, and when should, study populations reflect the population intended to use the product? Why be concerned about representation if the numbers of participants representing any subgroup will only very rarely be sufficient in any given clinical trial to support valid statistical analysis?

Generally, study populations in clinical research should (and often do) mirror the characteristics of the population affected by a particular illness or condition, or reflect the characteristics of the population intended to use the product.¹ Variability in treatment outcome among subgroups, when it exists, can best—and sometimes only—be studied when those subgroups are included in the clinical research.² Importantly, in the absence of diverse participation, individuals may not trust that data or conclusions apply to them, and they may be highly skeptical of the resulting evidence base.³ Understanding the foundations of heterogeneity of treatment effect and safety, and whether heterogeneity of efficacy or effectiveness, or differences in the safety profile, is related to underlying biology, genetics, metabolism, or many other factors (e.g., interaction with concomitant drugs or biologics, compliance, comorbidities), requires both the inclusion of diverse populations and the unbiased analyses of the results. However, in any clinical trial, rarely are there sufficient numbers of enrolled participants from subgroups to permit definitive subgroup analyses.⁴ In product development, however, there is generally a series of trials, not one, and those data can be pooled for analysis. There may also be other approaches to generate relevant estimates of heterogeneity, including innovative statistical methods, visualization, studies of relevant surrogate markers of outcome measures, combining studies using shared individual participant data, and studies using real world data

¹ Knepper TC, McLeod HL. When will clinical trials finally reflect diversity?. *Nature* 2018 May 557,157-159.

² Modeling, other simulation techniques, and newer analytic approaches may help approximate understanding of treatment and other outcomes.

³ As will be discussed later, the smaller the population (e.g., ultra-rare diseases, individuals over 90 years old, etc.) the more difficult to study and to derive statistically meaningful results. Further, data from these individuals may be more readily identifiable, challenging participant privacy and confidentiality expectations.

⁴ Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*. 2015 Dec 1;16(1):495.

after market approval of a product. These latter methods depend upon data that are interoperable, and that in turn depends upon collecting relevant data at the point of care, using common data standards and data dictionaries, robust metadata,⁵ and upon the willingness of researchers and research entities to share data. In the end of course, the individual—not a population—is the subject of any treatment, diagnostic, or preventive intervention; for the individual, what matters is *whether that intervention* is likely to work and with what safety profile (often a judgement considered in comparison to other options), rather than *how well* it may work.

There are situations, of course, when the study population is defined by a particular genetic variant that is associated with a particular demographic subgroup (e.g., Sickle cell disease, Tay-Sachs disease) and the lack of diverse representation is a reflection of biology and the underlying physiology. These situations may, on occasion, even distort summary statistics of diverse representation. For instance, if summary data combine all data from a year in which 5 large breast cancer trials have completed, it may appear that women are adequately represented in all trials as a consequence of the aggregation across trials. On the other hand, if 5 prostate cancer trials complete, it may appear that women are underrepresented in summary data, when in fact disambiguation of the data might be a more accurate reflection. Clinical trial enrollment of particular populations (that can be defined on the basis of sex, gender, race, ethnicity) in these circumstances is appropriate, but rare. The more common problem is underrepresentation of diverse populations, upon which we focus here.

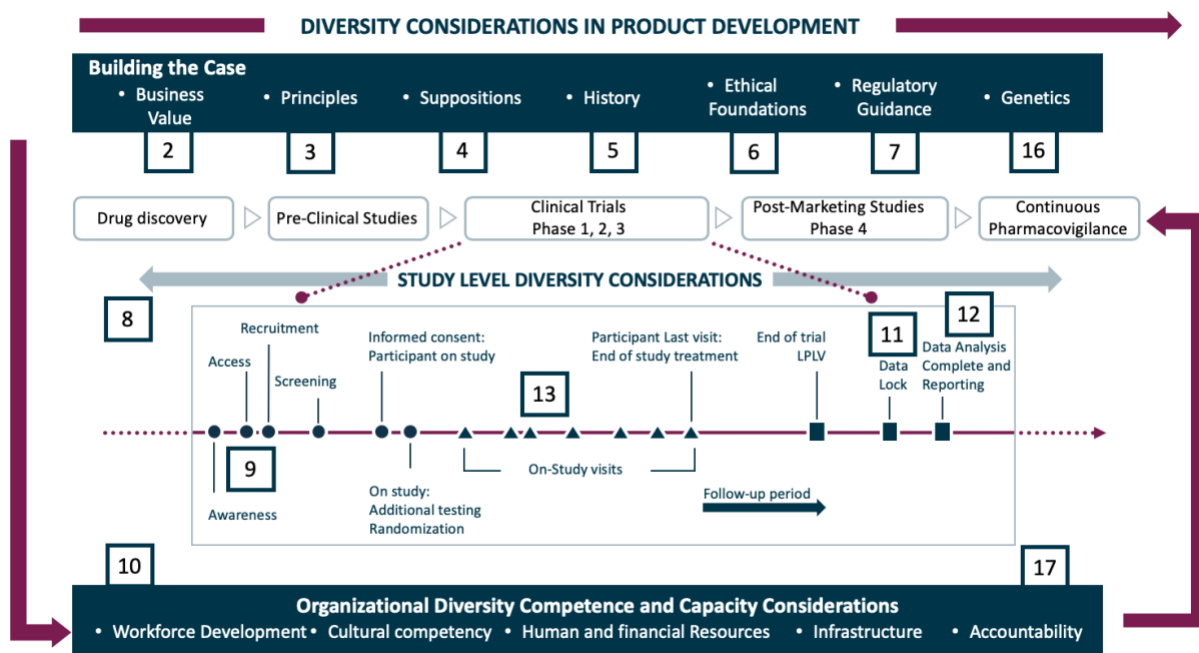
In addition to the biological importance of heterogeneity of treatment effect, there are reasons of health equity and social impact to support and promote appropriate inclusion of diverse populations in clinical research. As an important ethical principle, justice and fairness in distribution of the opportunities and potential benefits of participation in research drive an

⁵ Metadata are data that describe other data, such as an underlying definition, format (e.g., month/day/year versus day/month/year) and are necessary for managing, interpreting, and storing data elements.

affirmative commitment to diverse inclusion.^{6,7,8} Further, there are considerations of health equity, in which all persons should have access to equal opportunity for participation, given the utility and potential benefit of the knowledge gained for the population as well as the possibility of direct benefit to the individual. Finally, it is a matter of public trust.

The framework presented in “Achieving Diversity, Inclusion, and Equity in Clinical Research” is divided into Parts and Chapters (see Figure A).

Figure A: Layout of the Framework



⁶ Caplan A, Friesen P. Health disparities and clinical trial recruitment: Is there a duty to tweet? PLoS biology. 2017 Mar 1;15(3):e2002040.

⁷ United States. National Commission for the Protection of Human Subjects of Biomedical, Behavioral Research. The Belmont report: ethical principles and guidelines for the protection of human subjects of research. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; 1978.

⁸ This guidance generally focuses on underrepresentation in research, but we are sensitive to research that disproportionately burdens certain populations with the risks attendant to research, a concern that prompted the Belmont Report, the establishment of ethics committees, and regulatory oversight.

Clinical research during and after product development and approval involves many steps, each of which is considered in this document. The relevant chapters to be reviewed for in depth analysis, key considerations, and recommendations, where applicable, are shown in the blue circles. (e.g., “2” within a blue square refers to Chapter 2). Not all chapters are shown. (See also Figure 7 in this document.)

After presenting the objectives of the project (Chapter 1 “Objectives”), the scientific, ethical, and social arguments for diverse inclusion, as well as its business value with both potential benefit and cost considerations are considered (Chapter 2 “The Case for Diversity in Clinical Research”). Notably, we believe that the expectations for all trials, regardless of sponsor or funder (e.g., industry, academic, non-profit), and for all investigators and in all geographies are the same. Rarely does a patient or participant know who has sponsored a trial, just as individuals can only rarely identify the manufacturer of a product correctly. It is true that industry-sponsored trials are often within the context of a product development program, while academic trials often involve approved products; considerations of inclusiveness apply equally in both, although perhaps with a somewhat different emphasis or justification. But there should be no need to justify inclusion – its importance has never been so clear. The COVID-19 pandemic has demonstrated the urgent need to research both biology and social determinants of health, as underserved and vulnerable populations are disproportionately affected both in incidence and severity of infection for reasons that are not currently understood.

We adopt a broad definition of diversity, including invariant or unmodifiable factors, also termed demographic factors (e.g., race, ethnicity, [see Appendix 3], sex, age, genetics), as well as “non-demographic” factors (e.g., social determinants of health, comorbidities, organ dysfunction, concurrent medications, environmental factors, nutrition, compliance) that may change over time. Any individual, however, does not fit into only one dimension of diversity: an individual is of a certain age, sex, gender, race, ethnicity, with varying conditions and social contexts that are often interdependent and interrelated. Any—or many or all—of these dimensions may contribute directly or indirectly to the trial outcome measures. Dimensions of diversity are not independent variables but may influence one another. This intersectionality renders statistical analysis even more challenging, with likely multiplicity concerns, but is nevertheless important to consider, at least in some contexts.

The research question, clinical paradigm, and prior knowledge of the disease or condition, in addition to the proposed intervention itself, will affect the context in which diversity needs to be prioritized and considered. Not every dimension of diversity is relevant to the safety, efficacy, or effectiveness of every intervention. Careful analysis of pre-clinical and early clinical data, an assessment of outcomes of similar molecular entities, and prior evidence from other clinical trials or care are helpful. Whether and when to consider different subgroups in research, and in trial planning and analyses, can be determined through case-based analyses. What is known about a treatment or intervention will dictate some aspects of inclusion: the less that is known (e.g., a new molecular entity in a phase 1 or 2 trial), the more appropriate a conservative approach becomes. The entire drug development program, from early phase trials to novel, complex clinical trials, to post-marketing observational data, in single site to multi-national trials, should be considered. Diversity is context-specific, and the approach to and importance of diversity demands a context-specific analysis.

This document identifies a number of barriers to inclusion of diverse populations, and importantly, in Parts C through F, we address potential approaches and solutions to increase diversity. Many of the suggestions have been piloted by others, and we would do a disservice to summarize here the many specific recommendations without the commentary, case examples, and resources we include in the larger document. A comprehensive plan is necessary, and we have focused each chapter on different areas in clinical research where interventions might prove effective. Those include:

- The extraordinary value of partnerships with community, public, and patient participants (Chapter 8), important from pre-planning to execution of the trial (see Figure 11 “Application of patient engagement strategies across four different stages of research”)
- Extending patient and public awareness, knowledge, and access (Chapter 9)
- Workforce development, including efforts to diversify the workforce as well as training in implicit bias and cultural competence of the current workforce (Chapter 10)
- The form and substance of data acquisition, data standards, and common approaches for collection and reporting variables (Chapter 11)
- Approach to data analysis (Chapter 12), including the limitations of traditional approaches, potential innovative methods to consider, and the role of real world data

- Study design and study conduct considerations (Chapter 13), including the overall product development pathway, the choice of study question and study design, eligibility criteria, feasibility plans and site selection, recruitment strategy, study conduct, participant retention, and payment.
- The role of the IRB/REC in promoting diversity (Chapter 14)
- Considerations of special populations (Chapter 15) [reserved for later completion]
- The contribution of genetics to diversity in clinical research (Chapter 16)
- Accountability for promoting diversity in clinical research (Chapter 17), divided by each stakeholder as well as cooperative and interrelated responsibilities, and
- Future research and directions (Chapter 18)

The guidance is then followed by practical resources to facilitate change in what we have termed a *Toolkit*. While white papers and publications help disseminate the work such that it is findable, it can be challenging for well-intentioned individuals to transition from theory to practice. Decreasing the barrier to adoption requires practical tools and resources for implementation. The tools offered here are not perfect nor final; we anticipate that modifications will be made, and new and better ones developed. The tools, like the guidance document itself, are not meant to be prescriptive. Hopefully, they will be useful to inspire valuable revision.

We posit that as barriers to inclusion of diverse populations are identified; as resources, approaches, infrastructure, and technology are created to address those barriers; as study design evolves; as data terminology, collection, and analyses are standardized; and as regulatory science progresses, the costs to inclusion will decrease, as is common in a process of normalization. But an initial investment to address diverse inclusion is necessary, and while that investment may differ, all stakeholders, individually and collectively, have responsibility for change.

Proactive planning, dedicated execution, and metrics of progress are required to prioritize diverse inclusion appropriately along a product's clinical development and throughout all phases of the trial and product lifecycle (see Figure 34 "Achieving diverse enrollment requires planning, support, and accountability"). With metrics and data, iterative improvement

becomes possible, and individuals and organizations can monitor progress. This work is necessary but not easy, and it will take time to achieve meaningful change.